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Fitness attenuates long-term cardiovascular outcomes in women with ischemic heart disease and metabolic syndrome

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ABSTRACT

Background: The prevalence of metabolic syndrome continues to increase steadily while fitness remains relatively low. The contribution of fitness on longer-term cardiovascular outcomes and mortality in individuals with cardiovascular disease and metabolic syndrome remains unknown.
Design: Women's Ischemia Syndrome Evaluation (WISE) prospective cohort (enrolled 1996–2001) of women undergoing invasive coronary angiography with signs/symptoms of ischemic heart disease.
Methods: Investigated the association of fitness, defined as >7METs measured by self-reported Duke Activity Status Index (DASI), and both metabolic syndrome (ATPIII criteria) and dysmetabolism (ATPIII criteria and/or treated diabetes) with long-term cardiovascular outcomes and all-cause mortality risk.
Results: Among the 492 women followed for a median of 8.6 years (range 0–11 years), 19.5% were fit-metabolically healthy (reference), 14.4% fit-metabolic syndrome, 29.9% unfit-metabolically healthy, and 36.2% unfit-metabolic syndrome. Compared to reference, MACE risk was 1.52-fold higher in fit-metabolic syndrome women (HR 1.52, 95% CI 1.03–2.26) and 2.42-fold higher in unfit-metabolic syndrome women (HR 2.42, 95% CI 1.30–4.48). Compared to reference, mortality risk was 1.96-fold higher in fit-dysmetabolism (HR 1.96, 95% CI 1.29–3.00) and 3-fold higher in unfit-dysmetabolism women (HR 3.0, 95% CI 1.66–5.43).
Conclusions: In a high risk cohort of women with signs/symptoms of ischemic heart disease, unfit-metabolically healthy and fit-metabolically unhealthy women were at higher risk of long-term MACE and mortality compared to fit-metabolically healthy women; and women who were unfit and metabolically unhealthy were at the highest risk. Our study demonstrates that metabolic health and fitness play an important role in long term outcomes that warrants further investigation.
Registration: https://www.clinicaltrials.gov/ct2/show/NCT00000554 (NCT00000554)

1. Introduction

Cardiovascular disease (CVD) remains the leading cause of death in women, with recent data suggesting an increase in heart disease mortality in women 35–54 years of age [1]. Metabolic syndrome and diabetes are increasingly recognized as contributors to CVD outcomes and all-cause mortality [2,3]. Women have a 25% higher risk of metabolic syndrome than men [4,5]. According to National Health and Nutrition Examination Survey (NHANES) data, roughly one third of women are affected by metabolic syndrome and 13.8% have diabetes in

Abbreviation: Cardiovascular disease, (CVD); Coronary artery disease, (CAD); Duke Activity Status Index, (DASI); Women's Ischemia Syndrome Evaluation, (WISE); Major adverse cardiovascular events, (MACE).

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the United States [6,7]. Despite the cardiovascular and mortality benefits associated with fitness [8–11], more women report physical inactivity than men (35.2% vs. 29.7%) [12].

Metabolic syndrome is a cluster of metabolic risk factors including hypertriglyceridemia, low high-density lipoprotein cholesterol (HDL-C), hypertension, abdominal adiposity and fasting hyperglycemia. Higher fitness has been associated with lower risk of CVD outcomes and mortality in individuals with metabolic risk factors. However, studies to date are largely limited to healthy cohorts without a known history of CVD, cohorts predominatly composed of men, or focus on just one metabolic risk factor. [13–15] For example, Hung et al. showed higher fitness attenuated risk of major adverse cardiovascular events (MACE) and mortality in women with hyperlipidemia [16]. Fitness is also associated with lower risk of developing diabetes [17]; and in women with diabetes, fitness has been associated with lower risk of CVD outcomes and mortality [18]. However, the association of fitness and the cluster of metabolic risk factors that make up the metabolic syndrome on longer-term major MACE and mortality in women with CVD remains unknown.

We investigated the association of fitness and metabolic syndrome without and with diabetes (dysmetabolism) on the risk of obstructive angiographic coronary artery disease (CAD), and long-term MACE and all-cause mortality in women with ischemic heart disease undergoing invasive coronary angiography.

2. Methods

2.1. Study population

The study population consisted of women enrolled in the multicenter National Heart Lung and Blood Institute (NHLBI) Women's Ischemia Syndrome Evaluation (WISE) prospective study. The WISE cohort is comprised of women with signs and/or symptoms of ischemic heart disease clinically referred for invasive coronary angiography. Women were enrolled from 1996 to 2001 at 4 sites (University of Alabama at Birmingham; University of Florida, Gainesville; University of Pittsburgh, Pittsburgh, Pa; and Allegheny General Hospital, Pittsburgh, Pa) and followed for events up to 10 years as previously described [19]. Only participations with complete data for metabolic syndrome, Duke Activity Status Index (DASI) at baseline and cardiovascular events at follow-up were included in this analysis. Each woman provided informed consent approved by each site's institutional review board.

At the time of enrollment, each woman had a baseline evaluation that included collection of demographic information, medical history, DASI, a physical examination including assessment of blood pressure and waist circumference. Sampling of blood in the fasting state for lipids, glucose, insulin, and inflammatory markers (including interleukin [IL-6], and high sensitivity C-reactive protein [hs-CRP]) were collected at baseline and analyzed in core laboratories, as previously described [19].

2.2. Classification of metabolic syndrome and dysmetabolism

2001 ATP III criteria was used to classify study participants as being with or without metabolic syndrome based on the presence or absence of $\geq$3 of the following factors: (1) waist circumference >88 cm, (2) fasting triglycerides >150 mg/dL (measured by enzymatic assay at the WISE core lipid laboratory), (3) HDL-C <50 mg/dL, (4) hypertension (systolic blood pressure $\geq$130 mm Hg, diastolic blood pressure $\geq$85 mm Hg, or use of antihypertensive drug therapy), and (5) fasting glucose $\geq$110 mg/dL [13]. Of note, the ATP III criteria was the criteria utilized during the time of enrollement of the WISE study and therefore the criteria employed in this analysis. In this study women with treated diabetes (defined as use of oral hypoglycemic agents or insulin $N = 190$, 21.1%) were excluded from the metabolic syndrome group. An additional group was created labeled dysmetabolism which included women with metabolic syndrome and/or treated diabetes.

2.3. Fitness assessment

The DASI, questionnaire is a 12-item self-reported questionnaire, was used to assess fitness [20]. Positive response scores are summed to get a total DASI score ranging from 0 to 58, where a higher DASI score indicates a greater level of fitness. The total DASI score when divided by 3.5 gives an estimate of METs. As in our prior work and others, a DASI score greater than 25 (>7 METs) corresponding to stage 2 of the Bruce protocol was defined as fit and less than 25 as unfit [11,21,22]. In a secondary analysis, DASI score of greater than 35 (>10METs) was used to define highly fit women and less than 35 as unfit. DASI scores have been validated with measured oxygen uptake, the gold standard for cardiovascular fitness, ($r = 0.58, p<0.0001$)[20] and correlated within a subset of the WISE cohort with exercise treadmill testing [23].

2.4. Angiographic CAD assessment

Angiographic assessment for CAD was performed at baseline. As previously described, analysis of coronary angiograms was performed at the WISE angiographic core laboratory (Rhode Island Hospital, Providence, RI) by investigators blinded to all other subject data [19]. Angiographically determined obstructive CAD was defined as the presence of stenoses $\geq$50% in one or more epicardial arteries, minimal CAD as presence of stenosis between 20% to 49%, and no CAD as <20% stenosis in all coronary arteries. The WISE CAD severity score was assigned based on angiographic severity of stenoses, location of stenoses, and presence of partial or complete collateral flow with score range of 5.0 to 88.5 [24].

2.5. Follow-up and cardiovascular events

Follow-up for the occurrence of cardiovascular events was conducted by annual telephone interview by experienced site staff and/or mail contact. The primary outcomes of interest were the composite end point of MACE (death, nonfatal myocardial infarction, or hospitalization for congestive heart failure) and all-cause mortality. The National Death Index (NDI), a reliable tool to identify dead subjects, was used to determine mortality at the 10-year follow-up for the original WISE database, and verification was performed at the clinical sites. Women were considered alive unless reported as deceased in the NDI.

2.6. Statistical analysis

In the primary analysis, the sample size consisted of 492 women with complete data for metabolic syndrome and fitness. Women were stratified by combined fitness and metabolic status groups: fit-metabolically healthy (reference group), unfit-metabolically healthy, fit-metabolic syndrome, and unfit-metabolic syndrome. Differences in baseline demographics and clinical characteristics by fitness and metabolic status were assessed by chi-square tests for categorical variables and Student *t*-test or Wilcoxon rank sum tests for continuous variables.

Logistic regression analysis was used to obtain adjusted estimates of the odds of having obstructive angiographic CAD by fitness and metabolic status groups. All models were adjusted for known predictors of obstructive CAD as described in existing literature, including self-reported age, race, smoking status, and history of heart failure.

The Kaplan-Meier (KM) method was used to estimate cumulative incidence rates of MACE and all-cause mortality and the log-rank test was used to compare KM curves. Participants who did not experience the clinical outcome of interest were censored at either 10 years or the last date of follow-up before 10 years. Cox proportional hazards regression was then performed to estimate adjusted hazard ratios of MACE and mortality, in relation to fitness and metabolic status groups. Cox models were adjusted for known predictors of MACE and mortality as described

in existing literature, including self-reported age, race, smoking status, CAD severity score, and history of heart failure. We then conducted stepwise selection to refine the model. All variables in Table 1 were considered for inclusion, excluding those with >5% missing data. Furthermore, among highly correlated variables, we selected the one with the lowest univariable p-value for inclusion. Predictors were selected based on significance or trend toward significance ($p<0.10$). As a result of the stepwise selection, hemoglobin was added to MACE model and history of HRT use to the mortality model. In a sensitivity analysis, cardiac medications significant in univariate analysis were also added to the Cox models and as a result of stepwise selection calcium channel antagonists was added to the MACE model and calcium channel antagonists and antiplatelets were added to the mortality model. In secondary analysis, the cohort was redefined and highly-fit (DASI>35) metabolically healthy was used as the reference group and DASI≤35 defined as unfit and cox proportional hazards regression was performed to estimate adjusted hazard ratios of MACE and mortality. The cohort was also redefined based on blood glucose cutoff and fasting blood glucose of >100 to meet the ATP harmonized definition[25] and cox proportional hazards regression was performed to estimate adjusted hazard ratios of MACE and mortality. The proportional hazards assumption among all survival models was assessed using Kolmogorov-Smirnov supremum-type test.

Primary analysis was repeated with a sample size of 682 including women with dysmetabolism (metabolic syndrome and/or treated diabetes). Women were stratified by groups as follows: fit-metabolically healthy (reference group), unfit-metabolically healthy, fit-dysmetabolism, and unfit-dysmetabolism. Proportional hazards regression was used to estimate adjusted hazard ratios of MACE and all-cause mortality, in relation to fitness and metabolic status groups. All models were adjusted for age, race, smoking status, CAD severity score, and history of heart failure. A p-value ≤ 0.05 was considered significant for all analyses.

3. Results

3.1. Baseline characteristics by fitness and metabolic status

Among the 492 women, 19.5% were fit-metabolically healthy, 14.4%% fit-metabolic syndrome, 29.9%% unfit-metabolically healthy, and 36.2% unfit-metabolic syndrome. Table 1 shows significant trends with highest proportion of hypertension, dyslipidemia, smoking, and obstructive CAD in unfit-metabolic syndrome women and lowest proportion in fit-metabolically healthy. There were also significant trends with highest CAD severity score, BMI, arthropathic measures, systolic blood pressure, triglycerides, insulin, and inflammatory markers in

Table 1
Baseline characteristics by metabolic syndrome and fitness status groups.

Characteristics	Fit-Metabolically healthy (*N* = 96)	Unfit-Metabolically healthy (*N* = 147)	Fit-Metabolic Syndrome (*N* = 71)	Unfit-Metabolic Syndrome (*N* = 178)	*p*-value
Age, mean (SD), y	56.2 (11.2)	59.0 (11.3)	56.2 (11.0)	58.4 (12.3)	0.147
Nonwhite race, No. (%)	9 (9.4%)	29 (19.7%)	11 (15.5%)	32 (18%)	0.172
History of hypertension, No. (%)	26 (27.1%)	67 (45.6%)	42 (60.0%)	110 (62.1%)	<0.001
History of dyslipidemia, No. (%)	34 (36.2%)	67 (47.2%)	34 (49.3%)	94 (58.0%)	0.009
History of heart failure, No. (%)	2 (2.1%)	13 (8.9%)	3 (4.2%)	15 (8.5%)	0.112
History of myocardial infarction, No. (%)	9 (9.5%)	26 (18.4%)	10 (14.3%)	42 (24.1%)	0.021
History of PCI, No. (%)	9 (9.4%)	21 (14.3%)	8 (11.3%)	31 (17.4%)	0.275
History of CABG, No. (%)	1 (1.1%)	5 (3.4%)	2 (2.8%)	11 (6.2%)	0.217
Family history of CAD, No. (%)	59 (61.5%)	96 (68.6%)	53 (74.6%)	126 (72.8%)	0.188
Smoker at study entry, No. (%)	14 (14.6%)	31 (21.1%)	16 (22.5%)	48 (27.1%)	0.121
Ever smoked, No. (%)	46 (47.9%)	80 (54.4%)	36 (50.7%)	113 (63.8%)	0.048
Postmenopausal, No. (%)	69 (71.9%)	112 (76.2%)	49 (69.0%)	135 (75.8%)	0.610
History of HRT use, No. (%)	56 (58.3%)	82 (55.8%)	37 (52.9%)	89 (50.6%)	0.618
CAD severity score, mean (SD)	10.3 (11.8)	12.2 (12.5)	11.6 (10.8)	15.9 (15.0)	0.003
Obstructive CAD, No. (%)	18 (18.9%)	41 (28.1%)	19 (26.8%)	79 (44.4%)	<0.001
Medications, No. ((%)					
Aspirin	45 (46.9%)	86 (58.9%)	31 (43.7%)	113 (63.5%)	0.007
Antiplatelet	3 (3.1%)	7 (4.8%)	1 (1.4%)	12 (6.8%)	0.304
Statin	16 (16.7%)	36 (24.5%)	12 (16.9%)	39 (21.9%)	0.395
ACEI/ARB	10 (10.4%)	31 (21.1%)	18 (25.7%)	45 (25.3%)	0.025
Beta blocker	23 (24.0%)	50 (34.0%)	26 (37.1%)	80 (44.9%)	0.006
Calcium channel blocker	15 (15.6%)	42 (28.6%)	16 (22.5%)	54 (30.3%)	0.044
Nitrates	20 (20.8%)	44 (29.9%)	23 (32.4%)	71 (39.9%)	0.013
Arthropathic Measures, mean (SD)					
BMI, kg/m2	26.2 (5.4)	27.0 (6.4)	30.1 (5.2)	31.6 (6.2)	<0.001
Waist circumference, cm	81.1 (12.3)	84.8 (15.1)	94.1 (10.1)	102.6 (16.6)	<0.001
Waist-hip ratio	0.8 (0.1)	0.8 (0.1)	0.9 (0.1)	0.9 (0.1)	<0.001
Waist-height ratio	0.5 (0.1)	0.5 (0.1)	0.6 (0.1)	0.6 (0.1)	<0.001
SBP, mmHg	128.4 (20.2)	132.7 (22.1)	137.8 (17.3)	137.9 (21.3)	0.001
DBP, mmHg	76.6 (12.1)	75.5 (12.5)	76.2 (10.3)	78.2 (12.9)	0.230
Lipids, mean (SD), mg/dL					
Total cholesterol	208.4 (37.7)	205.9 (45.2)	216.2 (45.2)	216.7 (52.8)	0.175
HDL-C	59.9 (16.4)	60.5 (14.7)	46.9 (10.8)	44.9 (12.0)	<0.001
LDL-C	124.1 (32.1)	122.1 (41.5)	128.6 (38.6)	130.8 (49.5)	0.311
Triglycerides	120.2 (61.6)	121.2 (70.7)	196.1 (83.7)	219.7 (155.7)	<0.001
Fasting blood glucose, mg/dL, mean (SD),	90.6 (19.1)	87.1 (22.3)	115.6 (47.6)	110.3 (34.5)	<0.001
Insulin, μU/mL, mean (SD),	4.7 (7.1)	5.2 (4.7)	8.0 (7.3)	11.3 (11.9)	<0.001
Hemoglobin, g/dL, mean (SD),	13.2 (1.2)	12.9 (1.3)	13.4 (1.3)	12.9 (1.3)	0.008
Inflammatory markers, mean (SD),					
hs-CRP, mg/L	0.6 (1.0)	0.6 (0.9)	1.0 (1.9)	1.2 (2.3)	0.010
Interleukin-6, pg/mL	3.1 (2.8)	3.9 (3.3)	5.1 (5.0)	5.3 (5.4)	0.004

HRT, hormone replacement therapy; CAD, coronary artery disease; obstructive CAD defined as stenosis ≥50% in any major epicardial artery; ACEI/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; hs-CRP, high sensitivity C-reactive protein.

unfit-metabolic syndrome women and lowest proportion in fit-metabolically healthy. Fit women were less likely to have metabolic syndrome compared to unfit women (42.5% vs 54.8% $p = 0.010$, respectively).

3.2. Angiographic obstructive CAD by fitness and metabolic status

Coronary angiography at baseline demonstrated that 32.0% of the women had obstructive CAD. In adjusted logistic regression models, compared to fit-metabolically healthy women (reference), risk of obstructive disease was 1.99-fold higher in fit-metabolic syndrome women, 1.61-fold higher in unfit-metabolically healthy women and 3.2-fold higher in unfit-metabolic syndrome women (OR 3.20) (Table 2).

3.3. Major adverse cardiovascular events and all-cause mortality by fitness and metabolic status

Overall, 116 (23.6%) women had MACE, and 77 (15.7%) died. The median follow-up time for MACE was 5.9 years (range 0 to 9.3 years) and for all-cause mortality was 8.6 years (range 0 to 11.3 years). Analysis of time-to-MACE and all-cause mortality demonstrated significant group differences for each outcome (Fig. 1). The highest proportion of MACE events (51.7%, $p<0.001$) and all-cause mortality (51.9%, $p = 0.009$) was in the unfit-metabolic syndrome women.

We evaluated for interaction and found no significant interaction between low fitness and metabolic syndrome for obstructive CAD ($p = 0.4$), MACE ($p = 0.4$) or mortality ($p = 0.2$). Compared to fit-metabolically healthy women (reference), MACE risk was 1.52-fold higher in fit-metabolic syndrome women and 2.42-fold higher in unfit-metabolic syndrome women (Fig. 2A, Central Illustration). No significant difference in mortality by fitness and metabolic groups (Fig. 2B). Findings remained largely unchanged in sensitivity analysis that included cardiac medications in multivariable cox proportional hazards regression modes: MACE risk was higher in fit-metabolic syndrome women (HR 1.58; CI 1.07, 2.33) and higher in unfit-metabolic syndrome women (HR 2.32; CI 1.28, 4.20) compared to reference and no significant difference in mortality (Supplemental Table 1). In secondary analysis, compared to highly-fit metabolically healthy, unfit women with METs<10 and metabolic syndrome had 2.6-fold higher risk of mortality (Supplemental Table 2). Further, when metabolic syndrome was defined based on ATP Harmonized definition it was not associated with significant risk of MACE (HR 1.35 95% CI 0.9–2.0) or mortality (HR 1.22 95% CI 0.75–2.0).

Compared to fit-metabolically healthy women (reference), MACE risk was 2.02-fold higher in fit-dysmetabolism women, 1.69-fold higher in unfit-metabolically healthy, and 3.41-fold higher in unfit-dysmetabolism women (Fig. 3A, Central Illustration). Further, compared to fit-metabolically healthy women, risk of mortality was 1.96-fold higher in fit-dysmetabolism women and 3-fold higher in unfit-dysmetabolism women (Fig. 3B, Central Illustration).

4. Discussion

Our study fills an important knowledge gap in women who have a higher prevalence of metabolic syndrome and more likely to be unfit. In a high risk cohort of women undergoing invasive coronary angiography with signs/symptoms of ischemic heart disease, unfit-metabolically healthy and fit-metabolically unhealthy women were at higher risk of long-term MACE and mortality compared to fit-metabolically healthy women; and those who were unfit and metabolically unhealthy were at the highest risk.

Fit women were less likely to have metabolic syndrome, consistent with others who have demonstrated that exercise reduces risk factors such as visceral adiposity [26,27]. Further, compared to fit metabolically healthy women, women with metabolic syndrome who were unfit were at highest risk of MACE. These findings are consistent with and expand several cohort studies that have reported the cardioprotective effects of fitness in men with clustered metabolic risk factors without CVD [11,14,28]. Further, compared to fit metabolically healthy women, the higher risk of MACE in the fit women with metabolic syndrome was similar to risk in unfit metabolically healthy consistent with a European cohort [29]. In the contrary of what has been reported in men, in our primary analysis where we used a DASI cut- of greater than 25 (>7METs) to define fitness we did not find a significant relationship between metabolic syndrome and fitness with all-cause mortality [15]. This may be due in part to being underpowered to detect a mortality difference and also overestimation of fitness since fitness has been shown to decrease over time [30]. However, when we used a higher DASI cut-of greater than 35 (>10METs) to determine difference in highly fit women; we found that women with metabolic syndrome and METs<10 had a 2.6-fold higher risk of mortality compared to metabolically healthy highly fit women. These findings sugest that in women with ischemic heart disease higher fitness may be needed to improve mortality that warrants further research.

In this higher risk population of women, unfit women with dysmetabolism were at highest risk of MACE and all-cause mortality consistent with other studies in diabetics [14,31,32]. We also demonstrate that both fitness and a healthy metabolic status attenuate the MACE & mortality risk. Unfit women with dysmetabolism had 3.4-fold higher risk of MACE whereas the risk in fit with dysmetabolism was 2-fold and in unfit-metabolically healthy was 1.7-fold compared to the reference. In fit women with dysmetabolism the risk of mortality was 1.96-fold, whereas women who were unfit and had dysmetabolism had 3-fold higher risk. Together these findings demonstrate the importance of fitness in risk stratifying women, particularly those with metabolic syndrome and diabetes.

Subclinical systemic inflammation has been associated with metabolic syndrome and its components [33,34], physical inactivity [35], and CVD [36,37]. Insulin resistance associated with metabolic syndrome causes the myocardium to decrease glucose use and increase its use of fatty acids, thus decreasing a metabolic dysregulation that increases the heart's susceptibility to injury by reactive oxygen species [30,31]. This increase in reactive oxygen species would thus cause cardiac injury over time and thus release inflammatory mediators. Fitness inhibits the expression of leukocyte adhesion molecules and suppresses monocyte-endothelial cell interactions, inflammation, and release of pro-inflammatory cytokines from monocytes through its effects on oxidative stress in the cell [35]. This may help explain the trend we saw with lower levels of IL-6 and hs-CRP in fit-metabolic syndrome compared to unfit-metabolic syndrome supporting the hypothesis that fitness may decrease the subclinical systemic inflammation caused metabolic syndrome and therefore decrease the long-term risk. We do note that mean hs-CRP was low across all the groups which we hypothesize may be due to statin use which was between 16 and 24%.

The public health burden associated with metabolic syndrome and diabetes is substantial. This study highlights the importance of fitness assessments, easily obtained by a patient-reported measure, in risk stratification. Our findings have public health implications and calls for policies that increase access such design of communities with more public spaces for exercise, public health campaigns, increase access to

Table 2
Risk of obstructive coronary artery disease in relation to fitness and metabolic syndrome.

Fitness and Metabolic Status	n	OR (95% CI)[†]	*p*-value
Fit-Metabolically healthy	95	1.0 (referent)	—
Fit-Metabolic syndrome	71	1.99 (1.32, 3.00)	0.001
Unfit-Metabolically healthy	146	1.61 (1.02, 2.54)	0.041
Unfit-Metabolic syndrome	178	3.20 (1.77, 5.81)	<0.001

[†] Adjusted for self-reported age, race, smoking status, and history of heart failure.

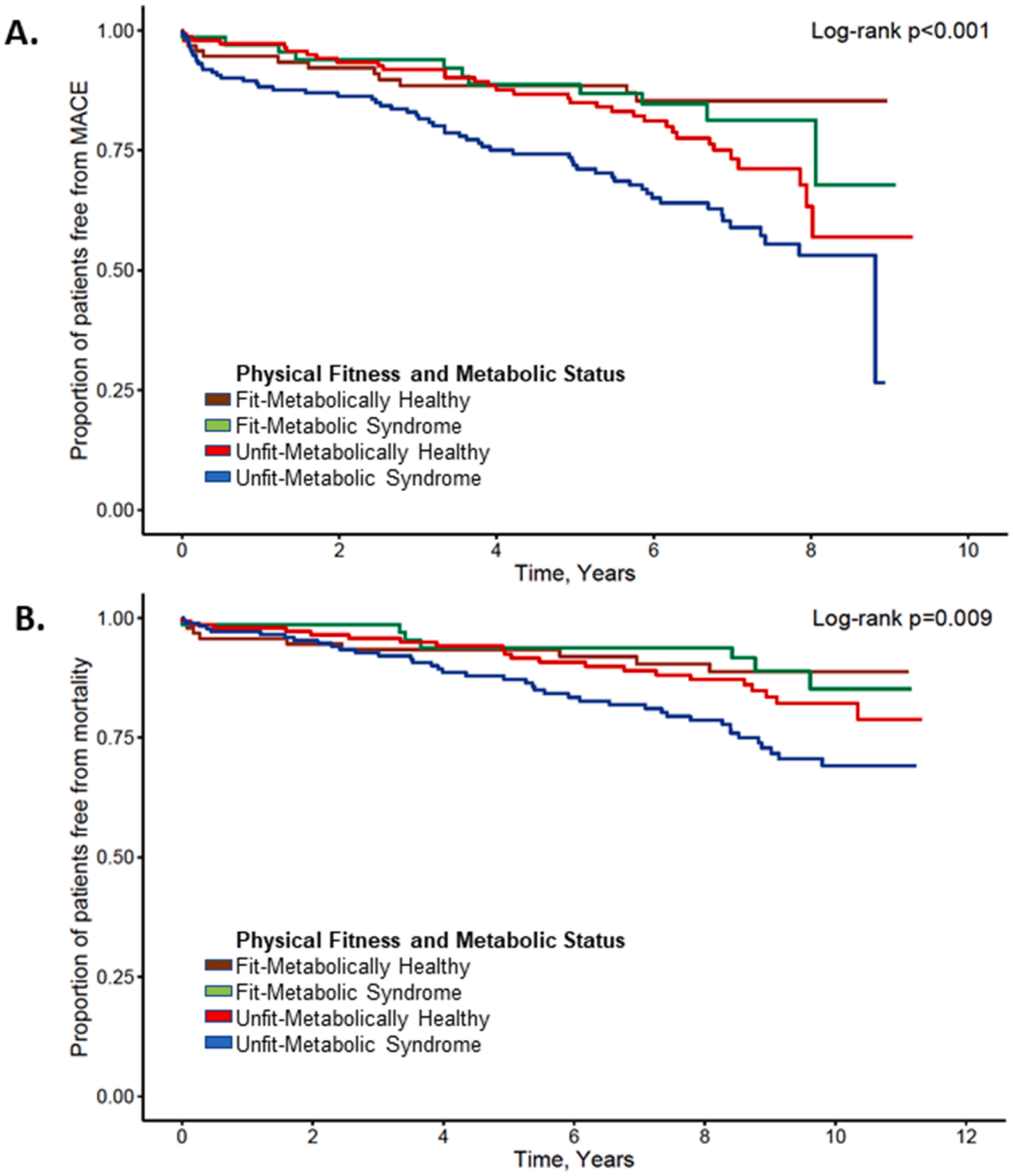

Fig. 1. Kaplan-Meier curves of MACE [A] and all-cause mortality [B] during long-term follow-up by fitness and metabolic syndrome.

community exercise programs, physician prescription for subsidized exercise programs that physicians can prescribe in patients at higher risk including those with metabolic syndrome and diabetes.

This study uses longitudinal data from a well-characterized cohort of women with signs and symptoms of ischemic heart disease undergoing coronary angiography. Despite this, limitations should be considered. Our prospective, observational study is limited in the assessment of causality. Because participants with poorer health are less likely to be fit, underlying disease may have introduced potential bias into our analyses; however, women with significant co-morbidities were excluded from the WISE cohort and we adjusted for significant comorbidities in our analyses. Although a tool based on self-reported assessment was used to measure fitness instead of a direct measure, these tools have been well validated in our cohort and others [23,38,39]. The study was based on baseline data collected at study entry and subsequent long-term cardiovascular events. Therefore, we cannot exclude the possibility that changes in fitness and metabolic risk profile over time could have influenced our results. For example, Andersen et al. showed that the association with physical activity and mortality can be underestimated by baseline measures of physical activity since they tend to decrease over time [30]. Small sample size may have underpowered our analyses, particularly mortality analyses. Further, survival bias due to lost to follow-up as result of an adverse event may have contributed to underestimation of longer-term adverse event rates.

5. Conclusions

To our knowledge, this is the first study to evaluate the association of fitness and metabolic syndrome without and with diabetes (dysmetabolism) with long-term cardiovascular outcomes and all-cause mortality in well-characterized high-risk cohort of women with signs and symptoms of ischemic heart disease. Unfit-metabolically healthy and fit-

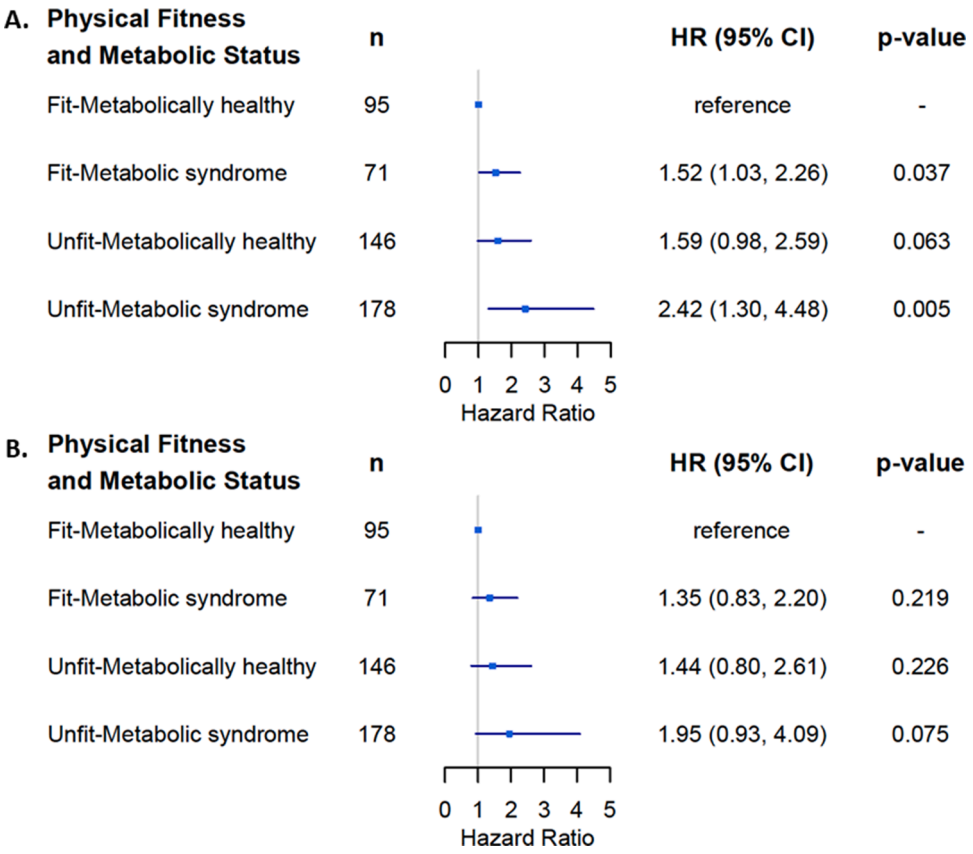

Fig. 2. Adjusted Risk of MACE [A] and all-cause mortality [B] during long-term follow-up in relation to fitness and metabolic syndrome.
Hazard ratios (HR) in relation to referent group (fit-metabolically healthy) adjusted for age, race, smoking, coronary artery disease severity, history of heart failure and hemoglobin in MACE and history of hormone replacement therapy in the mortality model.

metabolically unhealthy women were at higher risk of long-term MACE and mortality compared to fit-metabolically healthy women; and women who were unfit and metabolically unhealthy were at the highest risk. Our study demonstrates that metabolic health and fitness play an important role in outcomes that warrants further investigation.

Disclosures

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CRediT authorship contribution statement

Odayme Quesada: Conceptualization, Writing – original draft. **Marie Lauzon:** Formal analysis. **Rae Buttle:** Writing – review & editing. **Janet Wei:** Writing – review & editing. **Nissi Suppogu:** Writing – review & editing. **Galen Cook-Wiens:** Formal analysis. **Steven E. Reis:** Writing – review & editing. **Leslee J. Shaw:** Writing – review & editing. **George Sopko:** Writing – review & editing. **Eileen Handberg:** Writing – review & editing. **Carl J. Pepine:** Conceptualization, Methodology, Investigation, Writing – review & editing, Visualization, Supervision, Funding acquisition. **C. Noel Bairey Merz:** Conceptualization, Methodology, Investigation, Writing – review & editing, Visualization, Supervision, Funding acquisition.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Dr. C. Noel Bairey Merz reports financial support was provided by the National Heart, Lung and Blood Institute. Dr. C. Noel Bairey Merz reports financial support was provided by the National Institute on Aging. Dr. C. Noel Bairey Merz reports financial support was provided by the National Center for Research Resources. Dr. C. Noel Bairey Merz reports a relationship with iRhythm Technologies Inc that includes: board membership. Dr. C. Noel Bairey Merz, serves as Board of Director for iRhythm, fees paid through CSMC from Abbott Diagnostics and Sanofi. Dr. Janet Wei served on an advisory board for Abbott Vascular. Dr. Handberg reports grants from NIH/NHLBI, during the conduct of the study; grants from Aastom Biosciences, Amgen, Amorcyte, AstraZeneca, Biocardia, Boehringer Ingelheim, Brigham and Women's Hospital, Capricor, Cytori Therapeutics, Department of Defense, Direct Flow Medical, Duke Clinical Research Institute, East Carolina University, Everyfit Inc, Gilead, Ionis, Medtronic, Merck & Co., Mesoblast, PCORI, Relypsa, Sanofi Aventis, outside the submitted work. Dr. Pepine reports grants from NIH/NHLBI, during the conduct of the study; grants from NIH/NCATS, grants from BioCardia BC-14–001–02; Mesoblast, Inc.

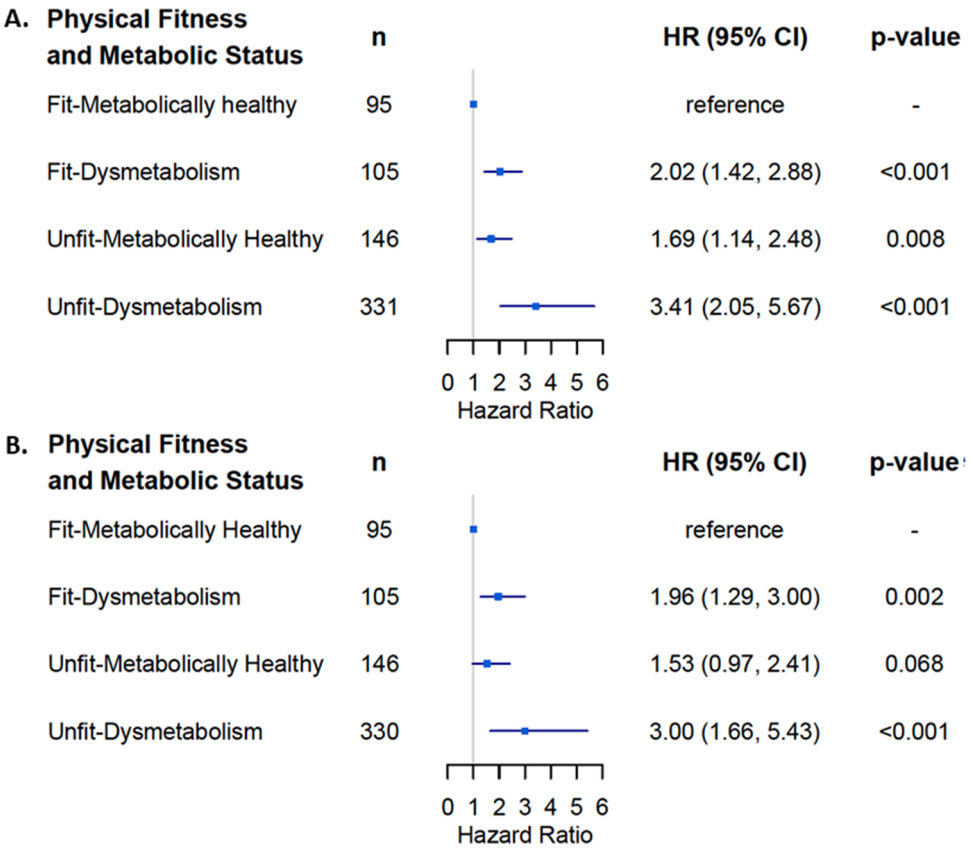
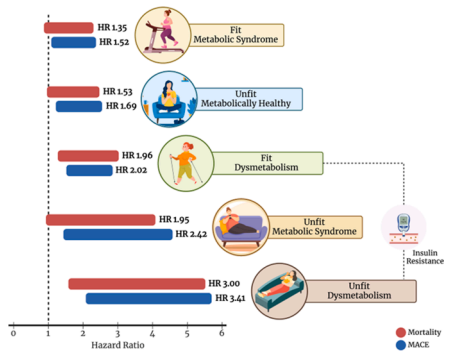


Fig. 3. Adjusted risk of MACE [A] and all-cause mortality [B] in relation to fitness and dysmetabolism.
Hazard ratios (HR) in relation to referent group (fit- metabolically healthy) adjusted for age, race, smoking, coronary artery disease severity, history of heart failure and hemoglobin in MACE and history of hormone replacement therapy in the mortality model.



Central Illustration. Risk of MACE and mortality by fitness and metabolic status.
Hazard ratios (HR) in relation to referent group (fit- metabolically healthy). Dysmetabolism defined as metabolic syndrome and/or diabetes.
Figure created using BioRender.com

MSB-MPC—CHF001; Ventrix, Inc.; Athersys Inc. AMI MultiStem; Verily Life Sciences LLC-Project Baseline OSMB; Ironwood MSB-MPC—CHF00-DMC, Imbria Pharmaceuticals Inc.; Milestone Pharmaceuticals Inc.; Caladrius Biosciences, Inc.; Gatorade Trust; and McJunkin Family Foundation, outside the submitted work.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ajpc.2023.100498.

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