The Interplay of the Global Atherosclerotic Cardiovascular Disease Risk Scoring and Cardiorespiratory Fitness for the Prediction of All-Cause Mortality and Myocardial Infarction: The Henry Ford ExercIse Testing Project (The FIT Project)

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Cardiorespiratory fitness (CRF) is inversely associated with atherosclerotic cardiovascular disease (ASCVD) risk. It is unclear whether the prognostic value of CRF differs by baseline estimated ASCVD risk. We studied a retrospective cohort of patients without known heart failure or myocardial infarction (MI) who underwent treadmill stress testing. CRF was measured by metabolic equivalents of task (METs) and ASCVD risk was calculated using the Pooled Cohorts Equations. Multivariable-adjusted Cox regressions analyses examined the association between METs and incident all-cause mortality and MI outcomes stratified by baseline ASCVD risk. The C-index evaluated risk discrimination while net reclassification improvement evaluated reclassification with CRF added to the ASCVD risk score. Our study population consisted of 57,999 patients of mean age 53 (13) years, 49% women, 64% white, 29% black. Over a median follow-up 11 years (interquartile range 8 to 14 years) there were 6,670 (11%) deaths, while there were 1,757 (3.0%) MIs over a median follow-up of 6 years (interquartile range 3 to 8 years). Among patients with ASCVD risk ≥20%, those with METs ≥12 had a 77% lower risk of all-cause mortality (Hazard ratio 0.23 95% confidence interval = 0.20, 0.27) and 67% lower risk of MI (Hazard ratio 0.33 95% confidence interval = 0.24, 0.46) compared to METs <6. Similar results were obtained for those with ASCVD risk <5%. Addition of METs to ASCVD risk score improved the C-statistic from 0.778 to 0.798 for all-cause mortality and 0.726 to 0.733 for MI (both p <0.001). Addition of METs to ASCVD risk score significantly reclassified risk of all-cause mortality (p <0.001) but not MI (p = 0.052). In conclusion, CRF is inversely associated with risk of all-cause mortality and MI at all levels of ASCVD risk, and provides incremental risk discrimination and reclassification beyond the ASCVD risk score. **(Am J Cardiol 2019;124:511−517)**

Prediction of atherosclerotic cardiovascular disease (ASCVD) is essential to effectively balance the risks and benefits of therapy for primary prevention. The American Heart Association (AHA)/American College of Cardiology (ACC)/Multisociety guidelines recommend using the Pooled Cohorts Equations as a first step in estimating 10-year absolute ASCVD risk in order to guide preventive therapy.[1−4] Cardiorespiratory fitness (CRF) is an important independent marker of cardiovascular heath in the general adult population.[5−14] To evaluate the prognostic significance of CRF in the context of the recent ACC/AHA guideline,[3] we used data from the Henry Ford ExercIse Testing (FIT) Project, a retrospective cohort of patients referred for exercise stress testing who were assessed at baseline for cardiovascular risk factors and followed for incident all-cause mortality and myocardial infarction (MI) events. We hypothesized that (a) CRF is associated with incident all-cause mortality and MI across all strata of baseline estimated ASCVD risk; and (b) that CRF provides incremental prognostic value over the ASCVD risk score.

Methods

The methods of the FIT Project have been previously described.[15] In summary, the FIT Project is a single health

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system investigator-initiated retrospective cohort study that used multiple data sources including directly measured exercise data and estimates of CRF. The FIT Project cohort included 69,885 consecutive patients who underwent physician-referred treadmill stress testing at Henry Ford Health System affiliated hospitals and ambulatory care centers in metropolitan Detroit, MI between 1991 and 2009. Patients younger than 18 years at the time of stress testing or patients undergoing pharmacological stress testing, modified Bruce, and other non-Bruce protocol tests were not included in the study. The FIT Project was approved by the Henry Ford Health System Institutional Review Board.[15] Patients with known coronary artery disease or with history of congestive heart failure at baseline were excluded from the present analysis (N = 10,190 and 877 respectively).

All patients underwent routine, clinically-indicated, symptom-limited maximal treadmill stress testing following the standard Bruce protocol.[16] In accordance with ACC/AHA guidelines, tests were terminated at the discretion of the supervising clinician for potentially life-threatening reasons that included significant arrhythmias, abnormal hemodynamic responses, diagnostic ST-segment changes, exercise-limiting symptoms such as chest pain or shortness of breath, or if the patient was unable to continue.[17] Patients exercised for 3 minutes in each stage of the Bruce protocol. Based on achieved speed and elevation, CRF (expressed in estimated metabolic equivalents of task; METs) was assessed using output data from the Quinton treadmill controller. METs results were categorized into 4 groups: <6, 6 to 9, 10 to 11, and ≥12 METs based on the distribution of the FIT data as these best divide the cohort into nearly four equal groups.[15] Prior studies have shown a graded lower risk of outcomes with these categories.[9,18–20]

On the day of the stress test a nurse and/or clinical exercise physiologist collected information on patients' age, sex, race, risk factor burden, past medical history, and active medication use. Race was defined exclusively by self-report. Current smoking was defined as self-reported active smoking at the time of the stress test. Diabetes mellitus was defined as a prior diagnosis of diabetes, use of hypoglycemic medications including insulin, or a database-verified prior diagnosis of diabetes. Hypertension was defined as a prior diagnosis of hypertension, use of antihypertensive medications, or a database-verified prior diagnosis of hypertension. The blood pressure at the time of the test was not used to diagnose hypertension. Dyslipidemia was defined by prior diagnosis of any major lipid abnormality, use of lipid-lowering medications, or a database-verified diagnosis of hypercholesterolemia or dyslipidemia. Medication use was supplemented using pharmacy claims data and categorized into common indications (antihypertensive, lipid-lowering, etc.). Laboratory results were identified (as available) through a retrospective search of the EMR and laboratory databases. Laboratory tests were performed within 90 days of the study and tests closest to the date of the stress test were selected for inclusion in the calculation of the ASCVD score. The ASCVD risk score was then calculated using the Pooled Cohorts Equations and categorized as <5%, 5 to 20%, and ≥20%.[3]

Mortality ascertainment was conducted through June 2013 using an algorithm for searching the Social Security Death Index Death Master File making use of social security number, first name, last name, and date of birth. Ascertainment was conducted following federal law changes in 2011 limiting reporting of certain deaths by state agencies. A complete algorithmic search of the Social Security Death Index Death Master File was completed in over 99.5% of patients.[15] Myocardial infarction was ascertained through June 2010 by linkage with administrative claims files from services delivered by the affiliated group practice and/or reimbursed by the health plan. Linkage was performed using appropriate International Statistical Classification of Diseases and Related Health Problems 9th (ICD-9) (410.xx). Patients were censored at their last contact with the integrated Henry Ford Health System group practice.

Baseline characteristics of the study cohort including stress test data were tabulated by METs categories and differences were tested using Chi-square tests for categorical variables and analysis of variance or nonparametric testing for continuous variables. Incidence rates of all-cause mortality and MI were calculated as number of events per 1000 person years for each CRF group according to ASCVD risk category and visualized using bar graphs.

Multivariable-adjusted Cox proportional hazard models were used to study the association of CRF with all-cause mortality and MI after testing and confirming the proportionality assumption using log-log plots. In continuous analyses, hazard ratios were calculated for each 1-unit higher METs. In categorical analyses, hazard ratios were calculated in each ASCVD risk group using METs <6 as the reference category. Results were stratified by baseline estimated ASCVD risk categories. We also performed a second categorical analysis using METs ≥12 and ASCVD risk <5% as the reference category. Models were adjusted for age, sex, race/ethnicity, cigarette smoking, hypertension, hyperlipidemia, diabetes mellitus, statin use, aspirin use, and antihypertensive medication use.

To account for differences in cardiorespiratory fitness between men versus women, we derived the FIT treadmill risk score for each patient, which was calculated as (percentage of maximum predicted heart rate + 12 [metabolic equivalents of task] − 4 [age] + 43 if female).[21] We divided this score in tertiles and examined the association with incident all-cause mortality and MI adjusting for the same covariates as a sensitivity analysis. The incremental ability of CRF to discriminate incident all-cause mortality and MI was examined using receiver operating characteristic curves (ROC). The C-index was calculated for the base model consisting of the ASCVD risk score and then after adding CRF. To evaluate the additive potential of CRF for risk reclassification we used categorical net reclassification improvement using an ASCVD risk score cut point of 20% (<20% vs ≥20%).

A two-sided p-value of <0.05 was considered statistically significant. All analyses were performed using Stata/IC version 13.1 (StataCorp, College Station, Texas).

Results

A total of 57,999 patients were included in our study of mean age 53 (SD 13), 49% women, 64% white, and 29% black. The baseline characteristics stratified by CRF are shown in Table 1. Compared to patients with METs ≥12, those with METs <6 were older and more likely to be

Table 1
Baseline characteristics of the study cohort by cardiorespiratory fitness categories

	Study cohort (N = 57,999)	Metabolic equivalents of task <6 (N = 7,626)	Metabolic equivalents of task 6–9 (N = 15,627)	Metabolic equivalents of task 10–11 (N = 21,323)	Metabolic equivalents of task ≥12 (N = 13,423)	p Value
			Demographics			
Age (years)	53 ± 13	64 ± 12	58 ± 12	51 ± 11	45 ± 10	<0.001
Female	28,151 (49%)	5066 (66%)	9875 (63%)	10,352 (49%)	2858 (21%)	<0.001
Race/Ethnicity						<0.001
White	37,152 (64%)	4317 (57%)	9228 (59%)	13,833 (65%)	9774 (73%)	
Black	16,724 (29%)	3000 (39%)	5472 (35%)	5803 (27%)	2449 (18%)	
Other	4123 (7%)	309 (4%)	927 (6%)	1687 (8%)	1200 (9%)	
			Cardiovascular risk factors			
Hypertension	35,640 (61%)	6331 (83%)	11,404 (73%)	12,260 (58%)	5648 (42%)	<0.001
Hyperlipidemia	24,806 (43%)	3262 (43%)	7379 (47%)	9183 (43%)	4982 (37%)	<0.001
Current cigarette smoking	23,972 (41%)	3139 (41%)	6729 (43%)	9069 (43%)	5035 (38%)	<0.001
Diabetes mellitus	10,445 (18%)	2368 (31%)	384s7 (25%)	3233 (15%)	997 (7%)	<0.001
Family history of coronary heart disease	29,745 (51%)	3467 (45%)	7933 (51%)	11,301 (53%)	7044 (52%)	<0.001
History of obesity	13,308 (23%)	1987 (26%)	5124 (33%)	4993 (23%)	1204 (9%)	<0.001
			Medication use			
Lung disease	5169 (9%)	956 (13%)	1634 (10%)	1787 (8%)	792 (6%)	<0.001
Antihypertensives	24,858 (43%)	5065 (66%)	8638 (55%)	8142 (38%)	3013 (22%)	<0.001
Statins	10,516 (18%)	1633 (21%)	3677 (24%)	3710 (17%)	1496 (11%)	<0.001
Aspirin	9997 (17%)	1797 (24%)	3164 (20%)	3424 (16%)	1612 (12%)	<0.001
Glucose lowering	4684 (8%)	1057 (14%)	1896 (12%)	1393 (7%)	338 (3%)	<0.001
			Atherosclerotic cardiovascular disease risk			
						<0.001
<5%	15,379 (27)	658 (9)	3105 (19)	6600 (31)	5016 (37)	
5–20%	17,642 (30)	1950 (26)	5136 (33)	6730 (32)	3826 (29)	
≥20%	24,978 (43)	5018 (66)	7386 (47)	7993 (37)	4581 (34)	

Atherosclerotic cardiovascular disease risk score is calculated using the pooled cohort equations.
Continuous variables: mean (standard deviation) or median (interquartile range)*. Categorical variables: count (percentage).

female and black. They also had higher prevalence of ASCVD risk factors including hypertension, hyperlipidemia, diabetes mellitus, and current cigarette smoking (all p <0.05). Furthermore, they were more likely to have higher predicted ASCVD risk (Table 1)

Over a median 11 years of follow up (interquartile range 8 to 14 years), 6,670 (11.3%) deaths occurred while 1,757 patients (3.0%) developed MI over a median follow up duration of 6 years (interquartile range 3 to 8 years). Figure 1a demonstrates a graded higher incidence rate of

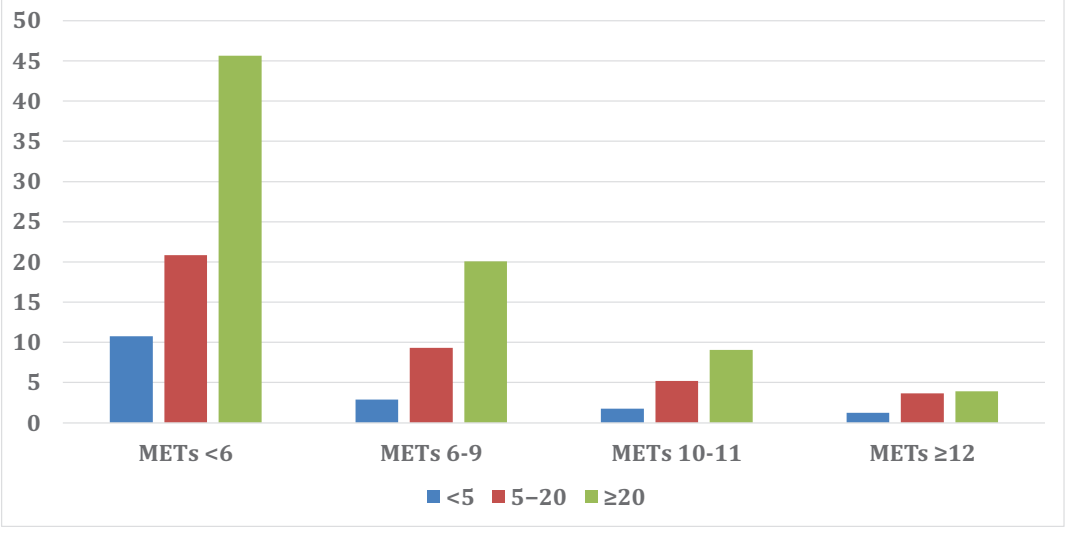

Figure 1a. Unadjusted incidence rates* of all-cause mortality by categories of estimated atherosclerotic cardiovascular risk¶ and cardiorespiratory fitness
*Incidence rates of all-cause mortality and myocardial infarction are expressed per 1000 person-years
METs = metabolic equivalents of task
¶Atherosclerotic cardiovascular disease risk is calculated using the pooled cohort equation.

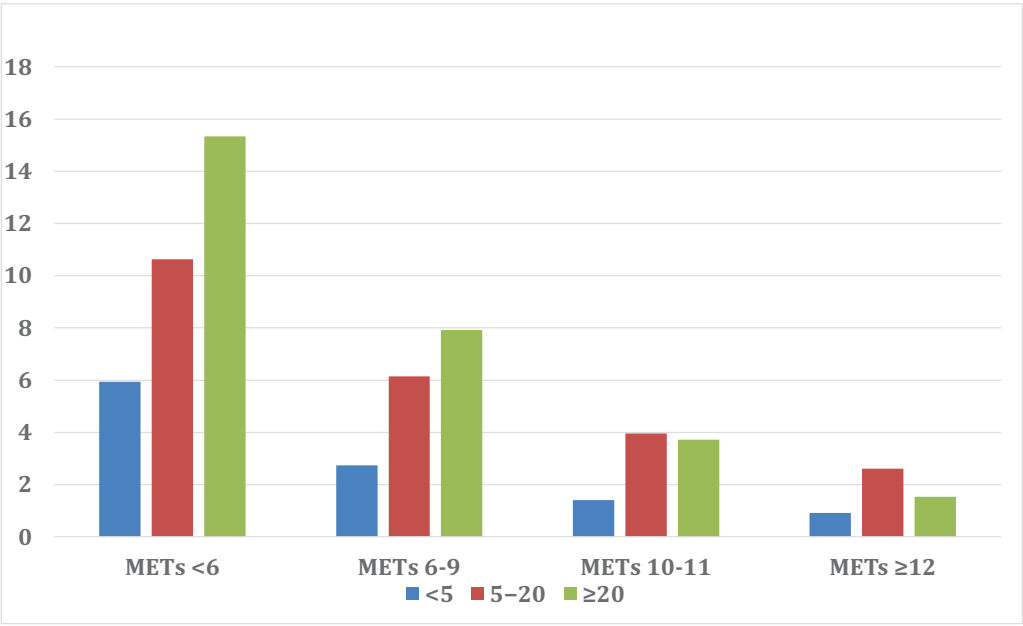

Figure 1b. Unadjusted incidence rates* of myocardial infarction by categories of estimated atherosclerotic cardiovascular disease risk¶ and cardiorespiratory fitness

*Incidence rates of all-cause mortality and myocardial infarction are expressed per 1000 person-years

METs = metabolic equivalents of task

¶Atherosclerotic cardiovascular disease risk is calculated using the pooled cohort equation.

all-cause mortality with higher ASCVD risk categories for all METs categories. Similarly, there was a graded higher incidence rate of MI with higher ASCVD risk categories among patients with METs <6 and 6 to 9 but not for those with METs 10 to 11 and ≥12 (Figure 1b). In particular, patients with ASCVD risk <5% and METs <6 had a higher incidence rate of these outcomes compared to those with ASCVD risk ≥20% and METs ≥12 (10.8 vs 3.9 for all-cause mortality and 5.9 vs 1.5 for MI; p-value <0.001 and 0.44 in Figures 1a and 1b respectively).

In multivariable-adjusted analyses there was a graded lower risk of all-cause mortality and MI with higher METs categories across all strata of baseline estimated ASCVD risk (Table 2). For example, among patients with ASCVD risk ≥20%, those with METs ≥12 had a 77% lower risk of all-cause mortality and 67% lower risk of MI compared to METs <6. Similar results were obtained in continuous analyses of 1-unit higher METs. Figure 2 demonstrates hazard ratios of all-cause mortality and MI using METs ≥12 and ASCVD risk <5% as the reference category. In this analysis

Table 2
Multivariable-adjusted hazard ratios for the association of cardiorespiratory fitness and incident all-cause mortality and myocardial infarction by categories of baseline estimated atherosclerotic cardiovascular disease risk

	Atherosclerotic cardiovascular disease risk <5%	Atherosclerotic cardiovascular disease risk 5−20%	Atherosclerotic cardiovascular disease risk ≥20%
Metabolic equivalents of task		**All-cause mortality**	
<6	1.00 (ref)	1.00 (ref)	1.00 (ref)
6−9	0.31 (0.23,0.42)	0.51 (0.45,0.58)	0.57 (0.53,0.61)
10−11	0.19 (0.14,0.26)	0.29 (0.25,0.34)	0.35 (0.32,0.39)
≥12	0.11 (0.07,0.15)	0.21 (0.17,0.25)	0.23 (0.20,0.27)
P for trend	<0.001	<0.001	<0.001
Per 1-unit higher	0.80 (0.77,0.83)	0.84 (0.82,0.85)	0.85 (0.84,0.86)
Metabolic equivalents of task		**Incident myocardial infarction**	
<6	1.00 (ref)	1.00 (ref)	1.00 (ref)
6−9	0.60 (0.37,0.99)	0.61 (0.49,0.77)	0.66 (0.57,0.76)
10−11	0.32 (0.20,0.53)	0.39 (0.30,0.51)	0.46 (0.38,0.56)
≥12	0.17 (0.10,0.32)	0.24 (0.17,0.34)	0.33 (0.24,0.46)
P for trend	<0.001	<0.001	<0.001
Per 1-unit higher	0.83 (0.79,0.88)	0.86 (0.83,0.89)	0.88 (0.86,0.91)

Model is adjusted for age, sex, race/ethnicity, cigarette smoking, hypertension, hyperlipidemia, diabetes mellitus, statin use, aspirin use, antihypertensive medication use.

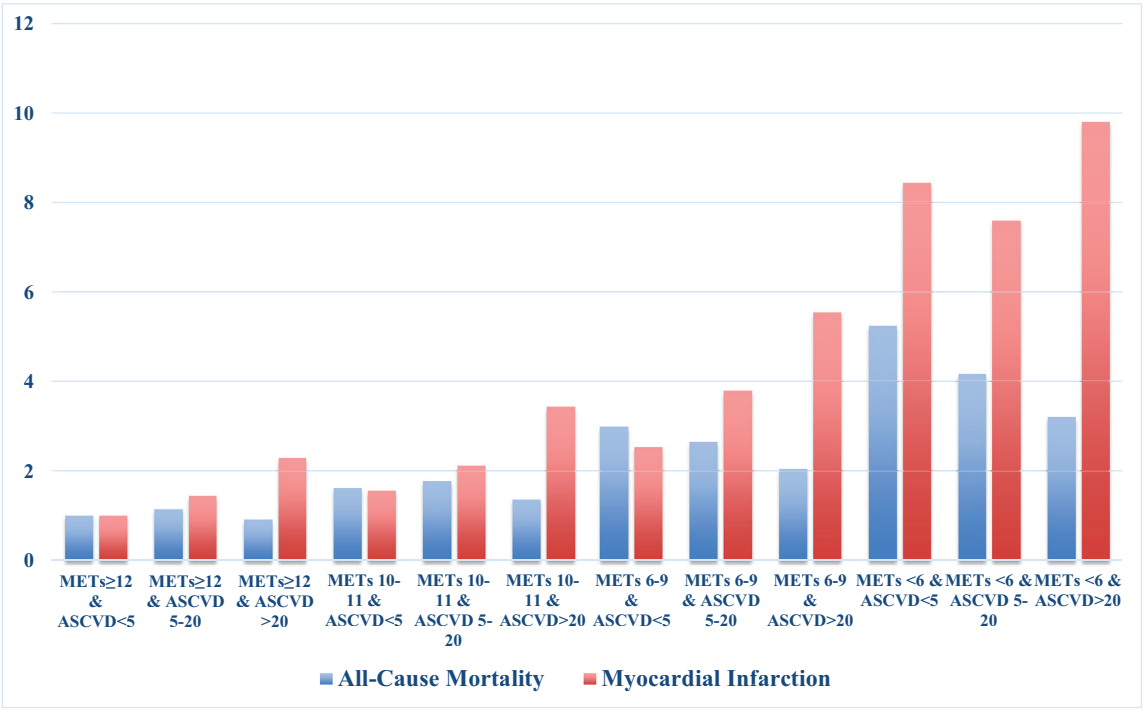

Figure 2. Multivariable-adjusted hazard ratios of all-cause mortality and myocardial infarction by categories of estimated atherosclerotic cardiovascular disease risk¶ and cardiorespiratory fitness

Model is adjusted for adjusted for age, sex, race/ethnicity, cigarette smoking, hypertension, hyperlipidemia, diabetes mellitus, statin use, aspirin use, antihypertensive medication use

¶Atherosclerotic cardiovascular disease risk is calculated using the pooled cohort equation.

there was a higher risk of events with higher ASCVD risk and lower METs categories.

In sensitivity analyses examining the FIT treadmill score, a similar graded lower risk of all-cause mortality and MI regardless of ASCVD risk category (Supplementary Table).

Addition of METs to ASCVD risk score incrementally improved the C-statistic for all-cause mortality and MI (both $p < 0.001$). Addition of METs to ASCVD risk score significantly reclassified risk of all-cause mortality but not MI. Among those who died, 672 deaths (15%) were correctly reclassified at higher risk while 166 (4%) were correctly reclassified as lower risk ($p < 0.001$). Among those who had incident MI, 18 (1%) were correctly reclassified at higher risk while 8 (0.1%) were correctly reclassified as lower risk ($p = 0.052$).

Discussion

In support of our research hypothesis, we found that higher CRF is inversely associated with risk of incident all-cause mortality and MI independent of traditional cardiovascular risk factors. This association is similar for individuals at high, intermediate, and low risk of ASCVD.

The FIT Project is the largest epidemiologic database of objectively assessed clinical exercise data to date. Our results are generalizable to modern day clinical patient cohorts since patients were referred by their primary care providers. This has distinct advantages over volunteer study populations who are typically healthier[22] and may experience lower rates of adverse outcomes. Our database also has significant racial diversity with nearly 30% of our cohort being black and 50% women. In addition, the duration of follow-up extends for a maximum 22 years for all-cause mortality, with more than 50% of patients followed for at least 10 years.

Prior studies have shown that CRF is inversely associated with adverse outcomes regardless of sex,[23] race,[24] family history of CHD,[25] history of MI,[20,26] and medication use.[27–30] The present study further demonstrates that the association between CRF and incident all-cause mortality and MI is similar across strata of baseline estimated ASCVD. In particular, individuals with low ASCVD risk and low METs in our study had a higher risk of outcomes than those with high ASCVD risk and high METs. This suggests that there is significant heterogeneity even within individuals of the same ASCVD risk stratum. The association between CRF and all-cause mortality appears to be stronger compared to MI, likely because CRF is associated independently with risk of mortality from various cancers.[14] As CRF is a marker of overall cardiovascular health, it integrates the effect of genetics, ASCVD risk factors, and health factors (physical activity, diet, exercise) over an individual's lifetime. On the other hand, estimation of 10-year ASCVD risk using the ASCVD risk score involves measuring risk factors at the time of risk assessment. Consistent with prior studies, we also showed that the addition of CRF to the ASCVD risk score leads to significant improvement in discrimination and reclassification of incident death and MI suggesting that CRF has the potential for further risk stratification.[14,31]

Our results should be interpreted in the context of important limitations. The FIT Project reports the experience of a

single center with its unique practice patterns and modes of operation. Although the cohort studied is diverse, the generalizability may be limited. Most of our patients underwent a clinically indicated stress test to assess symptoms or to address other clinical questions. Thus, the findings may not be generalizable to asymptomatic and otherwise healthy individuals where clinical exercise testing is not currently recommended. In addition, the exclusive reliance on the Bruce protocol may have resulted in a possible selection bias as patients who were older, overweight, or with physical limitations may have been tested using different protocols and were therefore not included in our study. Holding onto the railing for support during the test may have resulted in overestimation of the fitness level, especially given that metabolic testing for CRF (e.g., peak VO_2) was not performed. ECG results (i.e., ST segment changes) from the stress test were not available in our project, and therefore the Duke Treadmill Score, an important prognostic index for detecting obstructive coronary disease, could not be calculated. Furthermore, these outcomes were not adjudicated by an independent panel of clinical experts. The ASCVD risk score was not designed to be used in patients already on lipid lowering therapies nor to predict risk of all-cause mortality. Nevertheless we adjusted for statin use in our analyses and ASCVD risk score does predict cardiovascular causes of mortality, which represent a major cause of death.[32] It is important to note that the FIT Project does not currently have information on cause-specific mortality. Both physicians and patients were not blinded to the fitness results and therefore it is possible that the use preventive medications may have changed over follow up, which could have influenced our results. Lastly, although we adjusted for known risk factors for cardiovascular disease, we cannot exclude the possibility of residual confounding.

In conclusion, CRF is inversely associated with risk of all-cause mortality and MI at all levels of baseline ASCVD risk. Persons with low ASCVD risk and low METs were at higher risk of these outcomes than those with high ASCVD risk and high METs. CRF improved risk discrimination and reclassification around clinically important risk categories independent of the baseline ASCVD risk score. CRF may therefore represent a valuable tool for additional risk stratification although further studies are required to evaluate the use of CRF in guiding the allocation of primary preventive treatment.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.05.033.

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