Changes in mid-life fitness predicts heart failure risk at a later age independent of interval development of cardiac and noncardiac risk factors: The Cooper Center Longitudinal Study

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Aims Low mid-life fitness is associated with higher risk for heart failure (HF). However, it is unclear to what extent this HF risk is modifiable and mediated by the burden of cardiac and noncardiac comorbidities. We studied the effect of cardiac and noncardiac comorbidities on the association of mid-life fitness and fitness change with HF risk.

Methods Linking individual subject data from the Cooper Center Longitudinal Study (CCLS) with Medicare claims files, we studied 19,485 subjects (21.2% women) who survived to receive Medicare coverage from 1999 to 2009. Fitness estimated by Balke treadmill time at mean age of 49 years was analyzed as a continuous variable (in metabolic equivalents [METs]) and according to age- and sex-specific quintiles. Associations of mid-life fitness and fitness change with HF hospitalization after age of 65 years were assessed by applying a proportional hazards recurrent events model to the failure time data with each comorbidity entered as time-dependent covariates.

Results After 127,110 person years of Medicare follow-up, we observed 1,038 HF hospitalizations. Higher mid-life fitness was associated with a lower risk for HF hospitalization (hazard ratio [HR] 0.82 [0.76-0.87] per MET) after adjustment for traditional risk factors. This remained unchanged after further adjustment for the burden of Medicare-identified cardiac and noncardiac comorbidities (HR 0.83 [0.78-0.89]). Each 1 MET improvement in mid-life fitness was associated with a 17% lower risk for HF hospitalization in later life (HR 0.83 [0.74-0.93] per MET).

Conclusions Mid-life fitness is an independent and modifiable risk factor for HF hospitalization at a later age. (Am Heart J 2015;169:290-297.e1.)

Heart failure (HF) represents an increasingly important health problem because of the aging of the population and improved survival after acute coronary events.[1] Therefore, a broader understanding of HF prevention is needed. Recently, several observational studies have reported that both physical activity and cardiorespiratory fitness in healthy adults are inversely associated with HF risk.[2-6] The mechanisms through which exercise might lower HF risk in healthy adults have not been established, and it remains uncertain to what extent there may be a direct effect of exercise on HF risk, independent of established HF risk factors. Although most prior studies adjust for the effects of current risk factors, few studies allow for the adjustment of subsequent, downstream risk factors acquired after physical activity/fitness measurement. It is also unknown whether the risks related to physical inactivity are modifiable through exercise training because there are no adequately powered studies designed to test this question in healthy adults.

To better characterize the effects of exercise on HF risk, we linked the Cooper Center Longitudinal Study (CCLS) with individual claims data from the Center for Medicare and Medicaid Services (CMS). We sought to compare the association between both baseline fitness levels in middle age and changes in fitness levels with subsequent HF risk. We also sought to account for the influence of antecedent cardiovascular (eg, acute myocardial infarction [AMI],

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hypertension [HTN]) and noncardiovascular (eg, diabetes mellitus [DM], chronic kidney disease [CKD], chronic obstructive pulmonary disease [COPD]) comorbidities on these associations. We hypothesized that both baseline and fitness change values would be associated with a lower HF risk independent of the interval development of established risk factors for HF.

Methods

Subject population

Among 73,439 participants in the CCLS who underwent a complete clinical examination at the Cooper Clinic in Dallas, TX, between 1970 and 2009, 24,872 were eligible to receive Medicare coverage between 1999 and 2009 as described previously.[7,8] After excluding 3,885 participants lacking part A and B Medicare and health maintenance organization coverage, 819 individuals whose CCLS examination occurred after enrollment into Medicare fee-for-service, 55 participants with early Medicare benefits (younger than 65 years because of Medicare coverage for disability, end-stage renal disease, etc), 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. A subgroup of 8,683 participants underwent a second fitness examination 4.2 years after the initial examination and were included in the analyses of fitness change. Participants were followed up from the date of initiating Medicare coverage or 1999 (if already receiving Medicare coverage before 1999) until death or end of follow-up on December 31, 2009. No individual was excluded based on his or her performance on the exercise treadmill portion of the examination.

CCLS clinical examination

Details of the clinical examination and the study cohort have been published previously.[9,10] Participants underwent a comprehensive clinical examination, which included a self-reported personal and family history, standardized medical examination by a physician, fasting blood levels of total cholesterol, triglycerides, and glucose as well as a maximal treadmill exercise test. Body mass index (BMI) was calculated from measured height and weight.

Fitness was measured in the CCLS by a maximal treadmill exercise test using a Balke protocol as described previously.[9-11] In this protocol, treadmill speed is set initially at 88 m/min. In the first minute, the grade is set at 0% followed by 2% in the second minute and an increase of 1% for every minute thereafter. After 25 minutes, the grade remains unchanged but the speed is increased 5.4 m/min for each additional minute until the test is terminated. Participants were encouraged not to hold onto the railing and were given encouragement to exert maximal effort. The test was terminated by volitional exhaustion reported by the participant or by the physician for medical reasons. The test time using this protocol has been shown to correlate highly with directly measured maximal oxygen uptake (r = 0.92).[12,13]

In accordance with standard approaches to the analysis of fitness data,[9,10] treadmill times were compared with age- and sex-specific normative data on treadmill performance within the CCLS, allowing each individual's treadmill time to be classified into an age- and sex-specific quintile of fitness. These quintiles of fitness measures were then combined into 3 mutually exclusive fitness groupings: "low fitness", quintile 1; "moderate fitness", quintiles 2 to 3; "high fitness", quintiles 4 to 5. In addition, using well-characterized regression equations, treadmill times from the Balke protocol allow for estimated fitness level in metabolic equivalents (METs).[7,12]

The measurement of other baseline variables in the CCLS has been well described.[9,10,14] Body mass index was calculated from measured height and weight. Seated resting blood pressure was obtained with a mercury sphygmomanometer. Fasting venous blood was assayed for serum cholesterol and glucose using standardized automated techniques.

Medicare claims data

Medicare inpatient claims data were obtained from the CMS for surviving participants who were 65 years or older and who were thus eligible for Medicare benefits during the period from 1999—the first year CMS data are currently available for public use—through 2009. Center for Medicare and Medicaid Services data contain 100% of claims paid by Medicare for covered health care services. A beneficiary may be tracked over time to elicit a history of all the use of health care services. Inpatient hospitalization files from CMS provide all individual records for each medical service billed to Medicare, the date of service, primary diagnosis and up to 8 secondary diagnoses (*International Classification of Diseases, Ninth Revision* [*ICD-9*], codes), and procedure codes (*ICD-9* procedure codes).

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.[15] Comorbidities such as AMI, HTN, DM, COPD, CKD, obstructive sleep apnea (OSA), and obesity were also determined using the data from CMS. As described previously, AMI hospitalization was defined by *ICD-9* codes 410.0 to 410.9 as either a primary or secondary diagnosis[15-17] from the hospitalization files (ie, Medicare Provider Analysis and Review). The CMS Chronic Condition Warehouse was used to identify the presence of DM, CKD, and COPD during the Medicare follow-up period.[7] The presence of HTN was identified in study participants when *ICD-9* codes 401.xx were listed as an outpatient claim on 2 occasions at least 30 days apart within 2 years or when listed as a single inpatient claim.[18-20]