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ABSTRACT

PURPOSE: We conducted this study to investigate the association of cardiorespiratory fitness and all-cause mortality among patients with chronic kidney disease.

METHODS: We studied a retrospective cohort of patients from the Henry Ford Health System who underwent clinically indicated exercise stress testing with baseline cardiorespiratory fitness and estimated glomerular filtration rate measurement. Cardiorespiratory fitness was expressed as metabolic equivalents of task, and kidney function was categorized into stages according to estimated glomerular filtration rate. Multivariable-adjusted Cox proportional hazard models were used to examine the association between metabolic equivalents of task and all-cause mortality among patients with chronic kidney disease stages 3-5. Discrimination of mortality was assessed using receiver operating characteristic curves, while reclassification was evaluated using net reclassification index (NRI).

RESULTS: Among 50,121 participants, the mean age was 55 ± 12.6 years; 47.5% were women, 64.5% were white, and 6877 (13.7%) participants had chronic kidney disease stage 3-5. Over a median follow-up of 6.7 years, 6308 participants died (12.6%). Each 1-unit higher metabolic equivalents of task was associated with a significant 15% reduction in all-cause mortality (hazard ratio 0.85; 95% confidence interval [CI], 0.84-0.87). Metabolic equivalents of task improved discriminatory ability of mortality prediction when added to traditional risk factors and estimated glomerular filtration rate (area under the curve 0.7996; 95% CI, 0.789-0.810 vs 0.759; 95% CI, 0.748-0.770, respectively; P < .001). The addition of metabolic equivalents of task to traditional risk factors resulted in significant reclassification (6% for events, 5% for non-events: NRI = 0.13, P < .001).

CONCLUSIONS: Cardiorespiratory fitness improves mortality risk prediction among patients with chronic kidney disease. Cardiorespiratory fitness provides incremental prognostic information when added to traditional risk factors and may help guide treatment options among patients with renal dysfunction.

KEYWORDS: Cardiorespiratory fitness; Chronic kidney disease

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INTRODUCTION
Chronic kidney disease, which affects 10%-13% of the US population, is universally regarded as a major contributor to health care costs through significant effects on morbidity and mortality.1,2 Renal dysfunction predisposes patients to adverse cardiovascular disease outcomes through multiple pathophysiologic pathways. However, widely used cardiovascular disease risk calculators may not be well calibrated in this patient population, as individuals with chronic kidney disease were not well represented in the derivation cohorts used to construct these risk calculators. The addition of estimated glomerular filtration rate and albumin-to-creatinine ratio to traditional cardiovascular disease risk factors in patients with chronic kidney disease has been shown to improve the predictive accuracy of cardiovascular disease events.3,4 Therefore, additional efforts are needed to identify novel risk factors to refine prognostication in this patient population.

Cardiorespiratory fitness is an objective physiologic measure that describes the capacity of an individual’s circulatory and respiratory systems to transport and utilize oxygen in the metabolically active skeletal muscle during exercise. Importantly, it is an integrative measure influenced by several factors including physical activity habits, obesity, genetics, and traditional risk factors. Over the past 4 decades, numerous studies have demonstrated a favorable effect of cardiorespiratory fitness on long-term adverse outcomes.5-12 Higher cardiorespiratory fitness is associated with a reduction in cardiovascular disease risk factors, major adverse cardiac events, and overall mortality.13,14 Prior studies have shown that exercise leads to improved functioning in patients with chronic kidney disease.15-18 Poor cardiorespiratory fitness among patients with renal dysfunction is independently associated with a high burden of cardiovascular risk factors in addition to increased aortic stiffness, increased left ventricle afterload, and poor left ventricular function, providing a milieu of increased overall cardiovascular risk.19

To date, little is known about the prognostic significance of cardiorespiratory fitness in patients with chronic kidney disease. We aimed to evaluate the prognostic value of cardiorespiratory fitness for predicting mortality among patients with renal dysfunction. We hypothesized that cardiorespiratory fitness would provide incremental value to traditional risk factors in predicting mortality in this high-risk patient population. As chronotropic incompetence may contribute to low cardiorespiratory fitness, we also examined the interrelationship between chronotropic incompetence and cardiorespiratory fitness among patients with chronic kidney disease.

METHODS

Study Cohort
The Henry Ford Exercise Testing Project (FIT Project) is a retrospective cohort study that examined the long-term prognostic implications of cardiorespiratory fitness in an ethnically diverse cohort. The FIT Project consists of 69,885 patients who underwent physician-referred treadmill stress testing between 1991 and 2009. Study details have been previously described.20 The FIT project was approved by the Henry Ford Hospital Institutional Review Board.

Exclusion Criteria
Patients were excluded if they were <18 years old or if the testing protocol was not the standard Bruce protocol. We further excluded patients who had a history of heart failure (defined as prior clinical diagnosis of systolic or diastolic heart failure; n = 1579) and patients missing relevant covariate data, including creatinine (n = 17,434) or metabolic equivalents of task (n = 751).

Assessment of Outcomes
The primary end point of our analysis was all-cause mortality, which was verified through the Social Security Death Index master file using each patient’s social security number, first name, last name, and date of birth. The annualized mortality rate for each group was calculated by dividing the observed mortality rate during the follow-up duration by the mean follow-up time for the group. Secondary outcomes included major adverse cardiac events (defined as myocardial infarction or revascularization), which were ascertained through June 2010 using administrative claims files from services delivered by the affiliated group practice or reimbursed by the health plan. Linkage was performed using relevant International Statistical Classification of Diseases and Related Health Problems, ninth revision (410.xx). To minimize bias from loss to follow-up, patients were censored at their last contact with the Henry Ford Health System when ongoing coverage with the health plan could no longer be confirmed.

Treadmill Stress Testing and Metabolic Equivalents of Task
All patients underwent clinically indicated, symptom-limited maximal treadmill stress testing following the standard Bruce protocol and administered by clinical exercise physiologists or registered nurses. For individuals with repeat stress testing during the data collection period, only the
6 to 10, 10 to 12, and previous documented obstructive coronary heart disease by coronary intervention, coronary artery bypass surgery, or defined as previous myocardial infarction, percutaneous lipid-lowering medications, or a database-verified diagnosis of a previous diagnosis of any major lipid abnormality, use of verified diagnosis of diabetes. Dyslipidemia was defined by diabetes, use of hypoglycemic medications, or a database-verified diagnosis of diabetes. Renal insufficiency was defined as chronic kidney disease stage 3 or greater. Creatinine measurements were collected from the electronic patient record and the test conducted closest to the date of the stress test. The formula to calculate the estimated glomerular filtration rate was 180 × (标准化 serum creatinine / 1.73)². We evaluated the association between metabolic variables and cardiovascular outcomes using Cox proportional hazard models. The association between metabolic variables and cardiovascular outcomes was assessed using the National Kidney Foundation classification of kidney function.

Additional sensitivity analyses were conducted to determine the association between metabolic variables and cardiovascular outcomes. The Kaplan-Meier method was used to compare survival curves. The hazard ratio was obtained from the Cox proportional hazards model.

Assessment of Covariates

Details on medical history including age, sex, race, anthropomorphic data, cardiovascular risk factors, past medical history, and active medication use were obtained by nurses or exercise physiologists immediately prior to stress testing. The metabolic equivalent of task (MET) was calculated as the ratio of peak oxygen uptake to the predicted oxygen uptake at rest. The MET cutoffs used were 1.5 (low), 3.0 (moderate), and 5.0 (high).

Assessment of Renal Function

Creatinine measurements were collected from the electronic patient record and the test conducted closest to the date of the stress test. The formula to calculate the estimated glomerular filtration rate was 180 × (标准化 serum creatinine / 1.73)². We evaluated the association between metabolic variables and cardiovascular outcomes using Cox proportional hazard models. The association between metabolic variables and cardiovascular outcomes was assessed using the National Kidney Foundation classification of kidney function.

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history of smoking, statin use, aspirin use, beta-blocker use, glomerular filtration rate, and metabolic equivalents of task.

A P value < .05 was considered statistically significant. Statistical analyses were performed using SPSS (version 21.0; IBM Inc., Chicago, Ill) and STATA (IC Version 16; StataCorp, College Station, Texas). The analyzing software considered the correlated estimates of the model performance, given that the same dataset was used for comparison of the concordance statistics and in calculating the AUC. Of note, AUC for time-dependent receiver operating characteristic analysis has also been utilized successfully in several other publications.24

RESULTS

Baseline Characteristics

A total of 50,121 patients (mean age 55 ± 13 years, 48% female, and 29% black) were included in the analysis. Baseline characteristics of the study cohort are summarized in Table 1. Patients in higher chronic kidney disease stages were more often women, white, and had a high burden of cardiovascular risk factors including diabetes mellitus, hypertension, hyperlipidemia, and prior myocardial infarction (P < .001). The prevalence of cardioprotective medication use including cholesterol-lowering agents, beta-blockers, aspirin, diuretics, angiotensin-converting enzyme inhibitors, and aldosterone receptor blockers was higher among patients with higher chronic kidney disease stages (P < .001) (Table 2).

Outcomes

Over a median follow-up period of 6.7 years (25th to 75th percentiles; 3.9 to 10 years), 6308 patients (12.6%) died. The rate of death increased with worsening renal function, with the highest percentage seen in those with advanced renal disease (annualized death rate = 1.4%, 1.6%, 3.7%, and 9.8% for chronic kidney disease stage 1, 2, 3, and 4/5, respectively, P < .001).

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Table 1. Baseline Characteristics of the Study Cohort According to Chronic Kidney Disease Stages

<table>
<thead>
<tr>
<th>Chronic Kidney Disease</th>
<th>Total</th>
<th>Stage 1 CKD eGFR ≥90</th>
<th>Stage 2 CKD eGFR 60-89</th>
<th>Stage 3 CKD eGFR 30-59</th>
<th>Stage 4/5 CKD eGFR &lt; 30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>54 (46, 64)</td>
<td>50 (41, 65)</td>
<td>55 (48, 64)</td>
<td>65 (55, 73)</td>
<td>62 (51, 72)</td>
</tr>
<tr>
<td>Female sex</td>
<td>23,790 (47.5)</td>
<td>6189 (47.6)</td>
<td>13,993 (46.3)</td>
<td>3148 (53)</td>
<td>190 (44.4)</td>
</tr>
<tr>
<td>Race</td>
<td>32,342 (64.5)</td>
<td>6049 (46.6)</td>
<td>21,225 (70.2)</td>
<td>4875 (75.6)</td>
<td>219 (51.2)</td>
</tr>
<tr>
<td>White</td>
<td>14,329 (28.6)</td>
<td>5899 (45.4)</td>
<td>6968 (23)</td>
<td>1243 (19.3)</td>
<td>16 (3.7)</td>
</tr>
<tr>
<td>Black</td>
<td>3450 (6.9)</td>
<td>1042 (8)</td>
<td>2061 (6.8)</td>
<td>331 (5.1)</td>
<td>283 (6.3)</td>
</tr>
<tr>
<td>Other</td>
<td>28.7 (25.3)</td>
<td>29.3 (26.9)</td>
<td>30.8 (25.3)</td>
<td>38.2 (24.3)</td>
<td>28.3 (24.3)</td>
</tr>
<tr>
<td>Resting heart rate</td>
<td>73 (± 12.6)</td>
<td>74 (± 12.7)</td>
<td>72 (± 12.5)</td>
<td>71 (± 12.7)</td>
<td>73 (± 14.3)</td>
</tr>
<tr>
<td>Peak systolic blood</td>
<td>178 (± 27)</td>
<td>177 (± 27.3)</td>
<td>179 (± 26.5)</td>
<td>176 (± 27.8)</td>
<td>177 (± 33.7)</td>
</tr>
<tr>
<td>pressure (mm Hg)</td>
<td>Medical history</td>
<td>Diabetes</td>
<td>10,766 (21.5)</td>
<td>2837 (21.8)</td>
<td>1591 (19.5)</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td>33,844 (67.5)</td>
<td>8115 (62.5)</td>
<td>19,977 (66)</td>
<td>5332 (82.7)</td>
</tr>
<tr>
<td></td>
<td>Hyperlipidemia</td>
<td>24,202 (48.3)</td>
<td>5110 (39.3)</td>
<td>15,126 (41.5)</td>
<td>2534 (39.3)</td>
</tr>
<tr>
<td></td>
<td>History of smoking</td>
<td>21,325 (42.5)</td>
<td>6064 (46.7)</td>
<td>12,544 (41.5)</td>
<td>2534 (39.3)</td>
</tr>
<tr>
<td></td>
<td>Prior myocardial infarction</td>
<td>5092 (10.2)</td>
<td>1243 (9.6)</td>
<td>2744 (9.1)</td>
<td>983 (15.2)</td>
</tr>
<tr>
<td></td>
<td>Prior coronary artery disease</td>
<td>6422 (12.8)</td>
<td>1486 (11.4)</td>
<td>3485 (11.5)</td>
<td>1305 (20.2)</td>
</tr>
<tr>
<td></td>
<td>Prior coronary artery angioplasty</td>
<td>2288 (4.6)</td>
<td>510 (3.9)</td>
<td>1265 (4.2)</td>
<td>486 (7.5)</td>
</tr>
<tr>
<td></td>
<td>Prior CABG</td>
<td>1632 (3.3)</td>
<td>309 (2.4)</td>
<td>852 (2.8)</td>
<td>432 (6.7)</td>
</tr>
<tr>
<td>METs equivalents of task achieved:</td>
<td>METs &lt;6</td>
<td>7851 (15.7)</td>
<td>1595 (12.3)</td>
<td>4119 (13.6)</td>
<td>1895 (29.4)</td>
</tr>
<tr>
<td></td>
<td>METs 6-10</td>
<td>14,457 (28.8)</td>
<td>3652 (28.1)</td>
<td>8452 (27.9)</td>
<td>2229 (34.6)</td>
</tr>
<tr>
<td></td>
<td>METs 10-12</td>
<td>17,931 (35.8)</td>
<td>4937 (38)</td>
<td>11220 (37.1)</td>
<td>1718 (26.6)</td>
</tr>
<tr>
<td></td>
<td>METs ≥12</td>
<td>9882 (19.7)</td>
<td>2806 (21.6)</td>
<td>6463 (21.4)</td>
<td>607 (9.4)</td>
</tr>
</tbody>
</table>

BMI = body mass index; CABG = coronary artery bypass grafting; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; METs = metabolic equivalents of task.

All categorical data presented as total number (%), and continuous data presented as mean (standard deviation) or median (25th, 75th), as appropriate.
There was an incrementally higher risk of mortality with lower metabolic equivalents of task achieved across each chronic kidney disease category. For example, the annualized death rate was 10.4% vs 0.1% for metabolic equivalents of task $<6$ vs $\geq 12$ among patients with chronic kidney disease stage 4/5; $P < .001$ (Figure 1). The cumulative risk of mortality and major adverse cardiovascular events was higher among patients with chronic kidney disease stage 3 and greater, and also higher among those who did not achieve 85% of predicted target heart rate. Patients with at least chronic kidney disease stage 3 who did not achieve target heart rate had the worst survival for these outcomes (Figure 2).

### Table 2  Medication Use Across Chronic Kidney Disease Stages

<table>
<thead>
<tr>
<th>Medications:</th>
<th>Total</th>
<th>Stage 1 CKD</th>
<th>Stage 2 CKD</th>
<th>Stage 3 CKD</th>
<th>Stage 4/5 CKD</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medications:</td>
<td></td>
<td>eGFR $\geq$ 90 mL/min/1.73 m$^2$</td>
<td>eGFR 60-89 mL/min/1.73 m$^2$</td>
<td>eGFR 30-59 mL/min/1.73 m$^2$</td>
<td>eGFR $&lt;30$ mL/min/1.73 m$^2$</td>
<td></td>
</tr>
<tr>
<td>$\beta$-blocker</td>
<td>50,121</td>
<td>2549 (19.6)</td>
<td>6351 (21)</td>
<td>2193 (34)</td>
<td>167 (39)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Ca channel blocker</td>
<td>6903 (13.8)</td>
<td>1494 (11.5)</td>
<td>3843 (12.7)</td>
<td>1370 (21.2)</td>
<td>196 (45.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>10,235 (20.4)</td>
<td>2262 (17.4)</td>
<td>5877 (19.4)</td>
<td>1945 (30.2)</td>
<td>151 (35.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ARBs</td>
<td>1659 (3.3)</td>
<td>308 (2.4)</td>
<td>923 (3.1)</td>
<td>386 (6)</td>
<td>42 (9.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diuretics</td>
<td>10,698 (21.3)</td>
<td>2123 (16.3)</td>
<td>6000 (19.8)</td>
<td>2387 (37)</td>
<td>188 (43.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Aspirin</td>
<td>10,529 (21)</td>
<td>2499 (19.2)</td>
<td>6117 (20.2)</td>
<td>1779 (27.6)</td>
<td>134 (31.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cholesterol-lowering agents</td>
<td>13,111 (26.2)</td>
<td>2549 (19.6)</td>
<td>7997 (26.4)</td>
<td>2418 (37.5)</td>
<td>147 (34.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Insulin</td>
<td>1957 (3.9)</td>
<td>523 (4)</td>
<td>924 (3.1)</td>
<td>419 (6.5)</td>
<td>91 (21.3)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

ACE = angiotensin-converting enzyme; ARBs = angiotensin receptor blockers; Ca = calcium; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate.

All data are categorical and they presented as total number (%).

### Figure 1  Annualized mortality incidence rates (%) for the association of estimated glomerular filtration rates (GFR) and mortality stratified by cardiorespiratory fitness assessed using metabolic equivalents of task (Metabolic equivalents of task; unadjusted data).

CKD = chronic kidney disease; METs = metabolic equivalents of task.

### Multivariate Survival Analysis

There was a significantly lower risk of overall adjusted mortality with higher metabolic equivalents of task achieved among patients with chronic kidney disease (Table 3). For example, the adjusted hazard ratio (HR) (95% confidence interval [CI]) among those who attained $\geq 12$ metabolic equivalents of task, compared with those who attained $<6$, was 0.18 (0.12-0.28). Each 1 unit higher metabolic equivalents of task was associated with a significant 15% reduction in all-cause mortality (HR 0.85; 95% CI, 0.84-0.87).
Mortality Risk Discrimination and Reclassification

Metabolic equivalents of task improved the discriminatory ability for mortality prediction when added to traditional risk factors and estimated glomerular filtration rate (AUC 0.7996; 95% CI, 0.789-0.810 vs 0.759; 95% CI, 0.748-0.770, respectively, \( P < .001 \)). The addition of metabolic equivalents of task to traditional risk factors resulted in significant reclassification of mortality (6% for events, 5% for non-events: NRI = 0.13, \( P < .001 \)).

Sensitivity Analyses

The inclusion of stage 2 in our definition of chronic kidney disease demonstrated similar results with a graded inversely associated between higher metabolic equivalents of task and lower risk of all-cause mortality (Supplementary Table 1). In general, we found a consistent association between metabolic equivalents of task and all-cause mortality in all chronic kidney disease stages, with no evidence of effect modification (\( P \) for interaction = .49) (Supplementary Table 2). Failure to achieve target heart rate was associated with lower survival in the adjusted model (HR 0.79; 95% CI, 0.71-0.88).

DISCUSSION

In a large (n = 50,121) and diverse retrospective cohort of patients who completed a clinically indicated stress test, we found that cardiorespiratory fitness was independently and
inversely associated with mortality across the spectrum of chronic kidney disease stages. We also showed that cardiorespiratory fitness improves risk discrimination and reclassification of mortality events.

Our findings are consistent with prior studies showing that cardiorespiratory fitness predicts mortality and adverse events among patients with chronic kidney disease. Gulati et al. found that cardiorespiratory fitness improves mortality risk prediction among patients with chronic kidney disease, although the analysis included only women, whereas our large study cohort included both men and women and was ethnically diverse. In a separate study, Howden et al. noted that patients with chronic kidney disease and low cardiorespiratory fitness, as measured by peak maximal oxygen intake, had increased aortic stiffness, left ventricular afterload, and overall cardiovascular risk burden. In addition, the study found that chronic kidney disease was associated with lower levels of fitness. However, the cohort in the analysis was small, with only 136 patients with chronic kidney disease stage 3 or 4, and did not have follow-up for long-term outcomes.

We found that patients with renal dysfunction who had not achieved target heart rate had the worst survival. Previous studies have demonstrated an association between autonomic imbalance, adverse cardiovascular outcomes, and incidence of chronic kidney disease. Largely determined by sympathetic and parasympathetic activity, heart rate is the biggest driver of VO2 increase during exercise, along with maximal stroke volume and maximal arteriovenous oxygen difference. Chronic kidney disease leads to muscle catabolism through means of anorexia, uremia, and inflammation, and worsening renal function may lead to further inactivity and risk factor accumulation. Improved cardiorespiratory fitness may exert a survival advantage by not only attenuating traditional risk factors, but also through beneficial impact on the hematologic, vascular, and immune systems.

Future research should assess the effect of interventions aimed at improving cardiorespiratory fitness among patients with chronic kidney disease by examining change in cardiovascular factor profile, renal function, VO2 max and oxygen consumption, lean body mass, markers of inflammation, endocardial dysfunction, myocardial injury, and subclinical atherosclerosis. Such prospective studies could identify mechanisms by which cardiorespiratory fitness can affect survival among patients with chronic kidney disease. Additional research should examine the utility of incorporating cardiorespiratory fitness, if available, into clinical scoring models by validating our findings in other datasets.

Our results have important clinical implications. Because physical activity is the main lifestyle factor that can modify cardiorespiratory fitness, participating in at least 30 minutes per day of moderate-intensity exercise may carry a significant benefit to overall health and mortality. Improved cardiorespiratory fitness may exert a protective effect on reducing burden of cardiovascular risk factors and is associated with a lower incidence of coronary heart disease, stroke, cancer, and mortality. One metabolic equivalent of task is approximately equivalent to the resting metabolic rate, or the energy spent while sitting quietly. An additional metabolic equivalent is a multiple of this, and at the low end of the spectrum could be making your bed or folding, compared with sitting quietly or washing your car. At the higher end of the spectrum, it is the difference between running at a pace of an 8-minute mile and a 7-minute mile. It is important to counsel the most sedentary patients to perform at least moderate activities (>6 metabolic equivalents of task) such as biking, running, swimming, or participation in sports. Our results add to the already robust body of evidence related to the benefits of physical activity and reinforce the 2016 American Heart Association Statement on cardiorespiratory fitness as a clinical vital sign.

Our results should be interpreted in the setting of several key limitations:

1) The FIT Project is a retrospective cohort of patients who were recruited at a single health system with distinct practice norms, which may limit generalizability to other health care systems.
2) Temporal changes in risk factors and medication use may hinder generalizability of our results to modern-day populations.
3) Patients included in the current analysis underwent a clinically indicated stress test to rule out coronary artery disease. This raises the potential of selection bias and could attenuate the clinical impact of our results.
4) Furthermore, those with preexisting electrocardiogram abnormalities or significant functional limitations, prevalent in patients with advanced chronic kidney disease, likely underwent diagnostic tests other than exercise stress testing to rule out coronary ischemia. As patients who underwent pharmacological stress testing or other imaging modalities were excluded from the dataset, we could not compare our results with this group.
5) We only measured cardiorespiratory fitness and estimated glomerular filtration rate at a single point in time, but changes in fitness or renal impairment over time are also significant.
6) While chronic kidney disease guidelines both mandate use of angiotensin receptor blockers or angiotensin-converting enzyme inhibitor regardless of diabetes, a relatively small proportion of the cohort was compliant with these medications due to a significant portion of the study cohort preceding modern guidelines.
7) Estimated glomerular filtration rate was estimated using the Modification of Diet in Renal Disease equation as opposed to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, which may be more accurate.
8) We could not determine whether patients were on dialysis in those with chronic kidney disease stage 4/5, as this information was not available in the FIT database.

9) Our chronic kidney disease population was mostly stage 3, as opposed to 4/5, which may limit generalizability of results to patients with more advanced renal dysfunction. However, our results stratifying by chronic kidney disease stage showed consistent results for improved survival with cardiorespiratory fitness regardless of renal function.

10) Lastly, many but not all chronic kidney disease-related factors contributing to cardiovascular risk were included, which could result in residual confounding. For example, calcium phosphorus product, which becomes more relevant in later stages of chronic kidney disease, was not included.

11) We could not evaluate mechanistic pathways underlying the association between cardiorespiratory fitness and all-cause mortality given the observational nature of this study.

In conclusion, we observed that higher cardiorespiratory fitness is inversely and independently associated with all-cause mortality in patients with chronic kidney disease. Cardiorespiratory fitness may help reclassify the risk of mortality and may inform treatment decisions in this high-risk group.

References


## Supplementary Table 1  Association Between Metabolic Equivalents of Task Achieved and All-Cause Mortality in Patients with Chronic Kidney Disease Stages 2-5: Hazard Ratio (95% Confidence Interval)

<table>
<thead>
<tr>
<th>Cardiorespiratory fitness categories</th>
<th>Model 1</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6 METs</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>6-&lt;10 METs</td>
<td>0.49 (0.46-0.52)</td>
<td>0.61 (0.57-0.65)</td>
</tr>
<tr>
<td>10-&lt;12 METs</td>
<td>0.26 (0.23-0.28)</td>
<td>0.38 (0.35-0.41)</td>
</tr>
<tr>
<td>≥12 METs</td>
<td>0.14 (0.12-0.16)</td>
<td>0.23 (0.19-0.27)</td>
</tr>
</tbody>
</table>

P trend across categories as ordinal variable: < .001

**P** for interaction = .27

**METs** = metabolic equivalents of tasks.
Model 1 adjusted for age, sex, and race.
Model 2 adjusted for model 1 and hypertension, diabetes, dyslipidemia, body mass index categories, history of coronary artery disease, history of smoking, statin use, aspirin use, beta-blocker use, failure to achieve target heart rate, and estimated glomerular filtration rate.

## Supplementary Table 2  Association Between Metabolic Equivalents of Task Achieved and All-Cause Mortality Stratifying by Chronic Kidney Disease Stage: Hazard Ratio (95% Confidence Interval)

<table>
<thead>
<tr>
<th>Cardiorespiratory fitness categories</th>
<th>Stage 1 CKD eGFR ≥90 mL/min/1.73 m²</th>
<th>Stage 2 CKD eGFR 60-89 mL/min/1.73 m²</th>
<th>Stage 3 CKD eGFR 30-59 mL/min/1.73 m²</th>
<th>Stage 4/5 CKD eGFR &lt;30 mL/min/1.73 m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6 METs</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>6-&lt;10 METs</td>
<td>0.57 (0.50-0.66)</td>
<td>0.63 (0.58-0.69)</td>
<td>0.61 (0.54-0.68)</td>
<td>0.62 (0.46-0.83)</td>
</tr>
<tr>
<td>10-&lt;12 METs</td>
<td>0.40 (0.34-0.48)</td>
<td>0.39 (0.35-0.44)</td>
<td>0.40 (0.34-0.48)</td>
<td>0.29 (0.16-0.52)</td>
</tr>
<tr>
<td>≥12 METs</td>
<td>0.27 (0.20-0.35)</td>
<td>0.26 (0.22-0.31)</td>
<td>0.18 (0.12-0.28)</td>
<td>0.65 (0.15-2.83)</td>
</tr>
</tbody>
</table>

P trend across categories as ordinal variable: < .001

**P** for interaction = .27

**METs per 1 unit**

<table>
<thead>
<tr>
<th>METs per 1 unit</th>
<th>Stage 1 CKD</th>
<th>Stage 2 CKD</th>
<th>Stage 3 CKD</th>
<th>Stage 4/5 CKD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.86 (0.84-0.88)</td>
<td>0.86 (0.85-0.88)</td>
<td>0.86 (0.84-0.87)</td>
<td>0.86 (0.81-0.91)</td>
</tr>
</tbody>
</table>

**P** for interaction = .49

**CKD** = chronic kidney disease; **eGFR** = estimated glomerular filtration rate; **METs** = metabolic equivalents of task.
Model 1 adjusted for age, sex, and race.
Model 2 adjusted for model 1 and hypertension, diabetes, dyslipidemia, body mass index categories, history of coronary artery disease, history of smoking, statin use, aspirin use, beta-blocker use, failure to achieve target heart rate, and estimated glomerular filtration rate.