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Body Mass Index and Cardiorespiratory Fitness in Mid-Life and Risk of Heart Failure Hospitalization in Older Age

Findings from the Cooper Center Longitudinal Study

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ABSTRACT

OBJECTIVES This study evaluated the contributions of obesity and changes in body mass index (BMI) in mid-life to long-term heart failure (HF) risk independent of cardiorespiratory fitness (CRF) levels.

BACKGROUND Obesity and low CRF are well-established risk factors for HF. However, given the inverse association between CRF and obesity, the independent contributions of BMI toward HF risk are not fully understood.

METHODS We included 19,485 participants from the Cooper Center Longitudinal Study who survived to receive Medicare coverage, from 1999 to 2009. CRF was estimated in metabolic equivalents (METS) according to Balke treadmill time. Associations of BMI and BMI change with HF hospitalization after age 65 were assessed by applying a proportional hazards recurrent events model to the failure time data.

RESULTS After 127,110 person-years of follow-up, we observed 1,038 HF hospitalization events. Higher mid-life BMI was significantly associated with greater risk of HF hospitalization after adjusting for established HF risk factors (hazard ratio [HR]: 1.19; 95% confidence interval [CI]: 1.12 to 1.26) per 3 kg/m^2 higher BMI). This association was attenuated after adjusting for CRF (HR: 1.10; 95% CI: 1.03 to 1.17 per 3 kg/m^2 higher BMI). CRF accounted for 47% of the HF risk associated with BMI. BMI change was not significantly associated with risk of HF in older age after adjustment for CRF change.

CONCLUSIONS Higher BMI-associated risk of HF is explained largely by differences in CRF levels. Furthermore, BMI change is not significantly associated with HF risk after adjusting for CRF changes. These findings highlight the importance of CRF in mediating BMI-associated HF risk. (J Am Coll Cardiol HF 2017;■:■–■) © 2017 by the American College of Cardiology Foundation.

Cardiovascular disease (CVD) is the leading cause of death in the United States, accounting for one-third of all deaths (1). Within the spectrum of CVD, an estimated 5.7 million people have heart failure (HF), and by current projections, the prevalence will rise to over 9 million by 2030, given the aging population and increased survival following acute coronary events (1,2). Moreover, unfavorable lifestyle patterns are leading to increases in HF-related risk factors, contributing to the population burden of HF (1). Consequently, novel HF prevention strategies are greatly needed.

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ABBREVIATIONS AND ACRONYMS

BMI = body mass index

CMS = Center for Medicare and Medicaid Services

CVD = cardiovascular disease

HF = heart failure

METS = metabolic equivalents

Physical inactivity, low cardiorespiratory fitness (CRF), and obesity are well-established risk factors for HF (3-6). In recent studies from the Cooper Center Longitudinal Study (CCLS), we have demonstrated that low CRF in mid-life is strongly associated with risk of HF in older aged people independent of other risk factors (7,8). Similarly, observations from multiple cohort studies have also demonstrated a dose-dependent association between higher body mass index (BMI) and HF incidence (9). However, most of these studies did not account for differences in CRF levels, and the contributions of higher BMI to HF risk independent of CRF are not well understood. Furthermore, the impact of changes in BMI over intermediate-term follow-up independent of CRF change on HF risk has not been evaluated before.

Therefore, we sought to evaluate the association between mid-life BMI, CRF, and long-term HF risk independent of conventional HF risk factors. We also evaluated the association of age-related changes in BMI and CRF with HF risk in a subgroup of participants who underwent repeated examinations. We hypothesized that mid-life CRF would explain a substantial proportion of the observed association between BMI and HF risk. Furthermore, we hypothesized that the impact of changes in BMI on HF risk would also be attenuated after accounting for changes in CRF.

METHODS

STUDY POPULATION. The CCLS is an ongoing prospective study that began in 1970 at the Cooper Institute, Dallas, Texas. The details about this study have been described previously (10). All CCLS participants sign an informed consent for inclusion in the research database. The study is reviewed and approved annually by the institutional review board of the Cooper Institute.

Among 73,439 participants in the CCLS who received a clinical examination at the Cooper Clinic between 1970 and 2009, 24,872 were eligible to receive Medicare coverage between 1999 and 2009 as previously described (7). After excluding 3,885 participants who lacked both Part A and B Medicare coverage and those with Health Maintenance Organization exclusions; 819 individuals whose CCLS examinations occurred after enrollment in Medicare fee-for-service; 55 participants with early Medicare benefits (<65 years of age due to Medicare coverage for disability, end-stage renal disease, and other factors); and 628 participants with a self-reported history of myocardial infarction or stroke at study entry, 19,485 CCLS participants remained in the final study sample for the present analysis. Participants were followed from the date of initiating Medicare coverage until HF diagnosis or until the end of follow-up on December 31, 2009. A subset of the study participants (n = 8,683) had repeat CRF and BMI assessment 4.2 years after the baseline examination and were included in the analyses of BMI and CRF change.

CCLS CLINICAL EXAMINATION. Details of the baseline clinical examination and the study cohort have been previously described (10). Participants completed a comprehensive examination including self-reported personal medical and family history, a medical examination by a physician, fasting blood levels of glucose and cholesterol profile, and a maximal treadmill exercise test. Body mass index was determined from measured height and weight. Other baseline variables in the CCLS were obtained in accordance with standard protocols.

Cardiorespiratory fitness was estimated by time completed on the treadmill exercise test, using the Balke protocol. For this protocol, initial treadmill speed is set at 88 m/min (3.28 mi/h) at a 0% incline with an increase in grade by 2% after 2 minutes and a 1% increase every minute thereafter until completion. After 25 min, the grade is held constant but the speed is increased 5.4 m/min for each additional minute until completion of study. Participants were encouraged not to hold onto the treadmill railing and were encouraged to exert maximal effort. The test was terminated for either volitional exhaustion reported by the participant or for medical reasons at physician discretion. Time completed on the Balke protocol correlates highly with maximal Vo_2 uptake and is a standard method for assessing CRF (R = 0.92) (11).

Treadmill times were compared with age- and sex-specific normative data for treadmill performance within the CCLS, allowing subjects to be divided into age- and sex-specific CRF quintiles. Metabolic equivalent (METS) results were determined from standard regression equations according to Balke treadmill time (11).

MEDICARE CLAIMS DATA. Medicare inpatient claims data were obtained from Center for Medicare and Medicaid Services (CMS) for CCLS participants who were 65 years of age or older (Medicare-eligible) between 1999 (the first year CMS data are available for public use) and 2009. Center for Medicare and Medicaid Services data contain 100% of claims paid by Medicare for covered health care services. Inpatient hospitalization files from CMS provide individual records for each medical service billed to Medicare, the

date of service, primary diagnosis, and up to 8 secondary diagnoses (i.e., from International Classification of Diseases, 9th edition, [ICD-9] codes), procedures (ICD-9 procedure codes), beneficiary demographic information, and other additional data. In accordance with standard approaches, HF hospitalization was defined as a primary diagnosis of HF, as indicated by ICD-9 codes 428, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, and 404.93 (7,8).

STATISTICAL ANALYSES. The data contain Medicare claims for all CCLS participants who were ≥65 years of age during the period 1999 to 2009. The data are subject to censoring on the right and truncation on the left, with the possibility of multiple events per patient. Because of the unique structure of the Medicare claim files, we used attained age as the time scale and determined the intensity of recurrent HF hospitalization events by using the conditional model of Prentice et al. (12). As previously described, this model stratifies the at-risk population by the number of HF hospitalizations. At the time a participant develops HF hospitalization, they advance to the next at-risk stratum. Repeat HF hospitalizations within 30 days of a previous HF admission were considered a single event in the model. Consistent with our previous approaches (7,8,13), we estimated the associations of mid-life CRF, BMI with risk of HF hospitalization after age of 65 by applying a proportional hazards recurrent events model to the failure time data with other baseline risk factors entered as covariates (12). Different models were constructed to estimate the association between baseline risk factors and HF hospitalization during the years of Medicare eligibility. Model 1 was adjusted for age, sex, and BMI. Model 2 was adjusted for age, sex, systolic blood pressure, diabetes mellitus, smoking status, cholesterol, and BMI. Model 3 was additionally adjusted for baseline CRF levels. We also examined the extent to which CRF may mediate the association between BMI and HF risk. The percentage of BMI-associated HF risk explained by established risk factors and CRF was evaluated as previously described (14,15) as follows: [(hazard ratio [HR] without covariate adjustment − HR in adjusted model/(HR without covariate adjustment − 1) × 100].

Body mass index was assessed as both a continuous and as a categorical variable, with normal weight defined as BMI <25.0 kg/m^2, overweight defined as BMI 25.0 to 29.9 kg/m^2, and obese defined as BMI of 30.0 kg/m^2 or greater. CRF was assessed as both a continuous (METs) and categorical variable, with the lowest quintile (Q1) defined as "low fit"; Q2 to Q3 as "moderate fit", and the highest quintiles, Q4 to Q5, defined as "high fit."

Among participants with repeated CRF and BMI assessment, the association between continuous change in BMI [follow-up BMI − baseline BMI] and risk of HF were also assessed by applying proportional hazards recurrent events model to the failure time data and adjusted for conventional risk factors, baseline BMI, and baseline CRF, and change in CRF. Two separate BMI change models were constructed: Model 1 was adjusted for age, sex, systolic blood pressure, diabetes mellitus, smoking status, cholesterol, baseline BMI, baseline CRF levels, and time between each CRF examination. Model 2 was additionally adjusted for change in CRF levels between the 2 examinations. All statistical analyses were performed using SAS release 9.2 software (SAS Institute Inc., Cary, North Carolina) for Windows (Microsoft, Redmond, Washington).

TABLE 1 Participant Characteristics in the Cooper Center Longitudinal Study Stratified by Midlife Body Mass Index Level

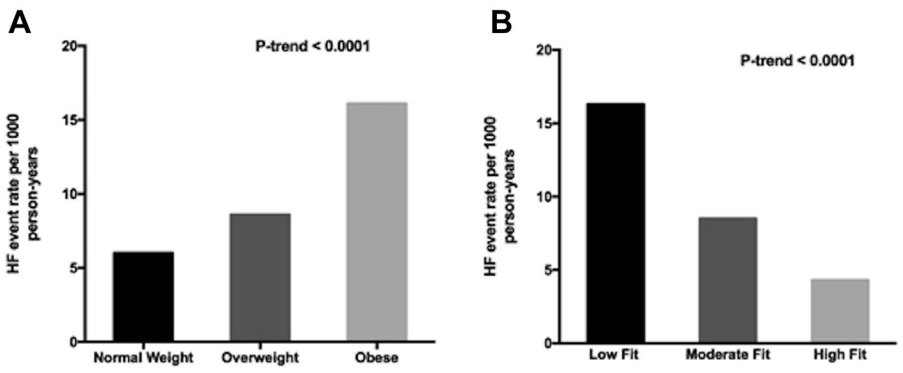
Participant Characteristics	Normal Weight (N = 8,924) (BMI <25 kg/m^2)	Overweight (N = 8,284) (30 > BMI ≥ 25 kg/m^2)	Obese (N = 2,277) (BMI ≥30 kg/m^2)
Mean ± SD age at CCLS entry, yrs	48.6 (8.9)	49.8 (8.7)	51.2 (8.6)
Mean ± SD age at Medicare entry, yrs	68.0 (5.1)	67.8 (4.8)	66.9 (4.0)
% of Women	34.6	9.5	10.5
% of Race/ethnicity			
White	98.4	98.3	97.7
Black	0.39	0.64	1.05
Others	1.05	0.93	1.06
Mean ± SD BMI, kg/m^2	22.7 (1.7)	27.0 (1.4)	32.9 (3.1)
% with Diabetes mellitus	2.1	2.7	4.6
% with Hypertension	12.2	20.4	32.0
% of current smokers	13.3	17.3	16.4
Mean ± SD Systolic blood pressure, mm Hg	118 (15)	123 (14)	128 (15)
Mean ± SD Total cholesterol, mg/dl	209 (37)	218 (40)	219 (41)
Mean ± SD Fasting glucose, mg/dl	97 (14)	102 (15)	109 (27)
Mean ± SD Fitness, METS	11.0 (2.6)	10.4 (2.0)	8.9 (1.8)

Data are mean ± SD or percentages.
BMI = body mass index; CCLS = Cooper Center Longitudinal Study; METS = metabolic equivalents.

RESULTS

Characteristics of the overall cohort are shown in Table 1, stratified by the baseline BMI. Overall, overweight and obese study participants had higher burden of conventional cardiovascular risk factors and lower CRF levels at entry into the CCLS. Baseline characteristics of the study participants stratified by their CRF levels have been reported previously (8). Participants with higher CRF had lower BMI and lower burden of conventional cardiovascular

FIGURE 1 Heart Failure Hospitalization Rate



Heart failure hospitalization rate among Cooper Center Longitudinal Study participants after age 65 across mid-life body mass index **(A)** and cardiorespiratory fitness **(B)** categories.

risk factors. After 127,110 person-years of Medicare follow-up (median Medicare follow-up duration = 6.67 years; interquartile range = 3.08 to 11.00 years), we observed a total of 1,038 HF events.

In unadjusted analyses, we observed a significant association between baseline BMI and HF event-rate, with higher BMI individuals having a higher HF event rate (Figure 1A). Furthermore, we also observed an inverse association between CRF levels in mid-life and HF event rate after age 65, with high-fit individuals having a lower HF event rate than those who were low fit (Figure 1B). When stratified by BMI and CRF levels, higher levels of BMI were associated with a higher HF event rate among low-fit and moderate-fit individuals (p-trend < 0.001 for both) (Table 2). However, there were no significant differences in HF event rates across BMI categories among high-fit participants (p-trend = 0.214) (Table 2). As expected, individuals who were low fit and obese had the highest HF event rate, whereas the high-fit and normal weight participants had the lowest HF event rates. The overall HF risk attributable to BMI was 12.5% without adjustment for CRF. With adjustment for CRF, the HF risk attributable to BMI was 8.4%. By CRF category, the HF risk attributable to BMI was 14.5% for low CRF, 7.2% for moderate CRF, and 1.1% for high CRF.

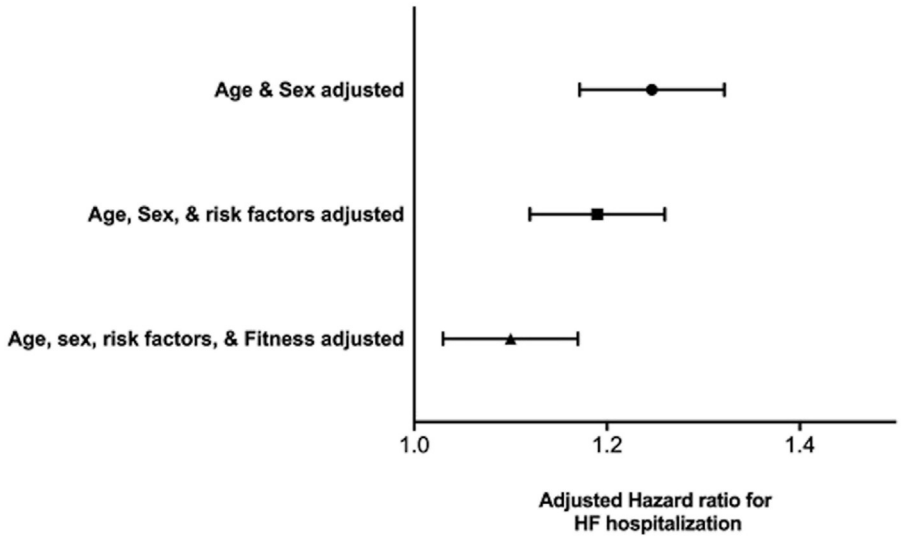
In adjusted analyses, higher BMI was significantly associated with higher risk of HF hospitalization after age 65, after adjustment for age and sex (hazard ratio [HR]: 1.25; 95% confidence interval [CI]: 1.17 to 1.32) per 3 kg/m^2 higher BMI) (Figure 2, model 1). After additional adjustment for prevalent CV risk factor burden, the association between BMI and risk of HF was slightly reduced (HR: 1.19; 95% CI: 1.12 to 1.26) per 3 kg/m^2 higher BMI) (Figure 2, model 2). After further adjustment for CRF levels, this association was substantially attenuated but remained statistically significant (HR: 1.10; 95% CI: 1.03 to 1.17) per 3 kg/m^2 higher BMI) (Figure 2, model 3). Established risk factors such as blood pressure, diabetes, smoking status, and cholesterol levels collectively accounted for 24% of the BMI-associated HF risk. In contrast, CRF explained a large proportion (47%) of higher BMI associated risk of HF in our study population. There was no statistical interaction between CRF and BMI on the risk of HF hospitalization (p value for interaction = 0.79).

TABLE 2 Heart Failure Hospitalization Rates Among Study Participants Stratified by Cardiorespiratory Fitness and Body Mass Index Levels

Fitness/Body Mass Index Categories	Follow-Up Time (yrs)	Number of Events	HF Hospitalization/ 1000 Person Years (95% CI)	p-Trend
Low fit				
Normal	6,100	83	13.6 (11.0–16.9)	<0.001
Overweight	10,390	150	14.4 (12.3–16.9)	
Obese	5,798	130	22.4 (18.9–26.6)	
Moderate fit				
Normal	21,499	155	7.2 (6.2–8.4)	<0.001
Overweight	25,413	217	8.5 (7.5–9.7)	
Obese	6,118	78	12.8 (10.2–15.9)	
High fit				
Normal	31,957	119	3.7 (3.1–4.5)	0.214
Overweight	18,264	97	5.3 (4.4–6.5)	
Obese	1,573	9	5.7 (3.0–11.0)	

HF = heart failure.

FIGURE 2 Multivariate-Adjusted Association Between Continuous Measures Of Body Mass Index and Risk of Heart Failure Hospitalization



Multivariate-adjusted association between continuous measures of body mass index and risk of heart failure hospitalization after age 65. The forest plot shows the hazard ratio estimates and 95% confidence intervals for heart failure hospitalization per 3-kg/m^2 higher body mass index in different multivariate-adjusted models.

A subgroup of participants (n = 8,683) underwent repeated measurements of CRF and BMI, available at a median follow-up duration of 4.2 years from the baseline examination. After adjustment for age, sex, CV risk factors, baseline BMI, baseline CRF and time between the 2 examinations, change in BMI was significantly associated with risk of HF hospitalization (HR: 1.08; 95% CI: 1.02 to 1.15 per 1 kg/m^2 BMI increase). Thus, 1 kg/m^2 increase in BMI was associated with 8% higher risk of HF hospitalization after age 65. After additional adjustment for change in CRF, the association between BMI change and HF risk was attenuated and no longer significant (HR: 1.05; 95% CI: 0.97 to 1.12 per 1 kg/m^2 BMI increase). In contrast, there was a significant inverse association between change in CRF and risk of HF in the most adjusted model (model 2) that accounted for interval change in BMI (HR: 0.91; 95% CI: 0.84 to 0.98 per 1 MET CRF increase).

DISCUSSION

We observed several important findings in the present study. First, we observed a significant, graded association between higher measurements of BMI in mid-life and risk of HF hospitalizations at ≥65 years of age. Second, the higher BMI-associated risk of HF hospitalization was more pronounced among low- and moderate-fit individuals than among high-fit participants. Third, mid-life CRF levels explained a large proportion of the HF risk associated with higher BMI levels. Finally, age-related changes in CRF but not BMI were significantly associated with HF risk. Taken together, these findings highlight the important contributions that CRF makes to the observed association between BMI and risk of HF.

INTER-RELATIONSHIP AMONG CRF, BMI, AND RISK OF HF. The inter-relationship among physical activity levels, BMI, and risk of HF has been assessed in 2 previous studies. Using the Physicians Health Study database, Kenchaiah et al. (16) observed that higher BMI was associated with a graded increase in HF risk among both active and inactive participants with no significant interaction between BMI and physical activity levels. In contrast, Hu et al. (17) reported a significant interaction between BMI and physical activity levels for HF risk in a cohort of Finnish participants. The discordant results between the 2 studies with respect to the interaction between physical activity and BMI for HF risk could be related to the differences in baseline characteristics of the study participants. Compared with the Physician Health Study (16), which included only men, the Finnish study (17) included both men and women with greater proportion of younger, more active and more obese

participants. In both of these analyses, physical activity levels were assessed by self-administered questionnaires and, thus, were subject to recall bias. The present study represents a significant addition to the existing research with examination of the interrelationship between objectively measured CRF levels and BMI for risk of HF in older age.

Recent interest has focused on a subgroup of obese individuals who are metabolically healthy or have high levels of CRF, a profile referred to as fit-fat or "benign obesity." In this regard, fit-fat individuals have lower mortality rates than those who are obese but low fit (18–20). Indeed, in a recent meta-analysis, it was shown that overweight and obese individuals who are fit have mortality rates similar to individuals who are of normal weight and fit (20). In addition, Lee et al. (21) observed that low-fit men of normal weight had a higher risk of all-cause mortality than obese men who were high-fit. Among patients with established HF, CRF has been shown to modify the relationship between adiposity and subsequent prognosis such that higher BMI is associated with improved survival only among those with low CRF (22). However, when considering incident HF as an endpoint, much less is known, because limited data are available from large CRF registries with HF outcomes. Therefore, using data from the CCLS merged with Medicare claims files, we were able to characterize the individual and combined impact of BMI and CRF levels on long-term HF risk. We observed that, in adjusted analysis, CRF explained a large proportion of the BMI-associated risk of HF in our study population.

MECHANISMS BY WHICH OBESITY AND CRF AFFECT HF RISK. The mechanisms underlying the association between BMI, CRF, and HF risk are not well understood. Both low CRF and higher BMI may indirectly increase HF risk through greater downstream incidence of established cardiovascular risk factors (23,24). Low CRF and obesity are also associated with several physiological perturbations that may contribute to the development of HF through a more direct effect of cardiac structure and function. Along these lines, recent studies have linked both low CRF and higher BMI with increased abnormal left ventricular remodeling, diastolic dysfunction, and decreased contractility, independent of other conventional cardiovascular risk factors (25–27).

AGE-RELATED CHANGES IN CRF, BMI, AND RISK OF HF. Previous studies have demonstrated that stable or improving CRF levels with aging is associated with a lower risk of all-cause and cardiovascular mortality independent of changes in BMI (28). Similarly, Kraigher-Krainer et al. (29) reported that a decrease in physical activity with aging was significantly associated with higher risk of HF independent of changes in BMI among participants of the Framingham Heart Study. Findings from the present study add to the existing research by evaluating the independent contributions of age-related changes in CRF and BMI change toward HF risk. We observed that, among CCLS participants with repeated CRF assessments, changes in CRF but not BMI were significantly associated with future risk of HF in the most adjusted model. This suggests that targeting improvements in CRF over weight loss in mid-life may represent a more useful strategy for HF prevention in older age.

FUTURE IMPLICATIONS. Given the burden of HF in the elderly, our observations could have important public health and research implications for HF prevention. The present study findings suggest that low CRF and higher BMI in mid-life may identify individuals at increased risk of HF in older age. Furthermore, implementation of lifestyle interventions aimed at improving CRF among low-fit individuals may be a useful strategy to lower HF burden. Along these lines, in the LookAHEAD trial, intensive lifestyle interventions with dietary weight loss and moderate-intensity exercise were associated with numerically lower risk of HF with a trend toward significance (HR: 0.80; 95% CI: 0.61 to 1.04) (30). Future adequately powered studies using supervised exercise training and/or intentional weight loss interventions are needed to evaluate the role of weight loss and CRF improvement in HF prevention. However, the present study would suggest that a priority should be placed on improving CRF over decreasing BMI.

STUDY LIMITATIONS. There are several limitations to this study. First, the CCLS cohort consisted of individuals whose socioeconomic status was relatively high, who were well educated, and who, overall, had a high level of CRF compared with the general population. However, the burden of conventional risk factors and lifetime risk of cardiovascular disease in the CCLS cohort were similar to lifetime risks in a larger, more representative cohort (31). Second, the CCLS cohort is made up of predominantly white male participants, and the study findings may not be applicable to women and other ethnic/racial subgroups. Third, we used HF hospitalization diagnoses from Medicare claims files rather than adjudicated clinical outcomes and may have missed some HF events, or some events might have been misclassified. However, measurement error tends to bias toward the null, and the use of administrative data for evaluation of HF hospitalizations is well

established (32,33). Fourth, directly measured peak oxygen uptake, the gold standard measurement of CRF, was not available in our study. However, previous studies conducted by investigators at the Cooper Institute among individuals with baseline characteristics similar to those of our study population have demonstrated a high degree of correlation between treadmill estimated CRF and directly measured peak oxygen uptake ($r = 0.92$) (11). Finally, we do not have data available for subtype of HF (HF with preserved ejection vs. HF with reduced ejection fraction) in the Medicare claims data.

CONCLUSIONS

We found that higher mid-life BMI was associated with increased risk of long-term HF; however, this risk was substantially attenuated after adjustment for mid-life CRF. Furthermore, age-related changes in CRF but not BMI were significantly associated with long-term HF risk. Taken together, these findings highlight the fact that much of the observed association between obesity and HF risk reflects the presence of low CRF.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Body mass index in mid-life is independently associated with risk of heart failure in older age. In addition, cardiorespiratory fitness accounts for a substantial proportion of BMI-associated risk of heart failure.

TRANSLATIONAL OUTLOOK: Future studies using supervised exercise training and/or intentional weight loss interventions are needed to evaluate the role of weight loss and cardiorespiratory fitness improvement in prevention of heart failure.

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