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Respiratory and skeletal muscle strength in COPD: Impact on exercise capacity and lower extremity function

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Abstract

PURPOSE—We sought to quantify the impact of respiratory muscle and lower extremity strength on exercise capacity and lower extremity function in patients with chronic obstructive pulmonary disease (COPD).

METHODS—In 828 persons with COPD, we assessed the impact of reduced respiratory (maximum inspiratory pressure, MIP) and lower extremity muscle strength (quadriceps, QS) on exercise capacity (6 Minute Walk Distance, 6MWT) and lower extremity function (LEF, Short Physical Performance Battery). Multiple regression analyses taking into account key covariates, including lung function and smoking, tested the associations between muscle strength and exercise and functional capacity.

RESULTS—For each ½ standard deviation (0.5 SD) decrement in QS, men walked 18.3 meters less during 6MWT (95% CI –24.1 to –12.4); women 25.1 meters less (95% CI –31.1 to –12.4). For each 0.5 SD decrement in MIP, men walked 9.4 meters less during 6MWT (95% CI –15.2 to –3.6); women 8.7 meters less (95% CI –14.1 to –3.4). For each 0.5 SD decrease in QS, men had a 1.32 higher odds (95% CI: 1.11 to 1.15) of poor LEF; women, 1.87 higher odds (95% CI: 1.54 to 2.27). Lower MIP (per 0.5 SD) was associated with increased odds of poor LEF in women (OR 1.18, 95% CI: 1.00 to 1.39), but not in men (OR 1.10, 95% CI: 0.93 to 1.31).

CONCLUSION—In COPD, reduced respiratory and lower extremity muscle strength are associated with decreased exercise and functional capacity. Muscle weakness is likely an important component of impairment and disability in patients with COPD.

Key words or phrases

Respiratory and skeletal muscle; chronic obstructive pulmonary disease; exercise capacity; lower extremity function

Poor exercise capacity is a major complaint among persons with chronic obstructive pulmonary disease (COPD).¹ Furthermore, as exercise capacity worsens patients are more likely to curtail their normal activities and thus, become disabled, consistent with classic models of disablement. Prevention of disability by clinicians, however, is hampered by a poor understanding of the specific causes of exercise limitation in COPD.^{2,3} Although lung function is the central physiologic impairment in COPD, spirometry data correlate poorly with the exercise capacity.⁴ Medical therapies have been developed that improve lung function and respiratory symptoms, but, in isolation, they do not improve exercise capacity reliably.^{5,6} To better prevent physical decline and disablement in COPD, the risk factors for exercise impairment must be elucidated clearly.

Muscle dysfunction of the lower extremities has been identified as a specific cause of exercise impairment in COPD.⁷ Indeed, clinicians have long observed that patients with COPD cite leg fatigue as a key exercise-limiting factor. Consistent with this primal role, formal exercise testing is frequently terminated due to patient reports of generalized or leg specific fatigue, rather than dyspnea.¹ Moreover, recent evidence indicates that COPD is a systemic disease that may affect muscle function in patients with this condition.^{2,8} Most studies of muscle function in COPD, however, have been conducted only among patients with moderate-to-severe disease in highly selected clinical samples.^{3,9,10} It remains unknown whether decreased peripheral muscle strength is associated with decreased exercise capacity across a broad spectrum of COPD severity. Clarifying who is at risk is a prerequisite to the development and targeting of interventions to prevent functional decline. To determine whether decreased leg and respiratory muscle strength are associated with exercise limitation and decreased lower extremity functioning in subjects over a broad range of COPD severity, we analyzed a subset of participants from a population-based cohort of adults across a wide spectrum of disease (the Function, Living, Outcomes, and Work [FLOW] Study cohort).

METHODS

The FLOW study is an ongoing prospective cohort study of adults recruited from the membership of an integrated health care delivery system.^{11,12} All subjects carry a physician diagnosis of COPD. Briefly, a cohort of 1,202 Kaiser Permanente Medical Care Program (KPMCP) members treated for COPD was recruited using a validated algorithm based both on recent health care utilization linked to COPD and pharmacy dispensing for COPD-related medications.¹² We also recruited a cohort of 302 referent KPMCP members without COPD by diagnosis, medication, or pulmonary function deficit and matched to the cases by age, sex, and race. Potential subjects were excluded from the FLOW study if they fell outside the age range of 40–65 years because a key outcome of the study is work disability. Potential subjects were also excluded if they lived beyond 30 miles of the research clinic, if they were not a current KP member, if they were too incapacitated to complete an interview or attend a clinic visit, or if they died between the time of the interview and subsequent clinic visit. In addition, 4 otherwise eligible subjects were excluded because they could not perform spirometry due to the presence of a tracheostomy.

At baseline assessment, we conducted structured telephone interviews that ascertained sociodemographic characteristics, COPD clinical history, and health status, including a selected checklist of nonpulmonary medical comorbidities (coronary artery disease or myocardial infarction, congestive heart failure, stroke, low back pain, diabetes mellitus, obstructive sleep apnea, and lung cancer). To determine health status and nonpulmonary medical comorbidities, subjects were asked whether they had ever been told by a physician they had the checklist diagnosis in question. We also conducted a research clinic visit to perform spirometry and other physical assessments. For this analysis of predictors of

disability, we limited the study to cases diagnosed with Global Initiative for Chronic Obstructive Lung Disease (GOLD) Stage ≥ 1 COPD ($n=828$), although we also utilized data from referent subjects ($n=302$) to derive normative values for muscle strength. The study was approved both by the University of California, San Francisco Committee on Human Research and the Kaiser Foundation Research Institute Institutional Review Board.

Main Independent Predictor Variables

Lower extremity skeletal muscle strength

Isometric skeletal muscle strength was assessed by standard manual muscle testing procedures. A hand-held dynamometer was used to improve the objectivity of the force estimates (MicroFet2 dynamometer; Saemmons Preston, Bolingbrook, IL).¹³ We focused on knee extensor (quadriceps) and hip flexor strength because these muscles are considered essential for walking and quadriceps weakness predicts reduced maximal exercise capacity in COPD.^{3,9,10} Peak force values were recorded for 3 trials on each side in alternating fashion.¹³

Respiratory muscle strength

Strength of the respiratory muscles, which includes the diaphragm and intercostal muscles, was measured using the MicroRPM Respiratory Pressure Meter (Micromedical Ltd, Rochester, Kent, UK). We measured the maximum inspiratory pressure (MIP) generated at the mouth during a forceful inspiration and the maximum expiratory pressure (MEP), which is the maximum pressure measured at the mouth that can be generated during expiration. Testing adhered to the American Thoracic Society (ATS)/ European Respiratory Society (ERS) guidelines.¹⁴

Pulmonary function

Spirometry was performed according to ATS Guidelines.^{14,15} We used the EasyOne Frontline spirometer (NDD Medical Technologies, Chelmsford, MA).¹⁶ Although we did not administer bronchodilators, 90% of COPD subjects had taken their own short-acting bronchodilator within 4 hours of spirometry or had taken a long-acting bronchodilator earlier in the same day. By definition, referents had not used such medications. We derived forced expiratory volume in 1 second (FEV_1) % predicted values directly from the linear regression equations developed from the National Health and Nutrition Examination Survey III.¹⁷

Main Study Outcomes

Exercise capacity

Exercise capacity was estimated using the 6 Minute Walk Test (6MWT) in accordance with ATS Guidelines.^{18,19} Subjects who routinely used home oxygen or who had a resting oxygen saturation $<90\%$ were supplied with supplemental oxygen via nasal cannula during the test.

Lower extremity functioning

Lower extremity function was quantified using the validated Short Physical Performance Battery (SPPB).^{20,21}

Other Covariates

We selected additional covariates that might confound the relationships between the predictor and outcomes measures of study interest, including sociodemographic

characteristics such as age, sex, and body mass index; medical comorbidities, and educational attainment.^{11,12} To control for the influence of medical comorbidities, we created 2 comorbidity binary indicator variables. One comorbidity indicator variable assumed a value of 1 if a subject reported only a single comorbidity. The other indicator variable assumed a value of 1 if a subject reported 2 or more comorbidities. We also included cigarette smoking history using questions developed for the National Health Interview Survey.²²

Statistical analysis

Statistical analysis was conducted using SAS software, version 9.1 (SAS Institute, Inc, Cary, NC). Muscle strength and lung function measures were normally distributed. Therefore, we used Pearson correlations to test the associations among muscle strength and lung function measures. The overall analytic goal was to elucidate the independent impacts of respiratory muscle strength and skeletal muscle strength on exercise capacity and lower extremity function.

We used the 302 referent subjects without COPD to generate predicted values for respiratory and skeletal muscle strength. Predicted values were generated using multivariable linear regression controlling for age, gender, body mass index, and height. These predicted values were then used to generate percentage of predicted estimates for respiratory and skeletal muscle strength measures for the 828 subjects with COPD included in the main analyses. We tested the proportion of cases with quadriceps strength less than 50% predicted using χ^2 testing.

We used multivariable linear regression analysis to examine the association between muscle strength and exercise capacity as estimated by the 6MWT. In the first model, all 4 muscle strength measures were simultaneously included (MIP, MEP, quadriceps strength [QS], and hip flexor strength). Because MIP and MEP were highly correlated ($r=.69$), we developed a residual variable for MEP from the linear regression of MEP on MIP.²³ The residual variable for MEP represents only that part of MEP that does not correlate with MIP. Specifically, the correlation between MIP and MEP residuals is zero and thus, precludes collinearity. By developing the residual variable for MEP, we were able to include both MIP and MEP (as a residual variable) in the regression models without concern for collinearity. A similar approach was used to develop a residual variable for hip flexor strength from its regression on QS because they were also strongly correlated ($r=.77$). Of note, the residual variables have the same units as the original variables. The second model controlled for lung function impairment (FEV₁ % predicted) and additional covariates (see above).

To study the impact of respiratory and skeletal muscle strength on lower extremity function, we defined poor lower extremity function as the lowest quintile of SPPB scores based on their distribution among the COPD cases. We used multivariable logistic regression in a strategy analogous to that outlined above. Because the scale of respiratory and skeletal muscle strength variables was not directly comparable, we standardized each predictor variable by dividing by one-half of its standard deviation.²⁴ In addition, because both respiratory and muscle strength measures were strongly associated with gender, we stratified these analyses on gender. As a sensitivity analysis, we repeated the key analyses limited to subjects with more severe airflow obstruction (GOLD Stage ≥ 3 ; $n=340$). The results were not substantively different from the primary analysis and are not further reported here.

We also evaluated the joint impact of respiratory and lower extremity muscle strength on exercise capacity. MIP and QS were chosen to represent respiratory and skeletal muscle strength, respectively, because they were most strongly associated with exercise capacity in the above analyses. Subjects who were in the lowest quartile of both MIP and QS were

defined as the lowest combined strength group. Those in the highest quartile of both MIP and quadriceps strength comprised the highest strength group.

We used the LOWESS procedure to graphically depict the relationship between percent predicted quadriceps strength and 6MWT distance stratified by gender. The LOWESS procedure fixes a flexible smoothed curve that does not impose a linear relationship.²⁵ We depicted QS, as it was the most strongly related to distance walked. In addition to the LOWESS curves, we superimposed fitted regression lines and the 95% confidence interval.

RESULTS

The cohort included 828 subjects with COPD; 89% were either current or former smokers (Table 1). Overall, the cohort manifested moderate airflow obstruction, with a mean FEV₁ of 1.55±.68 L (Table 2.). MIP and MEP were highly correlated ($r=.69$), as were quadriceps strength and hip flexor strength ($r=.77$) and measures of respiratory muscle with skeletal muscle strength ($r\geq.45$). Although most measures of muscle strength were also correlated with FEV₁, these correlations were modest only ($r=.01$ to $.26$). Despite matching referents to cases based on age, sex, and race, some differences remained. Referents were slightly younger than cases (58.5±6.2 yrs vs 59.4±5.7 yrs, respectively; $P=.025$) and were more predominantly women (61% vs 54% respectively; $P=.03$). Age and sex, however, were included in the control-derived normal values for strength that we used. Race categories were similar between referents and cases ($P=.37$).

Decreased leg muscle strength was associated with a substantial decrease in exercise capacity in both men and women (Table 3). Men walked 18.3 meters less during the 6MWT (95% CI: -24.1 to -12.4 meters; $P<.0001$) and women walked 25.1 meters less (95% CI: -31.1 to -12.4 meters; $P<.0001$) for each 0.5 SD decrease in QS. Furthermore, decrements in % predicted leg muscle strength were associated with decreased exercise capacity (Figure 1). Based on the LOWESS procedure, the association between % predicted leg muscle strength and exercise capacity was approximately linear in the range of 50% to 120% predicted. Notably, there was a sharp nonlinear decline in distance walked once QS fell below 50%. The frequency of subjects with QS less than 50% predicted was similar across GOLD Stages (Stage 1=11.1%, Stage 2=8.3%, Stage 3=10.3%, Stage 4=15.0%; $P=.23$).

Similarly, decreased respiratory muscle strength was associated with decreased exercise capacity in both men and women; although the effect was modest, it was still statistically significant (Table 3). Men walked 9.4 meters less during the 6MWT (95% CI: -15.2 to -3.6 meters; $P=.002$) and women walked 8.7 meters less (95% CI: -14.1 to -3.4 meters; $P<.0001$) for each 0.5 SD decrease in MIP.

The effects of concurrent decreased strength in leg and respiratory muscles markedly reduced exercise capacity in both men and women (Table 4). As shown, men in the lowest quartile of both QS and MIP walked 176 meters less (95% CI: -242 to -110 meters) than men in the highest quartile while women in this group walked 137 meters less (95% CI: -203 to -72 meters) than women in the highest quartile. Furthermore, the effect of concurrent decreased strength in legs and respiratory muscles demonstrated a step-up in effect, with each weaker quartile walking less than its adjacent stronger quartile (test for trend $P<.0001$ for both genders).

Decreased leg muscle strength was also associated with a higher risk of poor lower extremity functioning in both men and women (Table 5). Men had a 1.32 higher odds (95% CI: 1.11 to 1.57; $P=.001$) of poor lower extremity function, and women had a 1.87 higher odds (95% CI: 1.54 to 2.27; $P<.0001$) of poor lower extremity function for each 0.5 SD decrease in QS. MIP (per 0.5 SD decrease in strength) was also associated with increased

odds of poor lower extremity functioning in women (OR 1.18, 95% CI: 1.00 to 1.39; $P=.04$), but not in men (OR 1.10, 95% CI: 0.93 to 1.31; $P=.28$).

DISCUSSION

Our results show that decreased leg and respiratory muscle strength are independently associated with poorer exercise capacity and lower extremity functioning across a spectrum of COPD severity. Furthermore, the effect of concurrent leg and respiratory muscle weakness on exercise capacity suggests a negative combined effect leading to far worse impairment. Our results also demonstrate that decreased leg and respiratory muscle strength have similar independent and combined effects on exercise capacity and lower extremity function for both men and women.

By investigating the effects of muscle weakness on exercise capacity across the spectrum of airflow obstruction, our findings build on previous work limited to patients with more severe COPD who are known to have both respiratory and peripheral muscle weakness.^{3,10} Furthermore, in prior work focused on severe COPD, the severity of quadriceps weakness was associated with graded reductions in work capacity during exercise testing.¹⁰ Our work expands on these findings by showing that patients across the spectrum of airflow obstruction have both respiratory and peripheral muscle weakness and that quadriceps weakness is associated with graded reductions in work capacity, even in patients with mild airflow obstruction.

Three features of our study help to provide a more complete picture of these relationships. First, we evaluated subjects with the full range of airflow obstruction ranging from mild to severe. Second, our cohort was systematically recruited from a population shown to be similar to the regional population of northern California.¹¹ Third, because our study population was relatively large, we were able to make robust assessments of the independent and combined effects of leg and respiratory muscle weakness on exercise capacity in both men and women. These features expand our current knowledge of the effects of muscle weakness on exercise capacity to patients with a broad range of COPD severity, supporting the generalizability of our findings to patients being treated for COPD in general medical practice.

The relationship between leg muscle weakness and exercise capacity has multiple potential explanations. One is that skeletal muscles in COPD have diminished aerobic capacity.⁷ COPD patients exhibit a shift from type I to type II skeletal muscle fibers,^{26, 27} reduced mitochondrial density per fiber bundle,²⁸ and reduced capillary density.^{29, 30} Each of these can correlate with reduced capacity for aerobic metabolism and, ultimately, poorer muscle endurance. Furthermore, higher levels of C-reactive protein and pro-inflammatory cytokines (eg, interleukin-8, interleukin-6, and tumor necrosis factor [TNF]- α) are seen in COPD.^{31–35} TNF- α inhibits muscle contractility³⁶ and mitochondrial biogenesis,³⁷ and promotes muscle wasting via apoptosis.³⁸ Another explanation is disuse atrophy from decreased activity. Other explanatory factors, such as malnutrition, age, hypoxia, reactive oxygen species, and deficiencies in levels of oxidative enzymes have all been identified in patients with COPD.^{39–43}

We recognize that our study has some limitations. First, the generalizability of our findings may be limited by the clinically-derived sampling, even if population-based through a large closed-panel health maintenance organization. Further, although we limited our study to persons with at least GOLD Stage 1 COPD or greater, we did not include subjects with potential COPD-related respiratory symptoms (productive cough or dyspnea) without concomitant airflow obstruction. Additionally, examiners used a hand-held dynamometer to

measure leg strength rather than a computerized isokinetic dynamometer because they are also more feasible to deploy in epidemiologic studies, due to cost and complexity.^{44,45} While hand held dynamometers may be more subject to error, they have been shown to provide reliable and valid results that correlate strongly with isokinetic dynamometer results, and thus their use should not have systematically impacted our observations. Second, we used a relatively small cohort of referent subjects without COPD to generate predicted values for respiratory and leg muscle strength. This limited sample size could have introduced additional uncertainty for estimates of “normal” values, although it should not be a source of systematic bias. In addition, the percent predicted estimates were only used for the LOWESS procedure, while absolute measures for respiratory and leg strength, standardized to one-half standard deviation, were used for our regression models, providing a second approach independent of control values. Third, we used MIP and MEP as measures of respiratory muscle strength, which are effort dependent tests. While our measurement of MIP and MEP adhered to the ATS/ERS guidelines, it is possible that our findings could have been impacted by subject effort.

Another potential limitation is the possible misclassification of COPD. To reduce this bias, we developed and validated an algorithm that required utilization of COPD, concomitant treatment with COPD medications, and a physician diagnosis of COPD; then further limited the analysis to persons with pulmonary function obstruction meeting criteria for GOLD 1 disease or greater.^{11,12} Moreover, a sensitivity analysis limited to GOLD 3–4 only did not yield substantively different results.

Because our study population was relatively young with a broad spectrum of COPD severity, our findings have implications particularly relevant for disability prevention. For patients with severe COPD, pulmonary rehabilitation programs lead to improved exercise tolerance and health related quality of life.^{46,47} Evaluations of the exercise component of pulmonary rehabilitation programs have shown strength training of the lower extremities leads to improved muscle function and improvements in measures of submaximal and maximal exercise capacity in patients with COPD.^{46,48} While strength training of the respiratory muscles has been shown to improve inspiratory muscle function,⁴⁹ translating these findings into improved exercise capacity beyond the gains afforded by general exercise in pulmonary rehabilitation programs has yet to be convincingly demonstrated.^{50,51}

Targeting improved exercise capacity through pulmonary rehabilitation in patients with less severe disease has not yet been rigorously evaluated. Our findings suggest that earlier attention to skeletal muscle strength could be an important component of disability prevention. Future studies might focus on strength and/or endurance training of skeletal muscles to prevent or retard the loss of exercise capacity and lower extremity functioning in patients with earlier stages of disease. Our findings also suggest that clinicians might consider measuring leg muscle strength and/or recommending leg strengthening exercises to patients with COPD with complaints of exercise limitations irrespective of gender or their formal GOLD staging. Because we found that both respiratory and lower extremity skeletal muscles have independent effects on exercise capacity, our findings suggest that attention to both muscle groups might be important in maximizing the potential benefit of disability prevention programs.

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Figure 1.

Table 1

Baseline subject characteristics of the FLOW cohort study

Subject Characteristics	n (%) or mean $\pm$ SD
Age, y	59.4 $\pm$ 5.7
Female sex	448 (54)
Body mass index	30.5 $\pm$ 7.8
Race / ethnicity	
White, Non-Hispanic	590 (71)
Other	238 (29)
Cigarette smoking	
Never smoked	89 (11)
Current smoker	279 (34)
Exsmoker	460 (55)
Medical comorbidities	
0	143 (17)
1	294 (36)
≥ 2	391 (47)

Table 2

COPD Severity, Pulmonary Physiology and Muscle Strength stratified by GOLD Stage

Subject characteristics n = 828	Overall cohort n = 828	Gold Stage 1 n = 126	Gold Stage 2 n = 362	Gold Stage 3 n = 233	Gold Stage 4 n = 107
FEV ₁ , L	1.5 (1.0, 2.0)	2.1	1.8	1.1	0.7
FEV ₁ , % predicted ^a	52.7 (38.8, 67.4)	88.2	62.2	41.3	23.6
Respiratory muscle strength					
Maximal inspiratory Pressure, cm H ₂ O	69.0 (49.0, 92.0)	72.0	76.0	65.5	56.0
Maximal inspiratory Pressure, % predicted ^b	81.2 (58.2, 103.4)	87.5	87.8	78.6	64.3
Maximal expiratory Pressure, cm H ₂ O	109.0 (86.0, 134.0)	101.0	111.0	108.0	109.0
Maximal expiratory Pressure, % predicted ^b	89.7 (72.2, 107.4)	88.4	89.3	92.0	85.8
Skeletal muscle strength					
Quadriceps, lbs of force	59.7 (45.9, 75.5)	61.1	63.2	57.2	56.2
Quadriceps, % predicted ^b	84.1 (65.7, 101.6)	87.9	87.5	82.1	76.1
Hip flexors, lbs of force	36.7 (26.1, 49.5)	36.7	38.0	35.1	33.4
Hip flexors, % predicted ^b	81.9 (61.4, 103.8)	84.8	84.9	82.3	70.1
6 minute walk distance, m	416 (341, 479)	442	440	394	355
SPPB lowest quintile	240 (29%)	32 (25%)	96 (26.5%)	71 (30.5%)	41 (38%)

Data presented as median (25th, 75th percentile) or n (%).

^aFEV₁ % predicted values derived directly from the linear regression equations developed from the National Health and Nutrition Examination Survey (NHANES III).¹⁷

^bMuscle strength % predicted values generated from 302 age and sex matched control subjects without COPD. Linear regression equations for each muscle were generated controlling for age, gender, body mass index, and height. Poor lower extremity function was defined as the lowest quintile of SPPB scores based on their distribution among COPD cases.

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV₁, force expiratory ventilation in 1 second; GOLD, Global Initiative for Chronic Obstructive Lung Disease; SPPB, Short Physical Performance Battery.

Table 3Impact of respiratory and leg muscle strength on exercise capacity, stratified by gender^a

Muscle strength measurement	6 Minute Walk Distance, m	
	Mutually adjusted, no additional covariates ^b	Adjusted for all covariates in Table 1 ^c and FEV ₁ % predicted
Respiratory muscle strength decrement		
MIP (cm H ₂ O): men	-11.2 (-16.1 to -6.3) <i>P</i> <.0001	-9.4 (-15.2 to -3.6) <i>P</i> =.002
MIP (cm H ₂ O): women	-9.5 (-14.4 to -4.6) <i>P</i> <.0001	-8.7 (-14.1 to -3.4) <i>P</i> <.0001
MEP residuals (cm H ₂ O): men	1.4 (-2.8 to 5.7) <i>P</i> =.51	-7.7 (-12.4 to -3.1) <i>P</i> =.001
MEP residuals (cm H ₂ O): women	-5.8 (-10.6 to -0.9) <i>P</i> =.02	-4.2 (-9.5 to 1.0) <i>P</i> =.115
Leg muscle strength decrement		
Quadriceps (lbs of force): men	-21.9 (-27.3 to -16.5) <i>P</i> <.0001	-18.3 (-24.1 to -12.4) <i>P</i> <.0001
Quadriceps (lbs of force): women	-32.2 (-37.8 to -26.6) <i>P</i> <.0001	-25.1 (-31.1 to -19.1) <i>P</i> <.0001
Hip flexor residuals (lbs of force) men	-6.2 (-10.4 to -1.9) <i>P</i> =.004	-0.8 (-5.4 to 3.8) <i>P</i> =.72
Hip flexor residuals (lbs of force) women	-9.0 (-13.6 to -4.4) <i>P</i> <.0001	-8.1 (-13.7 to -2.6) <i>P</i> =.004

^a Results are expressed as mean change in 6 minute walk distance per SD decrement in each muscle strength measurement (95% confidence interval). Analysis was conducted with multivariable linear regression. MEP and hip flexor residuals were calculated and used in the analysis to address multicollinearity (see Methods). FEV₁ % predicted was significantly associated with distance walked for both men and women (regression coefficient 1.14, 95% CI: 0.74 to 1.53; *P*<.001 and 1.22, 95% CI: 0.92 to 1.53; *P*<.001, respectively)

^b Model includes all 4 respiratory and skeletal muscle strength measures simultaneously. The R² of the model for women was 0.23. The R² of the model for men was 0.22

^c Model includes all 4 respiratory and skeletal muscle strength measures plus FEV₁ % predicted, age, sex, body mass index, height, race, smoking history, educational attainment, and number of medical comorbidities. The R² of the model for women was 0.52. The R² of the model for men was 0.42.

Abbreviations: MIP, maximum inspiratory pressure; MEP, maximum expiratory pressure; FEV₁, forced expiratory ventilation in 1 second.

Table 4

Joint impact of low MIP and quadriceps strength on exercise capacity stratified by gender.

Muscle strength group	Exercise performance, m (mean decrement in 6MWT, 95% CI) ^a in men	Exercise performance, m (mean decrement in 6MWT, 95% CI) ^a in women
Lowest quartile of combined MIP and quadriceps strength	−176 m (−242 to −110) <i>P</i> <.0001	−137 m (−203 to −72) <i>P</i> <.0001
25–50th percentile of combined MIP and quadriceps strength	−41 m (−99 to 18) <i>P</i> =.169	−73 m (−137 to −3) <i>P</i> =.041
50–75th percentile of combined MIP and quadriceps strength	−37 m (−77 to 3) <i>P</i> =.07	−30 m (−100 to 40) <i>P</i> =.39
Highest quartile of MIP and quadriceps strength	Referent	Referent

Model includes FEV₁ % predicted, age, sex, height, body mass index, race-ethnicity, smoking history, educational attainment, and number of medical comorbidities.

^a *P*<.0001 for test of linear trend for both men and women.

Abbreviations: MIP, maximum inspiratory pressure; 6MWT, 6 minute walk test; FEV₁, forced expiratory ventilation in 1 second.

Table 5Impact of respiratory and skeletal muscle strength on lower extremity functioning stratified by gender^a

Muscle strength measurement	Risk of poor lower extremity functioning	
	Mutually adjusted, no additional covariates ^b	Adjusted for all covariates in Table 1 ^c and FEV ₁ % predicted
Respiratory muscle strength decrement		
MIP (cm H ₂ O): men	1.10 (0.98 to 1.24) P=.12	1.10 (0.93 to 1.31) P=.28
MIP (cm H ₂ O): women	1.16 (1.04 to 1.30) P=.008	1.18 (1.00 to 1.39) P=.044
MEP residuals (cm H ₂ O): men	1.06 (0.95 to 1.17) P=.30	1.15 (1.00 to 1.35) P=.05
MEP residuals (cm H ₂ O): women	1.01 (0.91 to 1.13) P=.84	1.09 (0.92 to 1.28) P=.33
Lower extremity muscle strength decrement		
Quadriceps (lbs of force): men	1.31 (1.15 to 1.50) P<.0001	1.32 (1.11 to 1.57) P=.001
Quadriceps (lbs of force): women	1.77 (1.55 to 2.03) P<.0001	1.87 (1.54 to 2.27) P<.0001
Hip flexor residuals (lbs of force) men	1.12 (1.01 to 1.25) P=.03	1.07 (0.94 to 1.23) P=.29
Hip flexor residuals (lbs of force) women	1.18 (1.06 to 1.32) P=.004	1.16 (0.98 to 1.37) P=.09

^a Poor lower extremity functioning is defined as the lowest quintile of the Short Physical Performance Battery (see Methods). Results are expressed as odds ratio per SD decrement in each muscle strength measurement (95% CI). Analysis was conducted with multivariable logistic regression. MEP and hip flexor residuals were calculated and used in the analysis to eliminate multicollinearity (see Methods).

^b Model includes all 4 respiratory and skeletal muscle strength measures simultaneously. The model χ^2 for women = 113.49. The model χ^2 for men = 36.34.

^c Model includes all 4 respiratory and skeletal muscle strength measures plus FEV₁ % predicted, age, sex, height, body mass index, race, smoking history, educational attainment and number of medical comorbidities. The model χ^2 for women = 169.61. The model χ^2 for men = 68.06.

Abbreviations: MIP, maximum inspiratory pressure; MEP, maximum expiratory pressure; FEV₁, forced expiratory ventilation in 1 second.