Original Research

Physical Activity and Systemic Biomarkers in Persons With COPD: Insights from a Web-Based Pedometer-Mediated Intervention

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Running Head: **Physical Activity and Biomarkers in COPD**

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Abbreviations: 6MWT=6-minute walk test; AE=acute exacerbations; BMI=body mass index; COPD=chronic obstructive pulmonary disease; CHF=congestive heart failure; CAD=coronary artery disease; FEV_1=forced expiratory volume in one second; CKMM=muscle-type creatine kinase; NT-proBNP=N-terminal pro-β-type natriuretic peptide; PA=physical activity; sRAGE=Soluble receptor for advanced glycation end products; SAMO=Improving Exercise Tolerance and HRQL in Veterans with COPD; WEB=walking and education to breathe; ESC=every step counts; VA=Veterans Affairs

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ABSTRACT

Background: The relationships between physical activity (PA) and exercise performance and systemic biomarkers in persons with COPD have not been well characterized. The impact of PA promotion on biomarkers reflecting myocardial stress, systemic inflammation, and muscle injury is unclear.

Methods: This secondary analysis used three previously published studies in persons with COPD, two examined a PA intervention that promoted community-based walking for 3 months, to explore these relationships. PA (daily step counts) and exercise performance (6-minute walk test; 6MWT) were assessed. Serum N-terminal pro-β-type natriuretic peptide (NT-proBNP), the soluble receptor for advanced glycation end products (sRAGE), and muscle-type creatine kinase (CKMM) were assayed at baseline and three months. General linear models examined associations between PA/exercise performance and systemic biomarkers at baseline and the effect of the PA intervention on change in biomarkers.

Results: Participants included 366 US Veterans – 98% male, mean age 70±8 years, and FEV1 % predicted 59±21%. Lower baseline NT-proBNP, but not sRAGE or CKMM, was associated with higher daily step count (-0.95 pg/ml per 1,000 steps/day, p=.060) and higher 6MWT distance (-0.80 pg/ml per 100 meters, p=.001). Change in daily step count, but not 6MWT, was significantly greater in the intervention (789±1,864) compared to the control group (-174±1,448; p=.002). The PA intervention had no significant impact on change in the systemic biomarkers.

Interpretation: Exercise performance is associated with NT-proBNP in persons with COPD. A 3-month community-based walking intervention is not associated with myocardial stress or muscle injury as assessed by NT-proBNP and CKMM, respectively.

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) results in dyspnea and reductions in exercise performance.[1] COPD is also associated with a wide range of systemic derangements that involve, to varying degrees, cardiovascular effects, systemic inflammation, and skeletal muscle dysfunction.[1-4] Physical activity (PA) promotion is standard of care and improves clinical outcomes for patients with COPD[1]. Independent of lung function, increased PA is associated with decreased risk of hospitalization, acute exacerbations (AE), and mortality.[5-10] Currently, it is unclear whether community-based PA promotion impacts cardiac and skeletal muscle responses and whether changes in systemic inflammation mediate the observed benefits of PA promotion on morbidity and mortality in persons with COPD.

N-terminal pro-β-type natriuretic peptide (NT-proBNP), the soluble receptor for advanced glycation end products (sRAGE), and muscle-type creatine kinase (CKMM) show promise as potential biomarkers of systemic response to exercise and PA promotion. In COPD, NT-proBNP is a cardiac hormone which independently predicts PA,[11] AEs,[12] and mortality.[13] A systemic biomarker for cardiac dysfunction, NT-proBNP levels increase as myocardial wall stress increases.[14,15] It is plausible that dynamic hyperinflation or increases in pulmonary arterial pressure during exercise in COPD would negatively impact cardiac function and increase NT-proBNP levels. Secondly, although exercise training or PA promotion have well-known benefits in COPD, an anti-inflammatory effect has not yet been established.[16-22] Most COPD studies have focused on only one or a limited number of markers of systemic inflammation and comparison between studies is limited by the heterogeneity of intensity, duration, frequency, and type of exercise studied.[16-22] The soluble form of the pattern recognition receptor RAGE (sRAGE) is found in serum. RAGE contributes to the pathogenesis of COPD by inducing inflammation and

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tissue injury, while sRAGE counteracts these effects by acting as a decoy receptor and preventing ligands from binding to RAGE.[23] Lower sRAGE levels are associated with greater cigarette smoking exposure and more severe emphysema.[24,25] Soluble RAGE (sRAGE) has emerged as a functionally relevant marker of systemic inflammation across many clusters in COPD.[26] Finally, changes in serum levels of CKMM, an indirect biomarker of skeletal muscle damage, have been studied after short, local, exhaustive exercise training in the laboratory in persons without[27] and with COPD.[28-31] It is unknown whether CKMM changes with community-based walking over longer periods of PA promotion.

The relationships between PA and exercise performance and NT-proBNP, sRAGE, and CKMM in persons with COPD are unclear. In addition, systemic biomarker responses to community-based PA promotion have not been well characterized in COPD. The current literature focuses on changes in these biomarkers in the laboratory setting after bouts of high intensity exercise rather than community-based walking which more accurately reflects patients' usual activities in their home environment. We have developed a web-based, pedometer-mediated PA intervention for persons with COPD[32-35] based on the Theory of Self-Regulation[36]. The intervention provides four key components to promote behavior change: individualized goal setting, iterative step-count feedback for self-monitoring, educational and motivational content for disease self-management, and social support in the form of an online community forum. In three randomized controlled trials in persons with COPD, the intervention has been shown to be efficacious in increasing PA as measured by daily step counts, compared to controls, over 3-6 months.[32-35] The PA intervention has been shown to be efficacious in improving daily step counts by 779[33], 804[35], and 1,312 steps per day[34], compared to controls. These improvements are both clinically and

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statistically significant based on published MCID's for daily step count that range from 350 to 1,100 steps per day[37,38] and their association with a decreased risk for acute exacerbations[39].

In this secondary data analysis, we explored the baseline cross-sectional associations between PA and exercise performance with NT-proBNP, sRAGE, and CKMM. We hypothesized that higher NT-proBNP, CKMM, and sRAGE would be associated with greater PA/exercise. As a separate goal, we explored whether the magnitude of changes in daily step counts resulting from a 3-month PA intervention that promotes community-based walking would impact these biomarkers. We hypothesize that a 3-month walking intervention would not change NT-proBNP or CKMM, and may decrease systemic inflammation as reflected by an increase in sRAGE.

METHODS

Participants and Characteristics

This secondary analysis uses data and bloods collected from three previously published PA studies: SAMO,[40] ESC,[35]and WEB.[34] SAMO was an observational study of daily step counts which enrolled participants with stable COPD from January 2009 to February 2011.[40] ESC and WEB were randomized controlled trials examining the efficacy of a web-based, pedometer-mediated intervention to increase PA compared to pedometer alone or a control group, respectively.[34,35] Participants were enrolled in ESC from April 2012 to August 2015.[35] They were randomized to one of two groups for three months: Omron HJ-720 ITC (Omron) pedometer and a web-based PA intervention or Omron alone with written materials about exercise (i.e., control).[35] Participants were enrolled in WEB from May 2015 to February 2019 from two Veterans Affairs (VA) Medical Centers;[34] the current analyses use data from only one VA Medical Center. WEB participants were randomly assigned to either a Fitbit Zip pedometer and

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the same web-based PA intervention or usual care and written instructions for walking and exercise (i.e., control) for six months.[34] For all three studies, data from assessments and blood draws conducted at baseline and three months were used in this secondary analysis. Detailed information about these three studies is published elsewhere.[34,35,40]

In all three studies, at baseline, the forced expiratory volume in one second (FEV_1) was measured using an Eaglet spirometer (nSpire Health, Inc).[41] Body mass index (BMI) was calculated after measuring participants' height and weight. Using self-report and medical chart review, we ascertained age, sex, race, pack-years, current supplemental oxygen use, history of coronary artery disease (CAD), history of congestive heart failure (CHF), and occurrence of AEs in the year prior to study entry.

Systemic Biomarkers

At the baseline and 3-month visits, peripheral blood was collected by venipuncture into vacutainer tubes with ethylenediaminetetraacetic acid anticoagulant. Blood was collected between 9:00 AM and 4:00 PM. Plasma was obtained by centrifugation at 1,459 x g for 15 min. The samples were stored at -80 degrees Celsius in liquid nitrogen from the time they were drawn in the parent studies until the assays were performed in July, 2021. There were no repeated freeze-thaw cycles. Plasma NT-proBNP, sRAGE, and CKMM levels were measured by the Clinical & Epidemiologic Research Laboratory, Children's Hospital, Boston, Massachusetts. NT-proBNP levels were determined using an electrochemiluminescent quantitative sandwich enzyme immunoassay technique on the Roche Cobas 6000 system from Roche Diagnostics (Indianapolis, IN). This immunoassay technique has a sensitivity of 5 pg/mL and day-to-day imprecision values at concentrations of 46, 125, and 32,805 pg/mL of 3.1, 2.7 and 2.7%,

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respectively. sRAGE levels were determined using an ELISA assay from R & D Systems (Minneapolis, MN), specifically an enzymatically amplified "two-step" sandwich-type immunoassay. This ELISA assay detected any form of soluble RAGE, including sRAGE, esRAGE, and MMP-cleaved membrane-bound RAGE. This assay has a sensitivity of 4.12 pg/mL, and day-to-day variabilities of the assay at concentrations of 519, 1,449, and 2,890 pg/mL are 8.2, 8.2 and 6.6% respectively. Lastly, CKMM levels were determined using an ELISA assay from Novus Biologicals (Centennial, CO) that uses the Sandwich-ELISA principle. This ELISA assay has a sensitivity of 0.94 ng/mL and day-to-day variabilities of the assay at concentrations of 257.1 and 500.8 ng/mL are 11.6 and 10.8%, respectively.

Physical Activity and Exercise Performance

In the three studies, PA was directly measured as daily step count at baseline and three months. In SAMO, daily step counts were captured using the Omron pedometer and monitored over 14 days at baseline and three months.[40] In ESC, participants also wore the Omron pedometer; daily step counts were monitored over seven days at baseline and three months.[35] In WEB, participants used the Fitbit Zip pedometer; daily step counts were monitored over 10 days at baseline and over 14 days at three months.[34] The Omron pedometer and the Fitbit Zip pedometer, both worn on the waist, accurately measure daily step counts in people with COPD[42,43]. Exercise performance was assessed by the 6-minute walk test (6MWT) at baseline and three months. The 6MWT was performed following American Thoracic Society guidelines, except that a practice test was not performed.[44]

Statistical Analysis

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All analyses were performed using SAS 9.4 (Cary, NC). Univariate analyses examined baseline sample characteristics: *t*-tests and analyses of variances assessed association of systemic biomarker levels with categorical variables. Pearson correlations examined associations between biomarker levels and continuous variables. For the models examining whether the PA intervention impacted systemic biomarker levels, we maintained the randomization group assignments. Since no SAMO participants received the web-based PA intervention, they were considered controls. General linear models (PROC GLM) explored associations between (1) baseline daily step count and 6MWT distance and baseline level of each systemic biomarker (NT-proBNP, sRAGE and CKMM), and (2) the effect of the PA intervention on change in systemic biomarkers, compared to controls.

Since systemic biomarker distributions were skewed, each value was natural log-transformed to meet model assumptions. Change from baseline to three months for all biomarkers was calculated after the natural log-transformation, i.e., ln(3 months) – ln(baseline). For ease of interpretation of results, we calculated the concentration levels of each systemic biomarker by exponentiating the natural log-transformed estimates using a base of *e*. Clinical and demographic characteristics that were significantly associated with baseline levels of biomarkers were included as covariates. CAD and CHF were included in the main models because they are not necessarily interchangeable and CHF is an essential comorbidity when studying NT-proBNP. Final models adjusted for study, age, race, sex, FEV_1 % predicted, BMI, CAD, CHF, oxygen use, and history of AEs in the year prior to study entry. Statistical significance was defined as $p < 0.05$.

RESULTS

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Participant Characteristics

Of the 375 participants enrolled in the three studies, 366 had valid step-count data, performed the 6MWT, and provided blood samples at baseline. Most participants were white (93%, n=341) males (98%, n=357) with mean age 70±8 years (Table 1). Mean daily step count was 3,141±2,352 and mean 6MWT distance was 375±97 m. Median NT-proBNP serum level was 132.80 pg/ml (IQR=60.93-383.80), median sRAGE serum level was 1,017.48 pg/ml (IQR=720.20-1,402.65), and median CKMM serum level was 513.71 ng/ml (IQR=399.71-676.06).

Higher GOLD stage (i.e., lower FEV_1 % predicted) was significantly associated with lower sRAGE, but not NT-proBNP or CKMM. Increased BMI was significantly associated with higher average CKMM (Table E1). Cigarette smoking history measured by pack-years was not associated with systemic biomarker levels (Table E2). Participants with a history of CAD had higher mean levels of NT-proBNP and sRAGE compared to those without CAD. Participants with a history of CHF had higher mean levels of all three biomarkers, compared to those without CHF. Those using supplemental oxygen had higher mean NT-proBNP and CKMM levels than those not on oxygen. There was no difference in the three systemic biomarkers among those with at least one AE compared to those with no AE in the year prior to study entry. Compared to participants in SAMO, those in ESC and WEB had significantly lower levels of NT-proBNP. Finally, there was no difference in systemic biomarker levels between those in the intervention versus control groups (Table E1).

Baseline Relationships

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At baseline, adjusted models showed an association between higher daily step counts and lower NT-proBNP levels (β=-0.95 pg/ml per 1,000 steps per day, 95% CI [-0.91, 1.00], p=.060; Table 2). Baseline daily step counts were not associated with sRAGE (Table E3) or CKMM levels (Table E4). There was a significant association between higher 6MWT distance and lower NT-proBNP levels (β=-0.80 pg/ml per 100 meters, 95% CI [-0.71, -0.92], p=.001) (Table 3). Baseline 6MWT distance was not significantly associated with sRAGE (Table E5) or CKMM (Table E6) levels.

Compared to participants in SAMO, those in the ESC study had significantly higher levels of sRAGE and those in the WEB study had significantly lower levels of CKMM. Age was consistently an independent predictor of NT-proBNP, sRAGE, and CKMM levels, such that the greater the age, the higher the systemic biomarker levels. Lower FEV_1 % predicted was significantly associated with lower sRAGE levels. Compared to those with normal BMI, those who were underweight had significantly lower CKMM levels, while those who were overweight or obese had significantly higher levels of CKMM. Compared to those with no history of CAD, participants with CAD had NT-proBNP concentrations that were 1.27 (p=.068) to 1.30 (p=.051) pg/ml higher. Finally, compared to those with no history of CHF, participants with CHF had NT-proBNP concentrations that were 2.62 to 2.80 pg/ml higher ($p \leq$.001).

Effect of the PA Intervention

By randomization group, the mean 3-month change in daily step counts, adjusted for covariates, was significantly greater in the intervention group (789±1864) compared to the control group (-174±1,448; β =801.61, 95% CI [295, 1,308], p=.002; Figure 1, top panel). There was no significant difference in mean 3-month change in 6MWT distance between the intervention group

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and control group (2.14±157.91 m versus 0.37 ±146.81 m, β=1.75, 95% CI [-43.43, 46.92], *p*=.939; Figure 1, bottom panel). There was no significant effect of randomization group on change in levels of NT-proBNP, sRAGE, or CKMM, compared to the control group (Figure 2).

DISCUSSION

In this secondary, exploratory data analysis, we show that at baseline, cross-sectionally higher exercise performance is statistically associated with lower NT-proBNP levels; there was no relationship between PA and exercise performance with sRAGE and CKMM. Additionally, we believe that for the first time, we show that a 3-month PA intervention promoting community-based walking has no negative impacts on myocardial stress or muscle injury as assessed by NT-proBNP and CKMM, respectively. Physical activity promotion over three months also has no effect on systemic inflammation measured by sRAGE. Our preliminary findings suggest that PA promotion in the form of community-based walking over 3 months (as opposed to bouts of high intensity exercise training in the laboratory) does not impact biomarker levels that would suggest cardiac dysfunction, skeletal muscle damage, or inflammation. These results may guide personalization of PA interventions by helping to identify who can tolerate increases in exercise intensity and duration (if no change in blood biomarkers) and who requires decreases in intensity (if increase in blood biomarkers).

History of CAD and CHF were independent predictors of higher NT-proBNP levels in this cohort of participants with COPD, similar to that shown in the general population.[45] We showed that higher exercise performance in persons with COPD is significantly associated with lower NT-proBNP levels, likely reflecting a complex interaction between COPD disease severity and cardiovascular comorbidities such as CAD.[3] Secretion of NT-proBNP increases as myocardial

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wall stress increases and is a systemic biomarker for heart failure.[46] It is plausible that PA or exercise in persons with COPD is associated with dynamic hyperinflation or elevated pulmonary arterial pressure that may negatively impact cardiac function, with accompanying higher NT-proBNP levels.[46-48] However, we showed no negative impact of our 3-month PA intervention on myocardial stress and no relationship between change in daily step count or change in 6MWT distance with change in NT-proBNP. These results suggest that the magnitude of changes in daily step count and 6MWT distance observed over three months, which spanned a wide range, do not negatively impact cardiac function.

More recently, there has been interest in sRAGE which has emerged as an inflammatory biomarker common across several clusters in COPD.[26] We showed that there is no significant association between daily step counts or 6MWT distance and sRAGE. We also showed that lower FEV_1 % predicted (i.e., greater COPD disease severity) is significantly associated with lower sRAGE (i.e., greater systemic inflammation) which is consistent with published findings.[23,24] Although exercise training, pulmonary rehabilitation, and PA promotion have demonstrated benefits in COPD, an anti-inflammatory effect of exercise has not yet been established.[16-22] Most COPD studies, heterogeneous with respect to intensity, duration, frequency and type of exercise studied, have focused on only one or a limited number of biomarkers of systemic inflammation.[16-22] We have previously shown cross-sectionally that greater PA as measured by daily step counts is associated with lower plasma levels of C-reactive protein and interleukin 6, two inflammatory biomarkers in COPD.[49,50]

There is conflicting literature on the impact of exercise training on biomarkers of systemic inflammation. The current results do not show an impact of our web-based, pedometer mediated promotion of community-based walking specifically on sRAGE. It is plausible that more

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strenuous exercise is needed to impact expression of sRAGE. In addition, three months may have been insufficient time to effect changes on sRAGE levels. There is one published study examining community-based PA in persons with COPD as promoted with a cell phone intervention that showed decreases in serum c-reactive protein and interleukin-8.[51] In the general population, a few studies have shown conflicting results in terms of the effects of exercise training and PA promotion on sRAGE.[52-54] Army recruits engaged in a 4-week exercise intervention had decreases in sRAGE[52] and community volunteers in Japan enrolled in a 6-month PA promotion program had decreases in sRAGE,[53] while a study of adults aged 30-65 with at least one cardiovascular risk factor engaged in an 8-month PA program had an increase in sRAGE.[54]

Finally, decreased PA in persons with COPD and the resultant progressive muscle deconditioning may lead to disuse atrophy.[4] A common symptom of COPD is 'muscle wasting,' in which several factors, including disuse and hypoxemia, lead to muscle atrophy.[48] We showed no significant cross-sectional associations between PA and exercise performance with CKMM. Since previous studies have examined short exhaustive exercise training in the laboratory, it is unclear what effects longer term PA promotion to counter deconditioning may have on skeletal muscles and CKMM levels. We demonstrated no changes in CKMM in response to our PA intervention. Our results suggest that community-based walking in persons with COPD over a 3-month timeframe, resulting in the magnitude of change in daily step count and 6MWT distance we observed, does not damage skeletal muscles as reflected in the lack of change in CKMM levels. Previous small studies of short exhaustive exercise training in the laboratory in persons with COPD have demonstrated mixed results with increased serum levels of creatine kinase, including CKMM, while others have shown no change in CK levels.[27-31] Interestingly, BMI is an

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independent predictor of CKMM, with those who are overweight or obese having higher CKMM levels and those who are underweight having lower CKMM levels, compared to those with normal BMI.

It is possible that we observed no changes in the biomarkers because the intensity and duration of our intervention were not sufficient to elicit changes. We see it as a good thing that there is no biomarker evidence for myocardial stress or muscle injury after a 3-month community-based walking PA intervention that has been shown to result in increases in daily step counts which are statistically and clinically significant. In the parent RCTs, the PA intervention has been shown to be efficacious in improving daily step counts by 779-1,312 steps per day, compared to controls[33-35]. These improvements are both clinically and statistically significant based on published MCID's for daily step count[37,38]. Importantly, we showed that this modest increase in daily step counts in this frail population is associated with a reduction in risk for acute exacerbations[39]. For these clinically significant and statistically significant observed changes in physical activity, we did not see any changes in the biomarkers. Our goal was not to develop an intervention of such intensity or duration that there would be deleterious impacts on the heart and skeletal muscles to see increases in NT-proBNP and CKMM.

While participants in the intervention groups in ESC and WEB, on average, improved their daily step count more than the control groups, there were participants in both randomization groups who experienced improvements from baseline. In analyses combining the groups and examining baseline and 3-month change values of daily step count and 6MWT distance and levels of systemic biomarkers, independent of group assignment, the results were similar to what we report. In our cross-sectional analyses, we presented the model estimates per 1,000 steps per day and per 100 meters for the 6MWT to view the numbers most easily. However, the clinical

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implications of these estimates remain unclear as these results are cross-sectional associations, precluding any conclusions about causal changes in NT-proBNP.

This secondary data analysis has many strengths including the well-characterized cohort of participants with COPD, a PA intervention with proven efficacy, and the ability to examine change in PA/exercise performance and change in systemic biomarker levels across three months in a large sample. The biomarkers examined represent a broad spectrum of systemic response to PA and exercise. Our novel finding that a PA intervention promoting community-based walking has no deleterious effects on myocardial stress, systemic inflammation, and muscle injury assessed by NT-proBNP, sRAGE, and CKMM, respectively, is useful in guiding clinical care. Although we did not observe significant relationships between changes in PA/exercise performance and changes in systemic biomarker levels, these results are important to inform how best to monitor systemic response to PA promotion in COPD.

We were limited in the exploratory nature of this data analysis that combined three separate studies with significant differences in sRAGE and CKMM between studies. Nevertheless, all models adjusted for study to account for these differences. We acknowledge the missing follow-up data and that the results reflect only the subset of participants who participated in follow-up. The demographics of the populations from each study were homogeneous, with most participants being white, male, U.S. Veterans, limiting the generalizability of these results to other populations. The follow-up time of three months was relatively short and may not have allowed enough time for changes in serum biomarker levels to occur. We acknowledge that it is unknown whether the biomarker levels assessed at 3 months reflect PA/exercise over the preceding 3 months or merely the preceding 3 hours or 3 days. However, it is certainly a different time point compared to the measurement collected at baseline since participants have been engaged in a 3-

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month PA intervention with ongoing community-based walking. There is very limited literature examining the long-term stability of these biomarkers. However, there is precedence for analysis of samples that have undergone long-term storage. For examples, three NHANES studies published in 2023 examined NT-proBNP in samples collected between 1999-2004 while the assays were performed 19-21 years later between 2018-2020[55-57]. We emphasize that we are not presenting absolute values as thresholds for clinical decision-making. If there is decay, the decline in values would affect both groups with no preferential bias for one group over another. The cohort included only 4 current smokers precluding any informative further subgroup analyses on smoking status. Although the parent RCTs would have balanced unmeasured confounders between groups, it is possible that variables such as chronic kidney disease and diuretic use may impact the results of our models. These relationships should be further explored in future studies, tracking systemic biomarker levels over longer periods of time with interventions of varying levels of exercise intensity to better understand systemic responses to PA promotion in persons with COPD.

CONCLUSIONS

Higher 6MWT distance is associated with lower NT-proBNP levels. A 3-month PA intervention promoting community-based walking has no negative impacts on myocardial stress or muscle injury as assessed by NT-proBNP and CKMM, respectively. It also has no effect on systemic inflammation measured by sRAGE. These results may help personalize PA interventions and identify who can tolerate increases in exercise intensity and duration. Further studies are needed to understand the systemic biomarker responses to PA and exercise promotion in persons with COPD.

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All authors contributed to the conception of the work; the analysis and interpretation of data for the work; drafting and revising the work critically for important intellectual content; and final approval of the version submitted for publication.

DECLARATION OF INTEREST

The authors have no conflicts of interest.

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Table 1. Baseline characteristics (N=366)

	Mean/n	SD/%
Age (years)	70	8
Gender		
Male	357	98%
Female	9	2%
Race		
White	341	93%
Other	25	7%
FEV_1 % predicted	59	21
Pack-Years	62	38
BMI Categories		
Extremely Obese (> 40 kg/m^2)	24	7%
Obese (30 to < 40 kg/m^2)	122	33%
Overweight (25 to < 30 kg/m^2)	134	37%
Normal (18.5 to < 25 kg/m^2)	80	22%
Underweight (< 18.5 kg/m^2)	6	2%
Intervention Exposure		
Control	258	70%
Intervention	108	30%
Study		
ESC	104	28%
WEB	100	27%
SAMO	162	44%
Coronary Artery Disease	93	25%
Congestive Heart Failure	38	10%
Oxygen Use	81	22%
≥1 Acute Exacerbation	76	21%
6MWT Distance (m)	375	97
Daily Step Counts	3,141	2,352
NT-proBNP* (pg/ml)	132.80	60.93-383.80
sRAGE* (pg/ml)	1,017.48	720.20-1,402.65
CKMM* (ng/ml)	513.71	399.71-676.06

Note: FEV_1 = forced expiratory volume in one second; BMI = body mass index; ESC = Every Step Counts; WEB = Walking and Education to Breathe; SAMO = Improving Exercise Tolerance and HRQL in Veterans with COPD; 6MWT = 6-Minute Walk Test; NT-proBNP = N-terminal pro-β-type natriuretic peptide; sRAGE = soluble receptor for advanced glycation end products; CKMM = muscle type creatine kinase. *Represents median and interquartile range.

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Table 2. General linear models between baseline daily step counts and baseline NT-proBNP levels (pg/ml)

	ln(NT-proBNP)		NT-proBNP		*p*-value
	Est.	SE	Est.	SE	
Daily Step Counts (1,000)	-0.05	0.03	-0.95	1.03	.060
Study (ref=SAMO)					
ESC	-0.19	0.14	-0.82	1.15	.156
WEB	0.09	0.16	1.09	1.18	.591
Age	0.08	0.01	1.08	1.01	<.001
Race (ref=White)					
Other	-0.02	0.22	-0.98	1.24	.914
Sex (ref=Male)					
Female	-0.11	0.36	-0.90	1.43	.767
FEV_1 % predicted	-1.18E-03	2.78E-03	-1.00	1.00	.671
BMI (ref=Normal)					
Extremely Obese	-0.24	0.24	-0.79	1.28	.323
Obese	-0.10	0.15	-0.90	1.16	.490
Overweight	-0.16	0.15	-0.85	1.16	.285
Underweight	0.51	0.42	1.67	1.53	.225
CAD (ref=No)					
Yes	0.26	0.13	1.30	1.14	.051
CHF (ref=No)					
Yes	1.03	0.19	2.80	1.21	<.001
Oxygen Use (ref=No)					
Yes	0.08	0.14	1.08	1.15	.569
Acute Exacerbation (ref=None)					
≥1 Event	0.12	0.16	1.13	1.17	.450

Note. NT-proBNP = N-terminal pro–B-type natriuretic peptide; Est. = Estimate; SE = Standard Error; BMI = Body Mass Index; CAD = Coronary Artery Disease; CHF = Congestive Heart Failure.

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Table 3. General linear models between baseline 6MWT distance and baseline NT-proBNP levels (pg/ml)

	ln(NT-proBNP)		NT-proBNP		*p*-value
Parameter	Est.	SE	Est.	SE	
6MWT Distance (100 m)	-0.22	0.07	-0.80	1.07	.001
Study (ref=SAMO)					
ESC	-0.21	0.13	-0.81	1.14	.126
WEB	0.08	0.16	1.08	1.17	.633
Age	0.07	0.01	1.07	1.01	<.001
Race (ref=White)					
Other	-0.06	0.22	-0.94	1.24	.772
Sex (ref=Male)					
Female	-0.25	0.36	-0.78	1.43	.490
FEV_1 % predicted	0.00	0.00	-1.00	1.00	.920
BMI (ref=Normal)					
Extremely Obese	-0.24	0.24	-0.79	1.27	.321
Obese	-0.13	0.15	-0.88	1.16	.381
Overweight	-0.16	0.14	-0.85	1.16	.263
Underweight	0.48	0.42	1.61	1.52	.254
CAD (ref=no)					
Yes	0.24	0.13	1.27	1.14	.068
CHF (ref=no)					
Yes	0.96	0.19	2.62	1.21	<.001
Oxygen Use (ref=No)					
Yes	0.01	0.14	1.01	1.15	.965
Acute Exacerbation (ref=None)					
≥1 Event	0.09	0.16	1.10	1.17	.561

Note. NT-proBNP = N-terminal pro–B-type natriuretic peptide; Est. = Estimate; SE = Standard Error; BMI = Body Mass Index; CAD = Coronary Artery Disease; CHF = Congestive Heart Failure.

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Figure 1. Distribution of 3-Month Change in Daily Step Count and 6-Minute Walk Test (6-MWT) Distance by Group Assignment. Values adjusted for study, age, race, sex, FEV_1 % predicted, BMI, CAD, CHF, oxygen use, and history of AEs in the year prior to study entry. Y-axis Percent reflects the percent within each randomization group (Daily Step Count: Control n = 170, Intervention n = 96; 6MWT distance: Control n = 177, Intervention n = 99).

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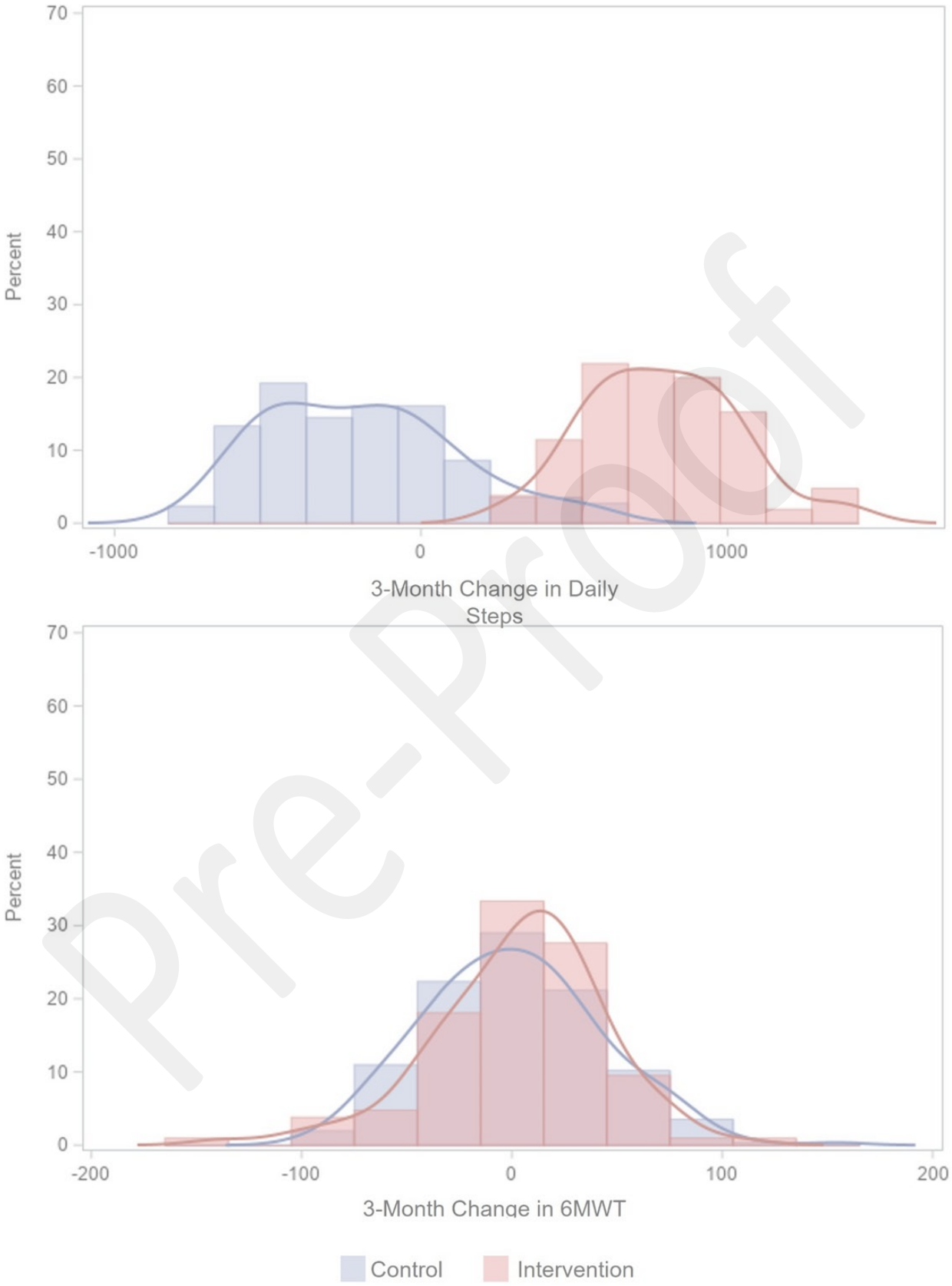

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Figure 2. Distribution of 3-Month Change in Systemic Biomarker Levels by Group Assignment. Values adjusted for study, age, race, sex, FEV_1 % predicted, BMI, CAD, CHF, oxygen use, and history of AEs in the year prior to study entry. Y-axis Percent reflects the percent within each group. (Control n = 174; Intervention n = 98).

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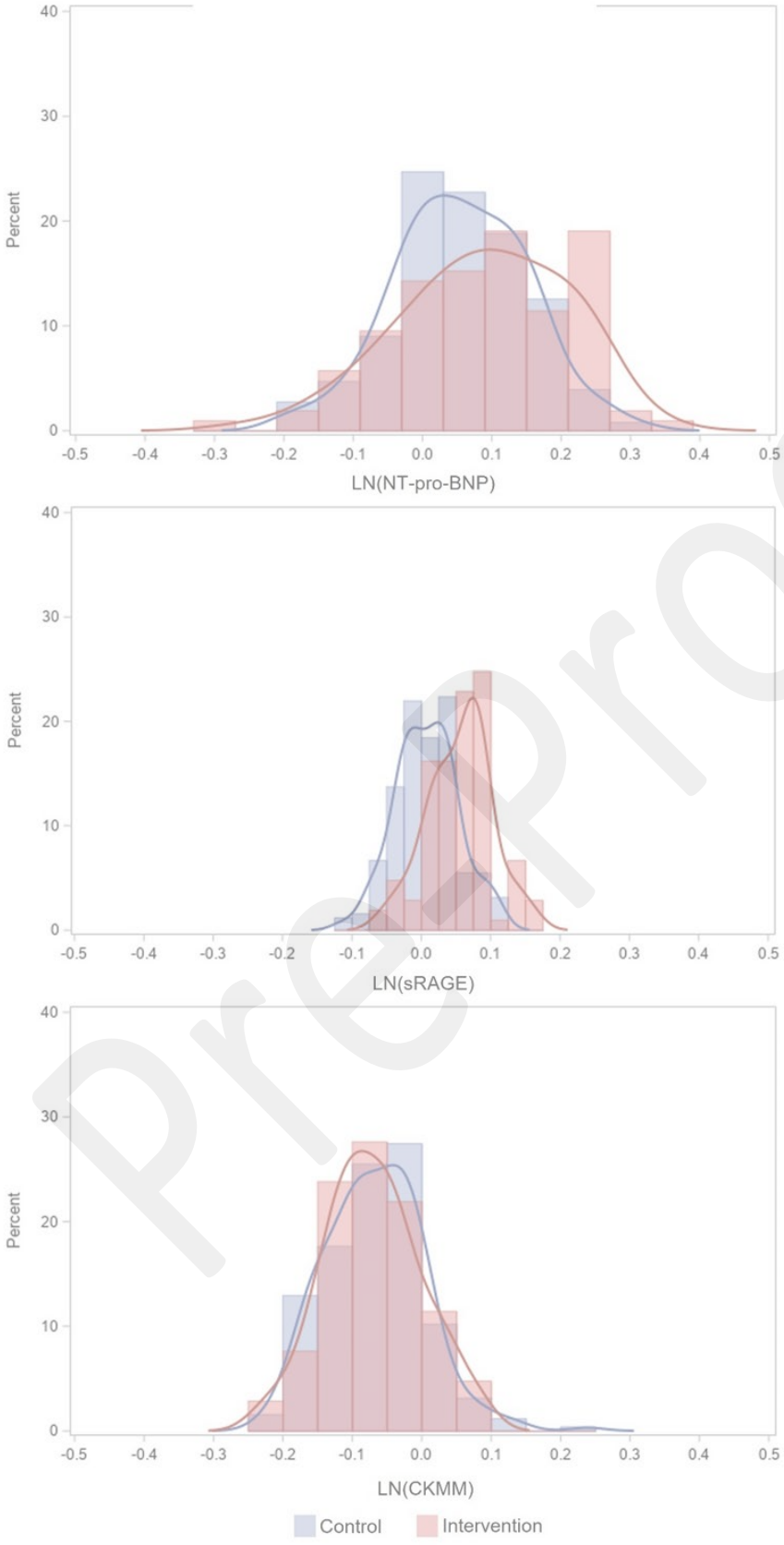

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Online Supplement

Table E1. Associations between systemic biomarkers and categorical variables

	NT-proBNP (pg/ml)			sRAGE (pg/ml)			CKMM (ng/ml)		
	Mean	SD	*p*	Mean	SD	*p*	Mean	SD	*p*
Study			<.001			.245			.062
SAMO	191.47	3.76		978.52	1.66		543.31	1.45	
ESC	104.04	3.18		1079.95	1.67		531.48	1.49	
WEB	159.61	3.35		1055.50	1.63		481.86	1.60	
Sex			.009			.130			<.001
Male	157.46	3.57		1033.90	1.65		528.56	1.50	
Female	51.55	1.52		799.16	1.70		330.59	1.39	
Race			.108						.216
White	157.69	3.52		1062.15	1.64	<.001	526.26	1.50	
Other	103.24	4.04		652.40	1.52		473.68	1.55	
GOLD Stage			.688			<.001			.407
1	131.42	3.97		1133.09	1.69		480.17	1.46	
2	162.39	3.21		1088.82	1.65		535.90	1.50	
3	155.23	4.10		961.73	1.63		523.03	1.52	
4	134.78	3.49		765.02	1.53		514.61	1.59	
BMI Categories			.877			.235			<.001
Extremely Obese	171.22	3.18		1078.89	1.51		605.30	1.54	
Obese	149.45	3.61		1004.98	1.64		542.65	1.51	
Overweight	143.37	3.64		1077.89	1.70		535.01	1.47	
Normal	170.96	3.64		994.63	1.63		474.47	1.50	
Underweight	165.07	2.19		697.03	1.53		287.81	1.44	
Coronary Artery Disease			<.001			.040			.224
Yes	263.56	3.37		1126.87	1.61		546.40	1.45	
No	127.34	3.45		995.52	1.67		514.55	1.53	
Congestive Heart Failure			<.001			.018			.012
Yes	478.19	3.55		1232.50	1.59		612.23	1.58	
No	134.29	3.34		1005.96	1.66		512.96	1.49	
Oxygen			.008			.120			.007
Yes	213.22	4.12		951.36	1.65		581.71	1.53	
No	139.45	3.36		1050.06	1.66		506.72	1.49	
Acute Exacerbation			.772			.304			.910
None	151.69	3.45		1013.22	1.66		523.13	1.49	
≥1	159.07	4.02		1083.22	1.62		520.01	1.59	
Exposure			.115			.115			.308
Control	163.94	3.64		1000.13	1.63		529.97	1.48	
Intervention	130.28	3.35		1095.48	1.72		505.09	1.56	

Note: NT-proBNP = N-terminal pro-β-type natriuretic peptide; sRAGE = soluble receptor for advanced glycation end products; CKMM = muscle-type creatine kinase; SD=Standard deviation; BMI=body mass index; Extremely Obese: BMI > 40 kg/m^2; Obese: BMI = 30 to < 40 kg/m^2, Overweight: BMI= 25 to < 30 kg/m^2; Normal: BMI=18.5 to < 25 kg/m^2; Underweight: BMI < 18.5 kg/m^2. *p*-value from independent samples t-tests (2 levels) and analyses of variances (ANOVAs; 3 or more levels).

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Table E2. Pearson correlation coefficients for systemic biomarkers and continuous variables

	Age	FEV_1 % predicted	Pack-Years	6MWT distance	Daily Step Count	NT-proBNP	sRAGE
FEV_1 % predicted	0.12	--					
p-value	.025	--					
Pack-Years	.035	-0.04	--				
p-value	.500	.485	--				
6MWT distance	-0.43	0.20	-0.06	--			
p-value	<.001	<.001	.217	--			
Daily Step Counts	-0.31	0.21	-0.07	0.52	--		
p-value	<.001	<.001	.204	<.001	--		
NT-proBNP	0.56	8.60E-4	9.20E-4	-0.43	-0.29	--	
p-value	<.001	.987	.986	<.001	<.001	--	
sRAGE	0.28	0.21	0.01	-0.10	-0.07	0.36	--
p-value	<.001	<.001	.921	.050	.199	<.001	--
CKMM	0.38	-0.01	-0.02	-0.24	-0.15	0.31	0.25
p-value	<.001	.890	.734	<.001	.004	<.001	<.001

Note: FEV_1 = forced expiratory volume in the first second, 6MWT = 6-minute walk test; NT-proBNP = N-terminal pro-β-type natriuretic peptide; sRAGE = soluble receptor for advanced glycation end products; CKMM = muscle-type creatine kinase. *p*-value from Pearson correlations.

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Table E3. General linear models between baseline daily step counts and baseline sRAGE levels (pg/mL)

	ln(sRAGE)		sRAGE		*p*-value
	Est.	SE	Est.	SE	
Daily Step Counts (1,000)	-0.01	0.01	-0.99	1.01	.545
Study (ref=SAM-O)					
ESC	0.14	0.06	1.15	1.07	.032
WEB	0.04	0.08	1.05	1.08	.559
Age	0.02	0.00	1.02	1.00	<.001
Race (ref=White)					
Other	-0.42	0.10	-0.66	1.11	<.001
Sex (ref=Male)					
Female	0.12	0.17	1.13	1.18	.473
FEV_1 % predicted	0.00	0.00	1.00	1.00	.009
BMI (ref=Normal)					
Extremely Obese	0.04	0.11	1.04	1.12	.721
Obese	0.00	0.07	-1.00	1.07	.970
Overweight	0.00	0.07	1.00	1.07	.984
Underweight	-0.25	0.20	-0.78	1.22	.208
CAD (ref=No)					
Yes	0.03	0.06	1.03	1.06	.611
CHF (ref=No)					
Yes	0.20	0.09	1.22	1.09	.024
Oxygen Use (ref=No)					
Yes	-0.10	0.06	-0.91	1.07	.139
Acute Exacerbation (ref=None)					
≥1 Event	0.06	0.07	1.06	1.08	.412

Note. sRAGE = soluble receptor for advanced glycation end products; Est. = Estimate; SE = Standard Error; BMI = Body Mass Index; CAD = Coronary artery disease; CHF = Congestive Heart Failure.

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Table E4. General linear models between baseline daily step counts and baseline CKMM levels (ng/mL)

	ln(CKMM)		CKMM		*p*-value
	Est.	SE	Est.	SE	
Daily Step Counts (1,000)	0.00	0.01	1.00	1.01	.628
Study (ref=SAM-O)					
ESC	0.03	0.05	1.03	1.05	.595
WEB	-0.16	0.06	-0.85	1.06	.009
Age	0.02	0.00	1.02	1.00	<.001
Race (ref=White)					
Other	-0.01	0.08	-0.99	1.08	.920
Sex (ref=Male)					
Female	-0.11	0.13	-0.89	1.14	.399
FEV_1 % predicted	0.00	0.00	-1.00	1.00	.315
BMI (ref=Normal)					
Extremely Obese	0.28	0.09	1.33	1.09	.002
Obese	0.18	0.05	1.19	1.06	.001
Overweight	0.14	0.05	1.15	1.06	.010
Underweight	-0.37	0.16	-0.69	1.17	.016
CAD (ref=No)					
Yes	-0.07	0.05	-0.93	1.05	.132
CHF (ref=No)					
Yes	0.14	0.07	1.15	1.07	.038
Oxygen Use (ref=No)					
Yes	0.07	0.05	1.08	1.05	.145
Acute Exacerbation (ref=None)					
≥1 Event	0.10	0.06	1.11	1.06	.081

Note. CKMM = muscle type creatine kinase; Est. = Estimate; SE = Standard Error; BMI = Body Mass Index; CAD = Coronary artery disease; CHF = Congestive Heart Failure.

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Table E5. General linear models between baseline 6MWT distance and baseline sRAGE levels (pg/mL)

	ln(sRAGE)		sRAGE		*p*-value
Parameter	Est.	SE	Est.	SE	
6MWT Distance (100 m)	-0.02	0.03	-0.98	1.03	.517
Study (ref=SAM-O)					
ESC	0.14	0.06	1.14	1.07	.034
WEB	0.04	0.08	1.04	1.08	.582
Age	0.01	0.00	1.02	1.00	<.001
Race (ref=White)					
Other	-0.42	0.10	-0.66	1.11	<.001
Sex (ref=Male)		.			
Female	0.11	0.17	1.11	1.19	.529
FEV_1 % predicted	0.00	0.00	1.00	1.00	.009
BMI (ref=Normal)					
Extremely Obese	0.04	0.11	1.04	1.12	.706
Obese	0.00	0.07	-1.00	1.07	.947
Overweight	0.00	0.07	-1.00	1.07	.995
Underweight	-0.25	0.20	-0.78	1.22	.204
CAD (ref=no)		.			
Yes	0.03	0.06	1.03	1.06	.636
CHF (ref=no)		.			
Yes	0.19	0.09	1.21	1.09	.029
Oxygen Use (ref=No)		.			
Yes	-0.10	0.07	-0.90	1.07	.127
Acute Exacerbation (ref=None)		.			
≥1 Event	0.06	0.07	1.06	1.08	.430

Note.sRAGE = soluble receptor for advanced glycation end products; Est. = Estimate; SE = Standard Error; BMI = Body Mass Index; CAD = Coronary artery disease; CHF = Congestive Heart Failure.

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Table E6. General linear models between baseline 6MWT distance and baseline CKMM level (ng/mL)

	ln(CKMM)		CKMM		*p*-value
Parameter	Est.	SE	Est.	SE	
6MWT Distance (100 m)	-0.02	0.02	-0.98	1.02	.463
Study (ref=SAM-O)					
ESC	0.03	0.05	1.03	1.05	.594
WEB	-0.15	0.06	-0.86	1.06	.011
Age	0.02	0.00	1.02	1.00	<.001
Race (ref=White)					
Other	-0.01	0.08	-0.99	1.08	.892
Sex (ref=Male)					.
Female	-0.12	0.13	-0.89	1.14	.364
FEV_1 % predicted	0.00	0.00	-1.00	1.00	.444
BMI (ref=Normal)					
Extremely Obese	0.28	0.09	1.32	1.09	.002
Obese	0.17	0.05	1.19	1.06	.002
Overweight	0.14	0.05	1.15	1.06	.008
Underweight	-0.38	0.16	-0.68	1.17	.014
CAD (ref=no)					
Yes	-0.07	0.05	-0.93	1.05	.130
CHF (ref=no)					
Yes	0.13	0.07	1.14	1.07	.056
Oxygen Use (ref=No)					
Yes	0.06	0.05	1.06	1.05	.228
Acute Exacerbation (ref=None)					.
≥1 Event	0.10	0.06	1.10	1.06	.092

Note. CKMM = muscle type creatine kinase; Est. = Estimate; SE = Standard Error; BMI = Body Mass Index; CAD = Coronary artery disease; CHF = Congestive Heart Failure.

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