# Cardiorespiratory Fitness and Reclassification of Risk for Incidence of Heart Failure

## The Veterans Exercise Testing Study

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***Background***—It is well established that cardiorespiratory fitness (CRF) is inversely associated with cardiovascular and all-cause mortality. However, little is known regarding the association between CRF and incidence of heart failure (HF).

***Methods and Results***—Between 1987 and 2014, we assessed CRF in 21 080 HF-free subjects (58.3±11 years) at the Veterans Affairs Medical Centers in Washington, DC, and Palo Alto, CA. Subjects were classified by age-specific quintiles of CRF. Multivariable Cox models were used to determine the association between HF incidence and clinical and exercise test variables. Reclassification characteristics of fitness relative to standard clinical risk factors were determined using the category-free net reclassification improvement and integrated discrimination improvement indices. During the follow-up (mean 12.3±7.4 years), 1902 subjects developed HF (9.0%; average annual incidence rate, 7.4 events per 1000 person-years). When CRF was considered as a binary variable (unfit/fit), low fitness was the strongest predictor of risk for HF among clinical and exercise test variables (hazard ratio, 1.91; 95% confidence interval, 1.74–2.09; $P<0.001$). In a fully adjusted model with the least-fit group as the reference, there was a graded and progressive reduction in risk for HF as fitness level was higher. Risks for developing HF were 36%, 41%, 67%, and 76% lower among increasing quintiles of fitness compared with the least-fit subjects ($P<0.001$). Adding CRF to standard risk factors resulted in a net reclassification improvement of 0.37 ($P<0.001$).

***Conclusions***—CRF is strongly, inversely, and independently associated with the incidence of HF in veterans referred for exercise testing. **(*Circ Heart Fail*. 2017;10:e003780. DOI: 10.1161/CIRCHEARTFAILURE.116.003780.)**

**Key Words:** cardiorespiratory fitness ■ cardiovascular system ■ exercise testing ■ heart failure ■ incidence ■ risk factor



Recent advances in the treatment of cardiovascular disease (CVD) have led to marked improvements in survival among patients experiencing a cardiac event. However, while these advances in treatment have led to a decline in most CVDs, marked growth in the prevalence of heart failure (HF) has occurred over the last 3 decades.[1,2] The growing prevalence of HF reflects a combination of increasing incidence, an aging population, and improvements in the treatment of both acute CVD and HF.[2] Older Americans are currently hospitalized for HF more than any other medical condition, and with the aging of the population, the impact of HF is expected to increase dramatically.[2,3] Given the considerable economic and societal burden of HF, strategies to prevent this condition should be considered.

**See Clinical Perspective**

In recent years, there has been increasing recognition that higher fitness is associated with improved health outcomes across a broad range of conditions.[4–6] Findings from large observational studies strongly support the concept that fitness level determined from a maximal exercise test is a more powerful determinant of freedom from all-cause mortality than the traditional risk factors.[4,7–9] Fitness is also inversely associated with the development of numerous health conditions, including CVD, diabetes mellitus, metabolic syndrome, and site-specific cancers.[4,6,10,11] These observations have recently led professional organizations to characterize fitness as an important health marker in both asymptomatic populations and patients with HF.[12–14] While a strong inverse association between exercise capacity and outcomes in patients with existing HF has been documented,[15–17] the association between fitness level and development of HF among individuals free of HF at baseline is largely unexplored. Berry et al[18] recently reported an ≈3.5-fold higher rate of hospitalization for HF in the least-fit quartile of subjects versus the highest-fit quartile among >20 000 subjects in the Cooper Center Longitudinal Study. These results underscore the potential importance of midlife fitness level and subsequent HF risk in later life. However, hospitalization rates were derived from Medicare

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claims data for a 10-year period; thus, HF outcomes were not captured prior to Medicare eligibility, limiting the sample to relatively older subjects.

Other than control of traditional risk factors (particularly blood pressure), treatment strategies to prevent HF are relatively limited.[19] Given both the societal burden and impact of HF on national healthcare expenditures, the demonstration of an inverse association between fitness and the development of HF, as has been observed for other conditions, would provide clinicians with further evidence to encourage physical activity among their patients and the public. In turn, this could provide an additional strategy to reduce the considerable and growing burden of HF. The aim of the current study was to address the association between fitness and incidence of HF across a broad range of US veterans.



## Methods

### Study Design and Sample

The cohort was drawn from the Veterans Exercise Testing Study, an ongoing, prospective evaluation of Veteran subjects referred for exercise testing for clinical reasons, designed to address exercise test, clinical, and lifestyle factors and their association with health outcomes. The Veterans Exercise Testing Study cohort includes >25 000 male veterans who had undergone a maximal treadmill test at the VA Washington DC Medical Center or the VA Palo Alto Health Care System between 1987 and 2014. Subjects who met the following criteria were excluded from the study: (1) existing HF at the time of the test; (2) those unable to complete the test for orthopedic, neurological, or similar reasons; (3) those with an implanted pacemaker; (4) subjects who were unstable or required emergent intervention; and (4) those with an exercise capacity <2 metabolic equivalents (METs). After these exclusions, the final sample included 21 080 subjects (13 264 black and 4870 white). The study was approved by the respective Institutional Review Boards at each institution, and all subjects gave written informed consent prior to undergoing their exercise test.

Detailed information on relevant demographic, clinical, and medication information, risk factors, and comorbidities as defined by *International Classification of Diseases* coding for all participants were obtained from the VA Computerized Patient Record System at the time of the exercise test. *International Classification of Diseases* Ninth Revision coding included categories 428.0 to 428.43, including acute and chronic systolic, diastolic, or unspecified HF. Each individual was asked to verify this information, including history of chronic diseases and smoking habits. Historical information that was recorded included previous myocardial infarction by history or presence of Q waves, cardiac procedures, HF, hypertension, hypercholesterolemia (>220 mg/dL, statin use, or both), claudication, chronic obstructive pulmonary disease, cancer, renal disease, diabetes mellitus, stroke, smoking status (current and past), and use of cardiac medications.

### Exercise Assessments

Subjects underwent symptom-limited treadmill testing using an individualized ramp treadmill protocol at Palo Alto[20] or a Bruce protocol in Washington DC. Standard criteria for termination were used, including moderately severe angina, >2.0 mm horizontal or downsloping ST depression, a sustained decrease in systolic blood pressure, or serious rhythm disturbances. The Borg 6–20 perceived exertion scale was used to quantify degree of effort.[21] Blood pressure was taken manually, and exercise capacity (in METs) was estimated from peak treadmill speed and grade using the ramp protocol[22] and exercise time using the Bruce protocol ($Vo_2$ max=14.76–(1.379×time)+(0.451×time$^2$)–(0.012×time$^3$). Subjects were encouraged to exercise until volitional fatigue in the absence of symptoms or other indications for stopping.[14,22] No test was classified as indeterminate, medications were not withheld, and age-predicted maximal target heart rates were not used as end points. The exercise tests were performed, analyzed, and reported using a standard protocol incorporating a computerized database with all definitions and measurements prospectively defined.[23] The primary outcome was incidence of HF, determined through review of Computerized Patient Record System and defined as a primary diagnosis of HF using *International Classification of Diseases* coding. Follow-up was completed through December 31, 2014.

The cohort was stratified into 5 age categories (<40, 40–49, <50, 50–59, 60–69, and ≥70 years). We then identified those with a MET level ≤20%, 21% to 40%, 41% to 60%, 61% to 80%, and >80% of predicted METs achieved within their respective age category as described previously.[24] The following 5 fitness categories were then established based on age-stratified quintiles of peak METs achieved: least-fit (mean 4.3±1.2 METs; n=4094); low-fit (6.0±1.2 METs; n=4683); moderate-fit (7.3±1.2 METs; n=4148); fit (8.7±1.3 METs; n=4637); and high-fit (11.8±2.4 METs; n=3518).

### Statistical Analysis

Follow-up time is presented as median, as well as mean±SD, determined from the date of the exercise test to the date of the event (incidence of HF). Rate of HF incidence was calculated as the ratio of time to HF diagnosis to the person-years of observation. Continuous variables are presented as mean±SD and categorical variables as relative frequencies (%). Comparisons between categorical variables were assessed using $\chi^2$ tests. Simple and multivariable linear regression was applied to evaluate differences between fitness categories for variables included in Tables 1 and 2. Age and body mass index were used as covariates for the dependent variables (resting heart rate, systolic and diastolic blood pressure, blood lipids, blood glucose, and exercise capacity).

Exercise capacity was expressed as a continuous variable in METs, as well as the 5 categories mentioned earlier. Survival analysis was performed using Cox proportional hazards analysis to determine which clinical and exercise test variables were independently associated with incidence of HF. Relative risks for mortality were determined using the 5 categories of fitness, with the least-fit group as the reference. For binary analyses, we combined the 2 lowest fitness categories to form the unfit group and the 3 highest fit to form the fit group. We then introduced this categorical variable into the fully adjusted proportional hazards model to further assess the impact of fitness on the incidence of HF with that of other risk factors (categorical covariates). Survival analysis was performed unadjusted, adjusted for age, and fully adjusted, including age, body mass index, ethnicity, sex, CVD, risk factors (hypertension, type 2 diabetes mellitus, dyslipidemia, and smoking), cardiac medications, hypoglycemic agents, chronic kidney disease, and HIV/AIDS. The proportional hazards assumption was evaluated and confirmed using scaled Schoenfeld residuals. Survival curves were constructed to compare fitness categories over the follow-up period, and the log-rank test was used to compare fitness categories over time. Survival analyses were performed using SPSS software version 22.0 (IBM SPSS Statistics for Windows, Version 22.0; IBM Corp, Armonk, NY).

To further evaluate the role of fitness in predicting incidence of HF, we assessed reclassification characteristics of fitness relative to the standard clinical risk factors mentioned earlier using the continuous category-free net reclassification improvement index (NRI) and the integrated discrimination improvement (IDI). These analyses were modified for right censored survival data according to the methods proposed by Pencina et al.[25] We corrected for overoptimism using 1000 bootstrap replicates and report the median results and bootstrap estimated 95% confidence intervals. NRI and IDI analyses were performed using R (R Foundation for Statistical Computing, Vienna, Austria).

## Results

### Demographic and Clinical Characteristics and Follow-Up Data

For the 21 080 participants, the mean age at the time of the exercise test was 58.2±11.0 years. The mean follow-up time

**Table 1. Demographic and Clinical Characteristics of the Entire Cohort and Those Who Did and Did Not Develop Heart Failure**

| | Entire Cohort | Incidence of Heart Failure | |
|---|---|---|---|
| | | Yes | No |
| N | 21 080 | 1902 | 19 178 |
| Age, y | 58.3±11.3 | 62.8±10.4 | 57.8±11.3 |
| Weight, kg | 89.1±17.7 | 90.6±18.8 | 89.0±17.6 |
| BMI, kg/m$^2$ | 28.8±5.3 | 29.4±5.7 | 28.7±5.2 |
| Resting HR, beats per minute | 73.7±13.7 | 73.8±14.3 | 73.6±13.6 |
| Rest systolic BP, mm Hg | 130±20 | 137±21 | 130±19 |
| Rest diastolic BP, mm Hg | 79.9±11.3 | 81.6±12.0 | 79.7±11.2 |
| Peak METs | 7.5±2.9 | 5.9±2.2 | 7.7±2.9 |
| Total cholesterol, mg/dL | 194±45 | 190±46 | 195±45 |
| LDL cholesterol, mg/dL | 131±46 | 139±53 | 130±46 |
| HDL cholesterol, mg/dL | 44.8±13.2 | 42.0±10.9 | 44.9±13.2 |
| Triglycerides, mg/dL | 130±96 | 135±79 | 131±96 |
| Glucose, mg/dL | 112±44 | 124±54 | 112±43 |
| Race | | | |
| Black, % | 13 264 (63) | 1398 (74) | 11 866 (62) |
| White, % | 4870 (23) | 427 (22) | 4443 (23) |
| Hispanic/other, % | 2946 (14) | 77 (4) | 2869 (15) |
| Family history of CVD, % | 1617 (7.7) | 175 (9.2) | 1442 (7.5) |
| Dyslipidemia, % | 10 494 (50) | 1127 (59) | 9367 (49) |
| Smoking, % | 8785 (42) | 917 (48) | 7868 (41) |
| Type 2 diabetes mellitus, % | 5514 (26) | 835 (44) | 4679 (24) |
| Hypertension, % | 12 646 (60) | 1532 (80) | 11 114 (58) |
| Sleep apnea, % | 1115 (5.3) | 139 (7.3) | 976 (5.1) |
| CKD, % | 1206 (5.7) | 324 (17) | 882 (4.6) |
| Drug/alcohol abuse, % | 1245 (5.9) | 117 (6.2) | 1128 (5.9) |
| Antihypertensive/ medication, % | 13 601 (64) | 1552 (82) | 12 049 (63) |
| Lipid agents, % | 7108 (34) | 887 (12) | 1015 (5.3) |
| Hypoglycemic agents, % | 4939 (23) | 759 (40) | 4180 (22) |

BMI indicates body mass index; BP, blood pressure; CKD, chronic kidney disease; CVD, cardiovascular disease; HDL, high-density lipoprotein; HR, heart rate; LDL, low-density lipoprotein; and METs, metabolic equivalents.

was 12.3±7.4 years, with a median of 11.7 years (6.5 and 17.2 years for the 25th and 75th percentiles, respectively), comprising a total of 258 678 person-years. There were 1902 HF events (9.0%), with an average annual incidence rate of 7.4 events per 1000 person-years. There were no interactions between site and fitness ($P$=0.40) or race and fitness ($P$=0.82); therefore, the data were not stratified by race or site.

Descriptive clinical and demographic data for the entire cohort and for those developing and not developing HF are presented in Table 1. Those who developed HF were older, were less fit (5.9±2.2 versus 7.7±2.9 METs; $P$<0.001), had higher systolic and diastolic blood pressures, and were more likely to be diabetic, dyslipidemic, and smokers, and had a higher prevalence of chronic kidney disease when compared with those who did not develop HF. Demographic, clinical, and exercise test characteristics comparing quintiles of fitness are presented in Table 2. Notable differences among higher-fit versus lower-fit subjects included lower body mass index, resting heart rate, triglycerides, and fasting glucose levels among higher-fit individuals, and higher prevalence of hypertension, diabetes mellitus, smoking, and medication use among lower-fit individuals.

## Predictors of HF Incidence

Significant predictors for developing HF among clinical, demographic, and exercise test variables are presented in Table 3. When fitness status was considered as a binary variable (unfit/fit), low fitness was a strong predictor of risk for HF (hazard ratio, 1.91; 95% confidence interval, 1.74–2.09; $P$<0.001) and was a stronger predictor of risk than traditional risk factors, including hypertension, diabetes mellitus, smoking, and sleep apnea. Each 1-MET increment in exercise capacity achieved was associated with a 19% reduction in risk for developing HF. Hazard ratios for the 5 fitness categories (unadjusted, age-adjusted, and fully-adjusted models) are shown in Table 4. In the fully adjusted model, and with the least-fit group as the reference, the risk for developing HF was 36% lower for the low-fit individuals (hazard ratio, 0.64; 95% confidence interval, 0.57–0.71; $P$<0.001). The risk declined progressively by 41% for the moderate-fit, 67% for the fit, and 76% for the high-fit individuals (Table 4 and Figure 1). When this analysis was repeated among subjects taking and not taking β-blockers, similar results were observed. The cumulative hazards for CHF risk for fitness categories across the follow-up period in the entire sample are illustrated by survival curves in Figure 2. Risk for incidence of HF was significantly higher as fitness level was lower ($P$<0.001).

NRI and IDI results are shown in Table 5. The addition of fitness to traditional risk factors resulted in a net reclassification of 37% (0.37±0.03; $P$<0.0001). The improved reclassification was largely because of superior ability to correctly classify absence of HF with the addition of fitness (0.65±0.01). The IDI was also net positive (0.03±0.03; $P$<0.01).

# Discussion

Although exercise capacity, and specifically directly measured peak $V_{O_2}$ and other cardiopulmonary exercise test variables, have been widely applied in recent years to stratify risk in patients with existing HF,[15] little is known regarding the association between fitness and future incidence of HF. This issue has major public health implications given that HF is the one cardiovascular condition that is increasing in prevalence and that HF remains a major cause of morbidity and hospitalization throughout the Western world, particularly in the elderly.[26,27] The current findings suggest that higher levels of fitness are strongly and inversely associated with the development of HF in veterans. This was evidenced by a graded inverse association between MET level achieved and HF incidence (Table 4 and Figures 1 and 2) and the fact that fitness level was the most powerful predictor of HF among clinical, demographic, and exercise variables (Table 3). Each 1-MET

**Table 2. Demographic and Clinical Characteristics According to Fitness Categories**

| Variables* | Least-Fit (n=4084) | Low-Fit (4461) | Moderate-Fit (n=4148) | Fit (n=4559) | High-Fit (n=3828) | *P* Value |
|---|---|---|---|---|---|---|
| Age, y | 58.2±11.2 | 59.6±11.2 | 58.0±11.4 | 57.5±11.2 | 58.0±11.4 | <0.001 |
| BMI, kg/m$^2$ | 29.8±6.5 | 29.5±5.6 | 29.2±5.0 | 28.2±4.5 | 27.0±4.0 | <0.001 |
| Resting heart rate, beats per minute | 77±15 | 75±14 | 73±13 | 71±13 | 73±13 | <0.001 |
| Resting systolic BP, mm Hg | 133±21 | 132±20 | 130±19 | 128±19 | 130±18 | <0.001 |
| Resting diastolic BP, mm Hg | 81±12 | 80±11 | 79±11 | 79±11 | 81±11 | <0.001 |
| Exercise capacity, METs | 4.3±1.2 | 6.0±1.2 | 7.3±1.2 | 8.7±1.3 | 11.8±2.4 | <0.001 |
| Total cholesterol, mg/dL | 192±48 | 191±45 | 193±45 | 194±44 | 200±44 | <0.001 |
| Triglycerides, mg/dL | 151±110 | 142±110 | 132±93 | 120±76 | 98±57 | <0.001 |
| LDL cholesterol, mg/dL | 130±48 | 126±46 | 127±46 | 129±45 | 142±45 | <0.001 |
| HDL cholesterol, mg/dL | 43±13 | 43±13 | 45±15 | 45±14 | 46±14 | <0.001 |
| Glucose, mg/dL | 119±47 | 113±41 | 114±46 | 107±41 | 102±29 | <0.001 |
| Race | | | | | | |
| Black, % | 2626 (64.3) | 2984 (66.9) | 2763 (66.6) | 2880 (63.2) | 2011 (52.5) | <0.001 |
| White, % | 962 (23.6) | 1089 (24.4) | 1046 (25.2) | 1157 (25.4) | 616 (16.1) | <0.001 |
| Hispanic/other, % | 506 (12.4) | 610 (13.7) | 339 (8.2) | 600 (13.2) | 891 (23.3) | <0.001 |
| CHF, % | 644 (33.9) | 478 (25.1) | 403 (21.2) | 250 (13.1) | 127 (6.7) | <0.001 |
| Risk factors | | | | | | |
| Hypertension, % | 2660 (21.0) | 2909 (23.0) | 2693 (21.3) | 2632 (20.8) | 1752 (13.9) | <0.001 |
| Diabetes mellitus, % | 1211 (22.0) | 1405 (25.5) | 1247 (22.6) | 1066 (19.3) | 585 (10.6) | <0.001 |
| Smoking, % | 1979 (22.5) | 1849 (21.0) | 1654 (18.8) | 1784 (20.3) | 1519 (17.3) | <0.001 |
| Dyslipidemia, % | 1855 (17.7) | 2279 (21.7) | 2374 (22.6) | 2423 (23.1) | 1563 (14.9) | <0.001 |
| Family history of CAD, % | 399 (24.7) | 384 (23.7) | 422 (26.1) | 342 (21.2) | 70 (4.3) | <0.001 |
| CKD/HIV/AIDS, % | 300 (22.3) | 364 (27.0) | 325 (24.1) | 286 (21.2) | 73 (5.4) | <0.001 |
| Sleep apnea, % | 234 (21.0) | 263 (23.6) | 316 (28.3) | 253 (22.7) | 49 (4.4) | <0.001 |
| Alcohol/drug abuse, % | 245 (19.7) | 283 (22.7) | 297 (23.9) | 286 (23.0) | 134 (10.8) | <0.001 |
| Antihypertensive agents | 2957 (21.7) | 3167 (23.3) | 2864 (21.1) | 2882 (20.7) | 1791 (13.2) | <0.001 |
| Hypoglycemic agents | 1083 (21.9) | 1260 (25.5) | 1107 (22.4) | 935 (18.9) | 554 (11.2) | <0.001 |
| Lipid agents | 1297 (18.2) | 1635 (23.0) | 1677 (23.6) | 1588 (22.3) | 911 (12.8) | <0.001 |

BMI indicates body mass index; BP, blood pressure; CAD, coronary artery disease; CHF, chronic heart failure; CKD, chronic kidney disease; HDL, high-density lipoprotein; HR, heart rate; LDL, low-density lipoprotein; and METs, metabolic equivalents.

*Continuous variables are presented as mean±SD.



increment in exercise capacity achieved was associated with a 19% reduction in risk for developing HF. Compared with subjects in the least-fit category, achieving the relatively modest fitness level of 6 METs (individuals in the next least-fit category) was associated with a 34% lower risk for HF, while risk for HF was 76% lower for individuals in the highest fitness category (≈≥12 METs). The impact of fitness on incident HF was independent, as underscored by the fact that adjustment for other risk markers had minimal influence on risk for developing HF (Table 4). Finally, adding fitness to standard risk factors resulted in an NRI of 0.37. Our results extend the recent findings of Berry et al,[18] using Medicare claims data in patients >65 years of age, in that we captured HF incidence from VA computerized records throughout the spectrum of age.

Risk factors for the development of HF include hypertension, smoking, and diabetes mellitus among others, and we generally observed a higher risk profile at baseline among subjects who subsequently developed HF (Table 1). Regular exercise generally has a favorable impact on these risk factors for HF,[4,14,28] as well as the development of fitness. Confirming a growing number of studies assessing all-cause mortality in apparently healthy subjects and patients with CVD,[4–14] fitness level was the strongest risk marker for incident HF in the current study. We also observed that a relatively small (1-MET) increment in exercise capacity had a considerable impact on incidence of HF (≈19% reduction). One to 2 METs is an amount typically achievable through a modest program of physical activity.[12,14,22] Thus, improvements in fitness through promoting physical activity have a potentially important role

**Table 3. Significant Predictors for Developing Heart Failure Among Clinical, Demographic, and Exercise Test Variables**

| | HR | 95% CI | *P* Value |
|---|---|---|---|
| Age (per year) | 1.05 | 1.04–1.05 | <0.001 |
| Family history of CAD | 1.26 | 1.07–1.48 | 0.004 |
| Sleep apnea | 1.29 | 1.08–1.55 | 0.006 |
| Smoking | 1.31 | 1.19–1.44 | <0.001 |
| Type 2 diabetes mellitus | 1.56 | 1.4–1.73 | <0.001 |
| Chronic kidney disease | 1.79 | 1.57–2.05 | <0.001 |
| Hypertension | 1.80 | 1.59–2.04 | <0.001 |
| Low fitness | 1.91 | 1.74–2.09 | <0.001 |

All variables are expressed as present/absent with the exception of age. Low fitness defined as <6.0 metabolic equivalents (METs). Model adjusted for age, body mass index, ethnic origin, β-blockers, calcium-channel blockers, angiotensin-converting enzymes, angiotensin receptor blockers, aspirin, diuretics, lipid-lowering agents, hypoglycemic agents, history of smoking, hypertension, diabetes mellitus, chronic kidney failure (stage <4), and HIV/AIDS. CI indicates confidence interval; CAD, coronary artery disease; and HR, hazard ratio.

in the prevention of HF.[18,29–33] However, incorporating fitness into the risk paradigm for the prevention of disease has generally not been integrated into clinical practice.[8,34] The salient clinical implications of these findings are that health professionals who treat patients with or at risk for HF should incorporate into their practices strategies for promoting physical activity, in addition to the routine treatment of hypertension and diabetes mellitus, the encouragement of smoking cessation, and the like. Such strategies may have a significant role in preventing the development of HF.

We used novel indices of risk reclassification, the NRI and IDI,[25] to provide further insight into the impact of fitness on predicting risk of HF. The NRI reflects clinically meaningful improvement in risk classification achieved with the addition of a risk marker; it is calculated as the net change in risk among subjects after the addition of a given marker to the baseline model (in the current case, standard clinical variables). The IDI expresses whether adding a new risk factor to a binary prediction model improves the discrimination slope. Our results extend previous findings by demonstrating that the addition of fitness to traditional risk markers correctly reclassified 37% of subjects beyond standard risk factors in terms of incidence of HF, and the discrimination slope of the updated model (after adding fitness) was improved by 3% points above the original (Table 5). The NRI for nonevents of 0.65 in particular suggests that adding fitness to the model markedly increases the specificity (ie, strongly identifies subjects who are at low risk for developing HF). Together, these findings suggest that in addition to being a strong independent risk marker, fitness powerfully supplements standard risk factors in correctly reclassifying risk for incidence of HF.

Three recent studies have also addressed the association between fitness and incident HF. Berry et al[18] reported an ≈3.5-fold higher rate of hospitalization for HF in the least-fit quartile of subjects versus the highest-fit quartile among >20 000 subjects from the Cooper Center Longitudinal Study. Each 1-MET increment in fitness was associated with ≈20% lower risk for HF hospitalization after the age of 65 years in men and women. Khan et al[29] studied 1873 men without HF at baseline and followed them for a mean of 21 years. Each 1-MET increment in fitness was associated with a 21% multivariable-adjusted risk of HF. Pandey et al[32] assessed >19 000 adults and observed that higher fitness in midlife was associated with a significantly lower risk of hospitalization because of HF during follow-up; each 1-MET higher fitness level was associated with an 18% reduction in risk for incidence of HF. In a subgroup of 8683 participants who underwent a second fitness examination a mean of 4.2 years after the initial examination, each 1-MET improvement in fitness was associated with a 17% reduction in HF risk. Echouffo-Tcheugui et al[33] developed a composite risk estimate from these studies in a meta-analysis and reported a random-effects model estimate of 21% lower risk of HF for each 1-MET higher fitness level. These studies are in close agreement with the present observation that each 1-MET higher fitness level was associated with a 19% reduction in future HF risk. The impact of a 1-U higher fitness level on incident HF is somewhat higher than that generally reported for cardiovascular and all-cause mortality by our group[7,24] and others.[6,9,12] For example, in a meta-analysis including >100 000 subjects, Kodama et al[9] reported that each 1-MET increment in exercise capacity was associated with 13% and 15% reductions in all-cause and cardiovascular mortality, respectively. Regardless, these observations collectively

**Table 4. Risk for Developing Heart Failure According to Quintiles of Fitness**

| Fitness Group (Mean METs±SD) | Patients (n) | Unadjusted HR (95% CI) | Age-Adjusted HR (95% CI) | Fully Adjusted HR (95% CI)* | *P* Value† |
|---|---|---|---|---|---|
| Least-fit (referent; 4.3±1.3 METs) | 4084 | 1 | 1 | 1 | … |
| Low-fit (6.0±1.2 METs) | 4461 | 0.68 (0.60–0.76) | 0.63 (0.56–0.70) | 0.64 (0.56–0.72) | <0.001 |
| Moderate-fit (7.3±1.2 METs) | 4148 | 0.62 (0.55–0.70) | 0.61 (0.54–0.69) | 0.59 (0.52–0.67) | <0.001 |
| Fit (8.7±1.4 METs) | 4559 | 0.33 (0.28–0.38) | 0.33 (0.29–0.38) | 0.36 (0.31–0.42) | <0.001 |
| High-fit (11.6±2.5 METs) | 3828 | 0.17 (0.14–0.21) | 0.17 (0.14–0.20) | 0.25 (0.21–0.31) | <0.001 |

CI indicates confidence interval; HR, hazard ratio; and METs, metabolic equivalents.

*Adjusted for age, body mass index, ethnic origin, sex, β-blockers, calcium-channel blockers, angiotensin-converting enzymes, angiotensin receptor blockers, aspirin, diuretics, lipid-lowering agents, hypoglycemic agents, history of smoking, hypertension, diabetes mellitus, chronic kidney disease (stage <4), and HIV/AIDS.

†For fully adjusted HR.

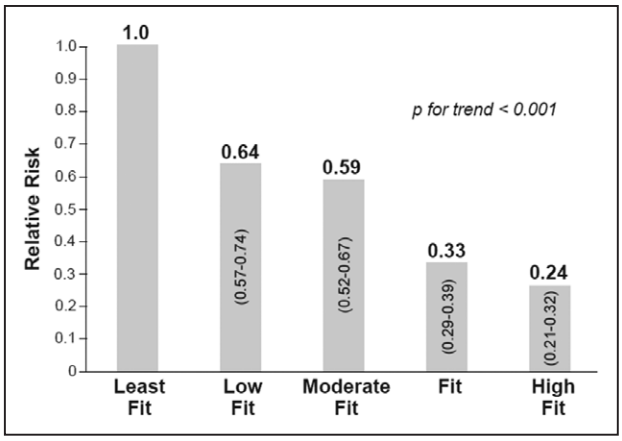


**Figure 1.** Relative risks of heart failure incidence between quintiles of fitness, with the least fit group (<6 METs) as the referent group. 95% confidence limits are in parentheses within each bar. Model is fully adjusted for variables listed in Tables 3 and 4. METs indicates metabolic equivalents.

underscore the message that small increments in exercise capacity yield considerable health outcome benefits in the context of HF prevention.

There are several potential explanations for the lower HF incidence among fitter subjects. Many of the risk factors for CAD and other forms of CVD are the same as those which increase risk for HF, including hypertension, smoking, and diabetes mellitus. Individuals who are relatively fit have a lower risk factor burden when compared with those who are poorly fit,[35,36] and we generally observed lower fitness and a higher burden of chronic disease among individuals who developed HF (Table 1). Fitter subjects have a marked attenuation in blood pressure trajectory with aging,[37] which could potentially reduce the risk of future HF. Left ventricular compliance is reduced in older individuals, and this can contribute to the development of HF in the elderly.[38,39] Elderly individuals who are physically active have higher ventricular compliance compared with sedentary individuals.[38] Brinker et al[40] recently studied 2925 men and women from the Cooper Center Longitudinal Study and reported that low fitness was associated with a higher prevalence of concentric remodeling

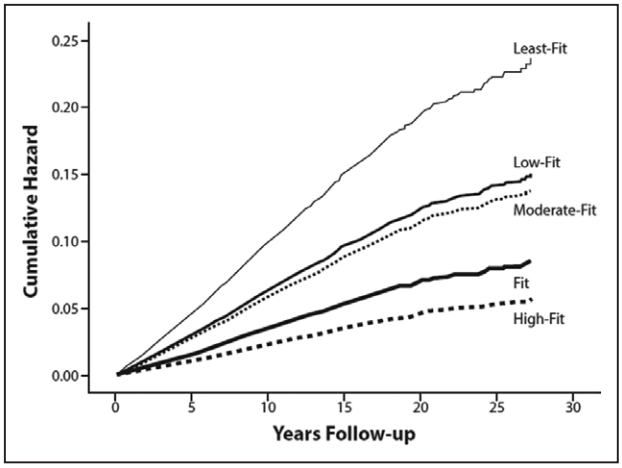


**Figure 2.** Survival curves by fitness category. Log-rank test $P<0.001$.

**Table 5. NRI and IDI for Incidence of Heart Failure by Adding Fitness to Standard Risk Factors**

| NRI: Subjects With Events (±SE) | NRI: Subjects Without Events (±SE) | NRI: All Subjects (±SE) | NRI *P* Value | IDI (±SE) | IDI *P* Value |
|---|---|---|---|---|---|
| −0.27±0.03 | 0.65±0.01 | 0.37±0.03 | <0.0001 | 0.03±0.02 | <0.01 |

IDI indicates integrated discrimination improvement; and NRI, net reclassification improvement.

and diastolic dysfunction, suggesting that regular exercise may lower HF risk through its favorable effects on cardiac remodeling and diastolic function. Regular exercise not only improves fitness but is associated with numerous other physiological benefits, including reduced blood pressure, improved insulin resistance, improved lipid profiles, and reduced obesity, which collectively may contribute to a reduction in the incidence of HF. Endothelial dysfunction is associated with various forms of CVD, and favorable adaptations in endothelial function have been consistently reported after exercise training among individuals with and without HF.[41–43]

## Study Limitations and Strengths

Our study has several notable limitations. First, the study was performed among men, and the extent to which the results apply to women is unknown. The incidence of HF among men >65 years is considerably higher than that of women,[44] although in the study of Berry et al,[18] the impact of fitness on incidence of hospitalization for HF was similar among men and women >65 years of age. Second, the inverse relationship between incidence of HF and fitness, while compelling, does not demonstrate cause. Third, we do not have data on physical activity patterns throughout the follow-up; physical activity patterns not only influence fitness level but may have a direct effect on HF incidence.[31,45] Fourth, the onset of other chronic conditions, their severity, and duration of therapy were not evaluated. In addition, we do not have information on the type of HF incidence (eg, systolic/diastolic). Strengths of the study include the large sample size (>21 000) with objectively determined fitness and the fact that the incidence of HF was derived directly from VA electronic medical records, which have been shown to be more accurate and complete than national databases, such as Medicare records.[46] The VA medical records system also allowed us to account for detailed antecedent risk factors that might influence the development of HF. Finally, unlike most observational studies, the VA Healthcare System provides services independent of a patient's financial status, which minimizes disparities in health care.

In conclusion, cardiorespiratory fitness is strongly, inversely, and independently associated with the incidence of HF in veterans referred for exercise testing. Adding fitness to traditional risk markers significantly reclassifies individuals for risk of developing HF. Even modest levels of fitness have a considerable impact on preventing the development of HF, suggesting the potential for regular physical activity to lower the incidence of HF in later life. Given the growing prevalence of HF and its increasing burden on the US healthcare system, these observations provide an additional impetus for healthcare providers to strengthen the public health message regarding physical activity.

## Disclosures

None.

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## CLINICAL PERSPECTIVE

It is well established that cardiorespiratory fitness (CRF) is inversely associated with cardiovascular and all-cause mortality, but little is known regarding the association between CRF and incidence of heart failure (HF). Between 1987 and 2014, we assessed CRF in 21 080 HF-free subjects. During average follow-up of over 12 years, 1902 subjects developed HF (9.0%; average annual incidence rate of 7.4 events per 1000 person-years). The results suggest that CRF is strongly, inversely, and independently associated with the incidence of HF and that adding CRF to traditional risk factors significantly reclassifies risk for the development of HF. Each 1-MET increment in CRF was associated with a 19% reduction in risk for developing HF. Adding CRF to traditional risk factors resulted in a net reclassification improvement of 37%. Given both the societal burden and impact of HF on national healthcare expenditures, the demonstration of an inverse association between fitness and the development of HF provides clinicians with further evidence to encourage physical activity among their patients and the public.

# Cardiorespiratory Fitness and Reclassification of Risk for Incidence of Heart Failure: The Veterans Exercise Testing Study

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