Prognostic value of exercise capacity among patients with treated depression: The Henry Ford Exercise Testing (FIT) Project

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Background: Exercise capacity is associated with survival in the general population. Whether this applies to patients with treated depression is not clear.

Hypothesis: High exercise capacity remains associated with lower risk of all-cause mortality (ACM) and nonfatal myocardial infarction (MI) among patients with treated depression.

Methods: We included 5128 patients on antidepressant medications who completed a clinically indicated exercise stress test between 1991 and 2009. Patients were followed for a median duration of 9.4 years for ACM and 4.5 years for MI. Exercise capacity was estimated in metabolic equivalents of tasks (METs). Cox proportional hazards regression models were used.

Results: Patients with treated depression who achieved ≥12 METs (vs those achieving <6 METs) were younger (age 46 ± 9 vs 61 ± 12 years), more often male (60% vs 23%), less often black (10% vs 27%), and less likely to be hypertensive (51% vs 86%), have DM (9% vs 38%), or be obese (11% vs 36%) or dyslipidemic (45% vs 54%). In the fully adjusted Cox proportional hazard regression model, exercise capacity was associated with a lower ACM (HR per 1-MET increase in exercise capacity: 0.82, 95% CI: 0.79–0.85, \( P < 0.001 \)) and nonfatal MI (HR: 0.92, 95% CI: 0.87–0.97, \( P = 0.004 \)).

Conclusions: Exercise capacity had an inverse association with both ACM and nonfatal MI in patients with treated depression, independent of cardiovascular risk factors. These results highlight the potential impact of assessing exercise capacity to identify risk, as well as promoting an active lifestyle among treated depression patients.

KEYWORDS
All-Cause Mortality, Depression and Antidepressant Medications, Exercise Capacity, Nonfatal Myocardial Infarction, The Henry Ford Exercise Testing (FIT) Project

INTRODUCTION

Depression is the most common chronic psychiatric disorder, currently affecting 1 in every 20 individuals worldwide.\(^1\)\(^–\)\(^3\) About 15.7 million adults are being treated for depression in the United States.\(^4\) This disorder is not only associated with premature mortality and morbidity, but also with increased sedentary lifestyle and utilization of healthcare resources.\(^5\)\(^,\)\(^6\) In particular, patients with depression are at >2-fold increased risk of suicide, cardiac mortality, and sudden cardiac death.\(^7\)\(^,\)\(^8\) Depressive symptoms are also associated with increased risk of coronary heart disease (CHD).\(^9\)\(^,\)\(^10\) Exercise has shown to beneficially impact the depressive symptoms.\(^5\)\(^,\)\(^11\)\(^,\)\(^12\)

Several studies evaluated the prognostic significance of exercise capacity.\(^13\) Reduced exercise capacity is associated with increased
risk of all-cause mortality (ACM) and nonfatal myocardial infarction (MI), independent of exercise-limiting risk factors.\textsuperscript{14,15} However, there are limited data addressing the prognostic value of exercise capacity among treated depression patients. This relationship is important to study, as it could help in improving the outcomes of patients affected by this major health care problem.\textsuperscript{16,17}

Therefore, we tested the hypothesis that exercise capacity is inversely associated with risk of ACM and nonfatal MI among treated depression patients.

2 | METHODS

2.1 | Study design

The Henry Ford Exercise Testing (FIT) Project is the largest project to date that combined the use of directly measured exercise data and estimates of physical exercise capacity. It is a retrospective cohort including 69,885 patients from Henry Ford Health System in southeastern Michigan who were referred for clinically indicated treadmill exercise stress testing between January 1991 and May 2009. Detailed study methods and design have been published elsewhere.\textsuperscript{18} Briefly, patients age > 18 years who underwent treadmill exercise stress testing following the Bruce protocol were included. Baseline characteristics including patient demographics, known medical history, other related risk factors, and current medications used (including antidepressant therapies) were obtained by trained nurses and exercise physiologists at the time of the testing. Furthermore, additional clinical information was collected by review of the electronic medical records.

The study data were collected retrospectively after obtaining local ethical approval, and informed consent was waived. This project was approved by Henry Ford Health System Institutional Review Board.

2.2 | Inclusion criteria and patient characteristics

In this analysis, we included patients who received antidepressant medications during their lifetime and completed a clinically indicated exercise stress test (N = 5128). Hypertension was defined as current use of antihypertensive medication or use of any antihypertensive medications. Diagnosis of prior diabetes mellitus (DM) was made by prior history of DM or use of hypoglycemic medications. Dyslipidemia was defined by use of lipid-lowering medication or prior diagnosis of a major lipid abnormality. Coronary artery disease (CAD) was defined by a prior diagnosis of MI, percutaneous coronary intervention, coronary artery bypass surgery, or coronary angiography with evidence of obstructive CAD (≥70% lumen stenosis).

2.3 | Exercise treadmill stress testing

The treadmill stress testing was done following American College of Cardiology/American Heart Association (ACC/AHA) guidelines using the standard Bruce protocol.\textsuperscript{19} Tests were terminated by the supervising physician if serious arrhythmias, abnormal hemodynamic response, diagnostic ST-segment changes, or exercise-limiting symptoms of chest pain or shortness of breath occurred. At the initiation of the test, resting heart rate and blood pressure were obtained. The maximal predicted heart rate (MPHR) was calculated based on the formula (220 – age). The target heart rate was considered 85% of the MPHR. Exercise capacity was expressed as metabolic equivalents of task (METs) and was categorized into 4 groups: <6 METs, 6 to <10 METs, 10 to 12 METs, and > 12 METs.

2.4 | Primary and secondary outcomes

The primary outcome of this analysis was ACM, ascertained in April 2013 via a search of the Social Security Death Index (SSDI) Death Master File (DMF) using Social Security number, first name, last name, and date-of-birth data. A complete algorithmic search of the SSDI DMF was completed in >99.5% of patients.

The secondary outcome of this analysis was nonfatal MI, ascertained in May 2010 through linkage with administrative claim files from services delivered in the Henry Ford Health System. Linkage was performed using appropriate International Classification of Diseases, Ninth Edition codes. To limit biases associated with loss to follow-up, patients were censored for nonmortality outcomes at their last contact with the integrated Henry Ford Health System group practice. Follow-up for MI events was available through May 2010.

2.5 | Statistical analysis

Continuous data are presented as mean ± SD and compared using 1-way ANOVA; then, post hoc analyses with the Bonferroni test were run to confirm where the differences occurred between groups. Categorical data are presented as percentage frequencies and compared between groups by the \( \chi^2 \) or Fisher exact test, as appropriate. Kaplan–Meier survival curves were computed for those with and without the events across exercise capacity groups and were compared using the log-rank test.

Multivariable Cox proportional hazard regression models were used to compute hazard ratios (HRs) and 95\% confidence intervals (CIs) of the independent predictors. The primary analysis was to assess the association between METs achieved (as METs groups and per 1-MET increase) and ACM after adjusting for 3 models. Subsequently, age, sex, race (baseline model), history of risk factors, medications, and reason referred for a stress test (model 2), and known CAD (model 3).\textsuperscript{13} The secondary analysis was used to assess the association between METs achieved (as METs groups and per 1-MET increase) and nonfatal MI after adjusting for the same models. Selection of variables for entry consideration was based on expertise of the investigators, clinical judgment, and the results of previous publications.\textsuperscript{12,20} In addition, effect modification on the results was assessed for the covariates of age, sex, and race. The \( P \) values for effect of modification were determined via Wald tests and \( F \) statistics. The \( P \) value was considered significant at <0.05. Statistical analyses were performed using SAS version 9.3 (SAS Institute, Inc., Cary, NC) and Stata version 14 (StataCorp LP, College Station, TX).
RESULTS

Table 1 shows the baseline characteristics of the study cohort. The mean age was 53.3 ± 11.0 years, and 67% were female. The mean peak METs achieved was 8.5 ± 2.8. Overall, patients who achieved high METs (≥12 METs, vs <6 METs) were younger (46.3 ± 9 years vs 61.0 ± 12 years, respectively; \(P < 0.001\)), more often male (59.4% vs 22.6%, respectively; \(P < 0.001\)), and had lower body mass index (25.7 ± 4 kg/m² vs 32.2 ± 8 kg/m², respectively; \(P < 0.001\)). Additionally, patients with poor METs achieved (<6 METs, vs ≥12 METs) were more often hypertensive (86.4% vs 50.6%, respectively; \(P < 0.001\)), had DM (38.0% vs 8.9%, respectively; \(P < 0.001\)) and dyslipidemias (54.2% vs 44.6%, respectively; \(P < 0.001\)), were obese (36.1% vs 11.0%, respectively; \(P < 0.001\)), and had more often a prior revascularization procedure (either percutaneous coronary intervention [7.0% vs 2.5%] or coronary artery bypass grafting [6.3% vs 0.8%], \(P < 0.001\); Table 1).

Over a median follow-up period of 9.4 years (interquartile range, 7.0–11.5 years), 551 (10.6%) patients developed ACM; and after a median follow-up period of 4.5 years (interquartile range, 2.3–6.9 years), 199 (3.8%) patients developed nonfatal MI. The proportion of ACM and nonfatal MI was inversely related with METs achieved in patients with treated depression. The poor-exercise-capacity group (<6 METs) was associated with a minimum 7-fold increase in the proportion of ACM and nonfatal MI (Figure 1).

Kaplan–Meier survival curves showed event-free survival during the period of follow-up stratified by their METs achieved in Figure 2. Better survival and fewer events (ACM and nonfatal MI) was associated with higher exercise capacity achieved.

In the fully adjusted Cox proportional hazard models, exercise capacity was associated with lower ACM and nonfatal MI risk per 1-MET increase to 17% and 7%, respectively (Table 2). Effect modification was assessed for age, sex, and race between exercise capacity and study ACM, which did not show a significant interaction between them (Table 3).

DISCUSSION

To the best of our knowledge, this is the first and largest analysis that has examined association of objectively determined exercise capacity...
Prior literature has shown that higher exercise capacity was associated with lower risk of depressive symptoms. It is also known that higher exercise capacity is one of the strongest negative risk factors of ACM and nonfatal MI in the general population.8 Our current study adds to the literature related to CHD prevention in patients with depression by showing a strong, consistent, and inverse relationship of increased exercise capacity with lower risk of ACM and nonfatal MI. This decrease in risk is on the order of 80% lower than in patients with poor exercise capacity. In addition, prior studies used a self-reported questionnaire for determining exercise capacity and were mostly limited to females. In contrast, our findings were consistent across various age groups, both sexes, and diverse ethnicities (Table 3).

In patients who already have prevalent depression requiring therapy, high exercise capacity was associated improved survival.26 This may imply that physical interventions to improve exercise capacity could be utilized as a primary and secondary preventive in depression management. Targeted level of exercise as a part of multidisciplinary therapy for patients who suffer depression may be needed with efforts to advocate active lifestyle and increase exercise capability.5 Multiple hypotheses have been presented to address the depression-exercise relationship.5,37 Autonomic dysfunction and increased levels of systemic inflammation have been shown to contribute to increased risk of CHD among patients with depression.38 Poor heart rate variability is also known to occur among patients with depression, which could contribute to CHD.39 Exercise improves autonomic dysfunction, heart rate variability, and inflammatory markers, and therefore it could potentially improve CHD outcome.40,41 In addition, exercise leads to release of endorphins that could improve mood and enhance the sense of well-being.42 Endorphins could further improve physical function and exercise capacity in return, and thus lead to decrease in arterial stiffness and, hence, improved endothelial

### TABLE 2  
Cardiorespiratory fitness and antidepressant medication use

<table>
<thead>
<tr>
<th>METs Achieved</th>
<th>Model 1a</th>
<th>Model 2b</th>
<th>Model 3c</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6 METs</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>6–9 METs</td>
<td>0.40 (0.33–0.50)</td>
<td>0.45 (0.37–0.56)</td>
<td>0.48 (0.39–0.59)</td>
</tr>
<tr>
<td>10–11 METs</td>
<td>0.22 (0.17–0.28)</td>
<td>0.25 (0.19–0.33)</td>
<td>0.27 (0.21–0.36)</td>
</tr>
<tr>
<td>≥12 METs</td>
<td>0.14 (0.09–0.21)</td>
<td>0.16 (0.10–0.26)</td>
<td>0.18 (0.11–0.29)</td>
</tr>
<tr>
<td>P-trend</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Per 1-MET increase</td>
<td>0.80 (0.77–0.82)</td>
<td>0.82 (0.79–0.85)</td>
<td>0.83 (0.80–0.86)</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

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<thead>
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<td>&lt;6 METs</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>6–9 METs</td>
<td>0.51 (0.35–0.72)</td>
<td>0.56 (0.39–0.81)</td>
<td>0.82 (0.57–0.20)</td>
</tr>
<tr>
<td>10–11 METs</td>
<td>0.39 (0.26–0.58)</td>
<td>0.47 (0.31–0.71)</td>
<td>0.76 (0.50–1.16)</td>
</tr>
<tr>
<td>≥12 METs</td>
<td>0.18 (0.09–0.37)</td>
<td>0.24 (0.12–0.49)</td>
<td>0.43 (0.20–0.89)</td>
</tr>
<tr>
<td>P-trend</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.047</td>
</tr>
<tr>
<td>Per 1-MET increase</td>
<td>0.84 (0.80–0.89)</td>
<td>0.87 (0.82–0.92)</td>
<td>0.93 (0.88–0.99)</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.024</td>
</tr>
</tbody>
</table>

Abbreviations: ACM, all-cause mortality; ASA, acetylsalicylic acid (aspirin); CAD, coronary artery disease; CI, confidence interval; CVD, cardiovascular disease; DM, diabetes mellitus; HR, hazard ratio; HTN, hypertension; MET, metabolic equivalent of task; MI, myocardial infarction; Ref, reference. P-trend provided testing trend of the HR across all METs groups.

a Adjusted for age, sex, and race.

b Adjusted for variables of model 1. history of risk factors (sedentary lifestyle, HTN, smoking, obesity, DM, family history of CVD and dyslipidemia), medications (ASA, β-blockers, statins, and pulmonary medication use), and reason referred for a stress test (symptoms, risk factors, preoperative assessment, or screening).

c Adjusted for variables of model 2 and known CAD.

with mortality and cardiac morbidity among patients with treated depression. We show that, in this population, higher exercise capacity was associated with lower risk of ACM and nonfatal MI.

Prior literature has shown that higher exercise capacity was associated with lower risk of depressive symptoms.21 It is also known that higher exercise capacity is one of the strongest negative risk factors of ACM and nonfatal MI in the general population. Depression is one of the important risk factors of CHD (HR for CHD mortality for depression: 2.33, 95% CI: 1.47–3.70), independent of other cardiac risk factors.22–24 The addition of depression as a risk factor to the Framingham risk score among individuals free of CAD at baseline improved the accuracy to predict CHD.25 Recent data suggested that exercise, either as monotherapy or in combination with antidepressant medication, was associated with decreased relapse rate, depending on the depression severity and associated symptoms.26–28 Though some studies focused on exercise monotherapy,29–32 others evaluated exercise as an adjuvant therapy to medical treatment.33–35 However, mortality and CHD outcomes had not been studied before in this specific population.8 Our current study adds to the literature related to CHD prevention in patients with depression by showing a strong, consistent, and inverse relationship of increased exercise capacity with lower risk of ACM and nonfatal MI. This decrease in risk is on the order of 80% lower than in patients with poor exercise capacity. In addition, prior studies used a self-reported questionnaire for determining exercise capacity and were mostly limited to females.8 In contrast, our findings were consistent across various age groups, both sexes, and diverse ethnicities (Table 3).

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### FIGURE 1  
All-cause mortality and nonfatal MI rate across treated depression patients. Abbreviations: MET, metabolic equivalents of task; MI, myocardial infarction
function. Improved endothelial function has shown to be associated with decreased risk of CHD. Additionally, a recent meta-analysis highlighted that brain structural changes associated with depression, such as volumetric reduction of certain areas and loss of networks integrity in between, might be enhanced by exercise treatment. Nevertheless, these relationships will need further exploration in the future.

We now know from this study that exercise capacity in patients on antidepressant treatment confers a survival benefit. Because CHD is a major contributor to mortality among these patients, a concerted effort to improve exercise capacity should be employed in patients diagnosed with depression. Patients with depression are frequently seen in cardiology clinics, but a discussion about their exercise capacity is not a part of formal lifestyle-modification counseling. Results of this study suggest that improving exercise capacity should be part of preventive cardiac care.

4.1 Study limitations

Our study is not without limitations. First, the data were retrospectively obtained from electronic medical records and claims data and could potentially suffer from misclassification bias. Additionally, we might have underestimated the number of patients with depression that were not on medical therapy in the same healthcare system. We adjusted for several cardiovascular risk factors in the analyses; however, in observational studies, the residual confounding cannot be entirely excluded. We also did not have treatment doses or types of antidepressant medications available. We also did not have information on changes in depression medications, electroconvulsive therapy sessions, other psychiatric comorbidities, medication compliance, severity of depression, illicit drug use, or behavioral therapy sessions, which could act as confounders. In addition, we did not have data about the socioeconomic background of the patients, which may have had some impact on the outcomes. The impact of exercise may vary according to other unmeasured factors, such as level of education and others. Despite all these limitations, the current study provides the largest study that suggests a strong beneficial relationship between exercise capacity and ACM and nonfatal MI in a large cohort of patients treated with antidepressants.

5 Conclusion

Exercise capacity had an inverse association with both ACM and nonfatal MI in patients with treated depression. Our study highlights the importance of exercise-capacity assessment among treated depression.
patients to identify individuals at risk for ACM and nonfatal MI. Improvement in exercise capacity should be part of lifestyle modification, and future studies should focus on therapies that could improve exercise capacity among patients with depression.

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Conflicts of interest

The authors declare no potential conflicts of interest.

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