Pulmonary Function, Muscle Strength, and Incident Mobility Disability in Elders

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Muscle strength, including leg strength and respiratory muscle strength, are relatively independently associated with mobility disability in elders. However, the factors linking muscle strength with mobility disability are unknown. To test the hypothesis that pulmonary function mediates the association of muscle strength with the development of mobility disability in elders, we used data from a longitudinal cohort study of 844 ambulatory elders without dementia participating in the Rush Memory and Aging Project with a mean follow-up of 4.0 years (SD = 1.39). A composite measure of pulmonary function was based on spirometric measures of forced vital capacity, forced expiratory volume, and peak expiratory flow. Respiratory muscle strength was based on maximal inspiratory pressure and expiratory pressure and leg strength based on hand-held dynamometry. Mobility disability was defined as a gait speed less than or equal to 0.55 m/s based on annual assessment of timed walk. Secondary analyses considered time to loss of the ability to ambulate. In separate proportional hazards models which controlled for age, sex, and education, composite measures of pulmonary function, respiratory muscle strength, and leg strength were each associated with incident mobility disability (all *P* values < 0.001). Further, all three were related to the development of incident mobility disability when considered together in a single model (pulmonary function: hazard ratio [HR], 0.721; 95% confidence interval [CI], 0.577, 0.902; respiratory muscle strength: HR, 0.732; 95% CI, 0.593, 0.905; leg strength: HR, 0.791; 95% CI, 0.640, 0.976). Secondary analyses examining incident loss of the ability to ambulate revealed similar findings. Overall, these findings suggest that lower levels of pulmonary function and muscle strength are relatively independently associated with the development of mobility disability in the elderly.

Keywords: mobility disability; pulmonary function; respiratory muscle strength; leg strength; aging

Mobility disability, defined as impaired activities of daily living due to difficulty walking, is exceedingly common in older persons and associated with an increased risk of adverse health outcomes (1, 2). Although catastrophic events such as broken hip, myocardial infarction, or stroke can result in the rapid onset of mobility disability, more commonly disability develops gradually over time, beginning with declining walking speed that at some point crosses a threshold and interferes with daily activities. In some elders, disability progresses to include a complete loss of the ability to ambulate (Figure 1) (3). We have previously shown that muscle strength, including both leg strength and respiratory

muscle strength, are relatively independently associated with the rate of mobility decline in community-dwelling elders. However, the factors linking muscle strength with mobility disability are not clear (4).

The identification of factors that mediate or link muscle strength with mobility disability is necessary to facilitate the development of interventions to prevent or modify the development of mobility disability in elders. Pulmonary function may be one of the factors which links muscle strength with mobility disability. Both pulmonary function and respiratory muscle strength play important roles in the respiratory network, which depends on intact neural circuitry that orchestrates the interplay between respiratory muscles and intrinsic pulmonary function to maintain adequate ventilation (5, 6). Thus, impaired respiratory muscle strength can lead to decreased pulmonary function (i.e., impaired pressure gradients and air exchange at the alveolar surface). In turn, the inadequate energy supply caused by decreased pulmonary function could lead to impaired leg strength, contributing to the development of mobility disability (7). Testing this hypothesized causal sequence requires examining all three of these factors together in the same models (8). However, we are unaware of prior studies that have examined pulmonary function, respiratory muscle strength, and leg strength together to examine how they contribute to the development of mobility disability (9).

We used data from 844 community-dwelling ambulatory older persons without dementia who were participating in the Rush Memory and Aging Project, a longitudinal epidemiologic study of aging, to test the hypothesis that pulmonary function mediates the association of muscle strength (i.e., respiratory muscle strength and leg strength) with incident mobility disability. Gait speed is a widely used performance-based measure of mobility that is associated with functional status in older adults and is a more sensitive indicator of mobility disability than self-reported disability (10). Therefore in the current study we based mobility disability on annual timed walking performance and used receiver operating curves (ROC) analyses to support the cut-point of less than or equal to 0.55 m/s (11).

MATERIALS AND METHODS

Participants

All participants were from the Rush Memory and Aging Project, a community-based, longitudinal clinical-pathologic investigation of chronic conditions of old age whose study design has been previously described (12). Participants agreed to annual detailed clinical evaluations and organ donation at the time of death. All evaluations were performed at the parent facility or the participants' homes to reduce burden and enhance follow-up participation (12). The study was conducted in accordance with the latest version of the Declaration of Helsinki and was approved by the Institutional Review Board of Rush University Medical Center.

The Memory and Aging Project began in 1997, and the overall follow-up rate is about 90% of survivors. Because of the rolling admission and mortality, the length of follow-up and

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Figure 1. Declining mobility performance and thresholds for mobility disability.

number of examinations varies across participants. Further, because the collection of data on respiratory function was not added until 2001, it was only available on a subset of Memory and Aging Project participants. To maintain the temporal relation between respiratory muscle strength and mobility, we included the first respiratory muscle strength test as the predictor and considered the mobility measure obtained at that evaluation the “baseline” for this study; all subsequent mobility measures available for each participant were used to calculate incident mobility disability. There were four requirements for inclusion in these analyses: (1) the absence of dementia at the baseline evaluation, (2) a valid respiratory muscle strength testing at baseline, (3) ambulatory at baseline, and (4) at least one valid follow-up gait testing to be able to calculate incident disability. Dementia was diagnosed in a three-step process. Nineteen cognitive tests were scored by a computer and reviewed by a neuropsychologist to diagnose cognitive impairment (13). Then participants were evaluated by a physician who used all cognitive and clinical data to diagnose dementia based on published criteria as previously described (12).

At the time of these analyses, 1,145 participants had enrolled and completed a baseline evaluation and had valid respiratory function testing. Of these, 189 were excluded, including 80 because of dementia and 5 because of invalid respiratory muscle strength; 34 were unable to ambulate at baseline, 35 died before their first follow-up, and 35 had not been in the study long enough for follow-up evaluation. Of 956 who were eligible for follow-up exam, 112 had missing follow-up data (participation rate of about 90%), leaving 844 for these analyses.

Assessment of Mobility Disability

In this study we defined mobility disability based on a gait speed that was derived from the structured annual evaluations of the time it took participants to walk 8 ft (2.4 m), and mobility disability was defined as a gait speed of less than or equal to 0.55 m/s (12). The decision about what constitutes disability based on gait speed depends on the position of the reference value (cut point). In preliminary analyses we sought to develop an objective measure of mobility disability that was well anchored in a common self-report mobility disability scale. Receiver operating curves were constructed to compare the sensitivity and specificity of gait speed of the current cohort at baseline in predicting self-report mobility disability using the Rosow-Breslau scale, which has been used to measure mobility disability

Figure 2. Receiver operator curve (ROC) for gait speed testing. This ROC curve shows the sensitivity (y axis) and 1-specificity (x axis) for gait speed testing for identifying participants with mobility disability based on the Rosow-Breslau scale.

(11, 14). This scale assesses three activities: walking up and down a flight of stairs; walking a half mile; and doing heavy housework like washing windows, walls, or floors. Participants were asked if they could perform each task without help, and those who reported being unable to do one or more were classified as being disabled. The relationship between sensitivity and specificity as a function of the cutoff point is presented graphically by ROC curves, which plot sensitivity against 1 minus specificity for all possible tests. Accuracy is measured by the area under the curve. Using ROC analyses, we determined a gait speed cut-point of 0.55 m/s would yield a sensitivity of 83.6% and specificity of 54.9%; with an area under the curve of 0.760 (95% confidence interval [CI], 0.731, 0.790) (see Figure 2). In secondary analyses we used a second important threshold of mobility disability, the loss of the ability to ambulate. Participants were defined as being unable to ambulate if they could not complete the annual 8-ft walk.

Assessment of Pulmonary Function

Pulmonary function was tested using a hand-held spirometer that measured forced vital capacity (FVC), forced expiratory volume in 1 second (FEV₁), and peak expiratory flow (PEF) (MicroPlus Spirometer MS03; MicroMedical Ltd., Kent, UK). Two trials were collected from each subject. Raw scores from each of the three averaged component pulmonary measures were converted to z scores using the means and standard deviations computed from the entire cohort. A composite pulmonary function score was created by converting the raw score from FVC, FEV₁, and PEF to z scores using the mean and standard deviation from all participants at baseline (Table 1) and averaging z scores for these three measures together as previously described (8).

Respiratory Muscle Strength

Respiratory muscle strength was based on measures of maximal inspiratory and expiratory pressures (5, 15). A hand-held device that contains a pressure sensitive transducer was used to assess

TABLE 1. COMPOSITE PULMONARY FUNCTION AND RESPIRATORY MUSCLE STRENGTH

Variable	Continuous Value Achieving z Score	
	z Score = 0	z Score = 1
Pulmonary function		
FVC, L	1.88	2.51
PEF, L/min	258	371
FEV ₁ , L	1.61	2.18
Respiratory muscle strength		
Maximal inspiratory pressure, mm H ₂ O	41	62
Maximal expiratory pressure, mm H ₂ O	66	92

The composite pulmonary function measure was constructed by converting the raw score from the three spirometric measures (FVC, PEF, and FEV₁) to z scores using the mean and standard deviation from all participants at baseline. The values in the table are approximations to the underlying measures that correspond to average performance at baseline (z = 0) and 1 SD better than average (z = 1). A similar procedure was employed to construct composite respiratory muscle strength based on MIP and MEP measures.

maximal inspiratory pressure (MIP in cm H₂O) and maximal expiratory pressure (MEP in cm H₂O) (MicroMouth Pressure Meter MP01; MicroMedical Ltd.). Two trials of both MIPs and MEPs were collected at baseline. The mean score for MIPs and MEPs were converted to z scores, using the mean and standard deviation of all study participants at baseline. Both z scores were averaged to yield a composite measure of respiratory muscle strength (16). As previously described, we used components of variance analysis to examine the contribution of trial-to-trial variation and subject to the subcomponents (MIP and MEP) of baseline composite respiratory muscle strength (4). On average, the contribution of the trial-to-trial variation to total variation of both subcomponents was (14.8%) and was much smaller than the variation due to subject (85.2%). The trial-to-trial variation is further reduced, since the two trials that were collected are averaged together to yield each of the two subcomponents. Since this process reduces an already small

source of variation, we have not employed other methods to compensate for variation due to trial.

Leg Strength

Hand-held dynamometers (Lafayette Manual Muscle Test System, Model 01163; Lafayette Instrument Co., Lafayette, IN), were used to assess muscle strength of four muscle groups in both lower extremities (hip flexion, knee extension, plantar flexion, and ankle dorsiflexion). The mean score for each muscle group was converted to a z score, using the mean and standard deviation of all study participants at baseline and the z scores of all the lower extremity muscles were averaged to yield lower extremity strength as previously described (16).

Other Covariates

Sex, age, and years of education were obtained at baseline evaluation. Weight and height were measured and used to calculate BMI. Physical activity was assessed using questions adapted from the 1985 National Health Interview Survey (17). Activities included walking for exercise, gardening or yard work, calisthenics or general exercise, bicycle riding, and swimming or water exercise. Minutes spent engaged in each activity were summed and expressed as hours of activity per week, as previously described (18). We summarized vascular risk factors as the number of the following risk factors: hypertension, diabetes mellitus, and smoking. Vascular disease burden was the number of four vascular diseases: myocardial infarction, congestive heart failure, claudication, and stroke, as previously described (19).

Analysis

Pearson correlations were used to examine the bivariate associations of pulmonary function and muscle strength with age, education, and other covariates and *t* tests to compare differences among men and women. Then we divided the participants into two groups with and without mobility disability

TABLE 2. PULMONARY FUNCTION, MUSCLE STRENGTH, AND INCIDENT MOBILITY DISABILITY

Model	Pulmonary Function (HR [95% CI] P Value)	Respiratory Muscle Strength (HR [95% CI] P Value)	Leg Strength (HR [95% CI] P Value)
Model A	0.627 (0.506, 0.776) P < 0.001		
Model B		0.642 (0.526, 0.783) P < 0.001	
Model C			0.692 (0.564, 0.849) P < 0.001
Model D	0.695 (0.557, 0.868) P = 0.001	0.700 (0.569, 0.861) P < 0.001	
Model E	0.667 (0.537, 0.828) P < 0.001		0.742 (0.602, 0.915) P = 0.005
Model F		0.682 (0.556, 0.837) P < 0.001	0.759 (0.617, 0.934) P = 0.009
Model G	0.721 (0.577, 0.902) P = 0.004	0.732 (0.593, 0.905) P = 0.004	0.791 (0.640, 0.976) P = 0.029
Model H	0.793 (0.627, 1.004) P = 0.054	0.692 (0.557, 0.860) P < 0.001	0.781 (0.631, 0.966) P = 0.023

The hazard ratios for the one unit difference in pulmonary function, respiratory muscle strength, and leg strength are summarized for a series of discrete-time proportional hazards models for time to incident motor disability, which were all adjusted for age, sex, and education. Each model includes additional terms for various combinations of pulmonary function, respiratory muscle strength, and leg strength as follows. Model A included a term for pulmonary function; Model B included a term for respiratory muscle strength; Model C included a term for leg strength; Model D included terms for pulmonary function and respiratory muscle strength; Model E included terms for pulmonary function and leg strength; Model F included terms for respiratory muscle strength and leg strength; and Model G included terms for pulmonary function, respiratory muscle strength, and leg strength. Model H includes all the terms in Model G as well as terms for body mass index (BMI), BMI*BMI, physical activity, vascular risk factors, and vascular diseases.

based on gait speed at baseline and used Student's *t* tests, Wilcoxon rank sum tests, or chi-square tests to compare their characteristics at baseline.

We first constructed a series of separate proportional hazards models for discrete (tied) data to estimate risk of developing mobility disability associated with pulmonary function, respiratory muscle strength, and leg strength alone (Table 2, *Models A–C*). These initial models and all subsequent models controlled for age, sex, and education. Then we examined the various combinations of these three factors together, first in combinations and then finally with all three in a single model (Table 2, *Models D–G*). In these models, an attenuation of the association of muscle strength with mobility disability when pulmonary function was added into the model would support the hypothesis that muscle strength and mobility disability are linked (mediated) by pulmonary function (8, 20). In a final model (Table 2, *Model H*), we added terms for a number of potential confounders that might affect these associations with mobility disability. In secondary analyses we repeated similar models using the first occurrence of the loss of the ability to ambulate as the outcome. We employed both linear and

TABLE 3. CHARACTERISTICS OF THE COHORT AT BASELINE

Variable	Mobility Disability Present (<i>n</i> = 270)	Mobility Disability Absent (<i>n</i> = 574)
Age, yr	82.9 (6.84)	79.5 (7.09)*
Sex, % female	225 (83.3%)	403 (70.2%)*
Education, yr	13.9 (2.85)	14.8 (2.93)*
Mini-mental status exam	27.5 (2.25)	28.3 (1.91)*
FEV ₁ /FVC < 0.7	21 (7.8%)	21 (3.7%)†
Pulmonary function (composite)	−0.32 (0.79)	0.19 (0.90)*
FVC, L	1.7 (0.55)	2.0 (0.61)*
FEV ₁ , L	1.4 (0.50)	1.7 (0.55)*
PEF, L/min	216 (89.0)	282 (112.4)*
Respiratory muscle (composite)	−0.31 (0.78)	0.15 (0.87)*
Maximal expiratory pressure, mm H ₂ O	59 (21.5)	70 (24.7)*
Maximal inspiratory pressure, mm H ₂ O	33 (18.0)	44 (20.2)*
Leg strength (composite)	−0.21 (0.75)	0.10 (0.85)*
BMI, kg/m ²	28.1 (6.10)	27.0 (4.76)†
Physical activity, h/wk	2.7 (3.66)	3.4 (3.74)*
Vascular risk factors, number	1.2 (0.81)	1.1 (0.57) ^{NS}
Smoking	101 (41.1%)	236 (37.4%) ^{NS}
Diabetes	41 (15.2%)	66 (11.5%) ^{NS}
Hypertension	187 (69.3%)	326 (56.8%)*
Vascular diseases, number	0.5 (0.75)	0.3 (0.79)*
Myocardial infarction	41 (39.8%)	62 (10.8%) ^{NS}
Congestive heart failure	16 (6.8%)	21 (4.3%) ^{NS}
Claudication	36 (13.3%)	29 (5.1%)*
Stroke	40 (13.9%)	44 (7.7%)†

Definition of abbreviations: BMI = body mass index; NS = not significant.

* *P* < 0.001.

† *P* < 0.01.

The cohort was divided on the basis of presence or absence of mobility disability at baseline (gait speed ≤ 0.55 m/s). Mean (SD, range). For the mini-mental state exam (possible range, 0–30), a higher score indicates a higher level of cognition. Pulmonary function refers to composite measure of pulmonary function based on *z* score of vital capacity, forced expiratory volume, and peak expiratory flow; a higher score indicates a higher level of pulmonary function. Composite measure of respiratory muscle strength was based on *z* score of maximal expiratory and inspiratory pressures; a higher score indicates a higher level of cognition. Composite measure of leg strength was based on mean *z* score of strength of hip flexion, knee extension, ankle dorsiflexion, and ankle plantar flexion bilaterally; a higher score indicates higher strength. Physical activity refers to self-reported frequency of participation in five physical activities (h/wk); a higher score indicates more frequent participation. Vascular risk factors refers to number of three risk factors (smoking, diabetes, and hypertension), self-reported. Vascular diseases refers to number of four vascular diseases (of myocardial infarction, congestive heart failure, claudication and stroke), self-reported.

TABLE 4. ASSOCIATIONS OF RESPIRATORY FUNCTION, LEG STRENGTH AND DEMOGRAPHICS

Variable	Sex*	Age†	Education‡
Pulmonary function	−15.91 (298), <i>P</i> < 0.001	−0.31‡	0.21‡
Respiratory muscle strength	−12.01 (321), <i>P</i> < 0.001	−0.26‡	0.14‡
Leg strength	−6.06 (341), <i>P</i> < 0.001	−0.21‡	0.10§

* From *t* tests comparing the means for women to those of men for each variable.

† Pearson correlation.

‡ *P* < 0.001.

§ *P* < 0.01.

quadratic terms for BMI, since both high and low BMI may be associated with adverse health outcomes. Model assumptions were examined graphically and analytically and were adequately met (21). Programming was done using SAS software (SAS Institute, Cary, NC) (22).

RESULTS

Baseline Pulmonary Function, Respiratory Muscle Strength, and Leg Strength Properties

There were 844 participants (74.4% female) included in these analyses, and their characteristics at baseline are included in Table 3. Measures were structured such that higher scores indicated better performance for all three measures. Baseline pulmonary function ranged from −2.3 to 3.2 (mean = 0.03; SD = 0.89). Baseline respiratory muscle strength ranged from −2.0 to 3.2 (mean = 0.001; SD = 0.87). Baseline leg strength ranged from −1.7 to 4.7 (mean = −0.001; SD = 0.83).

Pulmonary function, respiratory muscle strength, and leg strength were inversely related to age and positively associated with education, and men performed better than women on all three measures (Table 4). Pulmonary function was associated with respiratory muscle strength (*r* = 0.55, *P* < 0.001); leg strength was related to both pulmonary function (*r* = 0.35, *P* < 0.001) and respiratory muscle strength (*r* = 0.37, *P* < 0.001).

Pulmonary Function, Muscle Strength, and Incident Mobility Disability

Of the 574 persons without mobility disability at baseline, during an average follow-up of 4.0 years (SD = 1.39 yr), 264 (46.0%) developed mobility disability. In separate proportional hazards models controlling for age, sex, and education, pulmonary function, respiratory muscle strength, and leg strength were all associated with incident mobility disability (Table 2, *Models A–C*). For example, a 1-unit lower level of pulmonary function at baseline was associated with a 1.6-fold increase in the risk of developing mobility disability (Table 2, *Model A*). Similar effects were seen for a 1-unit lower level of respiratory muscle strength and leg strength at baseline (Table 2, *Models B and C*).

Another way of expressing the magnitude of the risk of developing mobility disability associated with a 1-unit lower level of baseline pulmonary function is to compare the estimate for pulmonary function with that of age. As noted above, we controlled for age in these analyses, and increased age at baseline was also associated with an increased risk of developing mobility disability (age hazard ratio [HR], 1.05; 95% CI, 1.03, 1.07). Age for these analyses was centered at 80 years; thus, there was about a 5% increase in the risk of developing mobility disability for each year above 80 at baseline. Comparison of the estimates for pulmonary function and age shows that the risk of developing mobility disability associated with a 1-unit lower level of pulmo-

nary function at baseline was comparable to a participant being more than 9 years older at baseline (pulmonary function: estimate, 0.467 vs. age: estimate, 0.050). A similar comparison would show that a 1-unit decrease in respiratory muscle strength at baseline was comparable the risk of being about 8 years older at baseline, and a 1-unit decrease in leg strength was comparable to being 6.5 years older at baseline.

Next, we conducted a series of models to determine whether the associations of pulmonary function, respiratory muscle strength and leg strength with mobility disability were attenuated when considered in combination and finally with all three together in a single model. In all four models, pulmonary function, respiratory muscle strength, and leg strength all remained associated with incident mobility disability (Table 2, *Models D–G*). In a final model, we repeated *Model G* and added possible confounders including BMI, physical activity, vascular risk factors including smoking, and vascular diseases. In this model, results were unchanged with the exception that the association of pulmonary function with incident mobility disability was slightly attenuated (Table 2, *Model H*).

Pulmonary Function, Muscle Strength, and Loss of the Ability to Ambulate

To further examine the robustness of the associations of pulmonary function, respiratory muscle strength, and leg strength with mobility disability, we examined their association with an alternative outcome, the loss of the ability to ambulate. Of the 844 persons ambulatory at baseline, 137 (16.2%) lost the ability to ambulate during follow-up (mean, 3.9 yr; SD = 1.39 yr). In separate proportional hazards models controlling for age, sex, and education, pulmonary function, respiratory muscle strength, and leg strength were all associated with the loss of the ability to ambulate (Table 5, *Models A–C*). For example, a 1-unit lower level of pulmonary function at baseline was associated with a 1.7-fold increased risk of losing the ability to ambulate. Similar effects were seen for a 1-unit lower level in respiratory muscle strength and leg strength at baseline.

We then examined a series of models to determine if pulmonary function, respiratory muscle strength, and leg strength attenuated one another's associations with loss of the ability to ambulate when considered in various combinations. In all three models, pulmonary function, respiratory muscle strength, and leg strength remained associated with risk of becoming unable to ambulate (Table 5, *Models D–F*). We then included terms for pulmonary function, respiratory muscle strength, and leg strength in a single model. Respiratory muscle strength and leg strength remained associated with the loss of the ability to ambulate but the association of pulmonary function with the loss of the ability to ambulate was slightly attenuated (Table 5, *Model G*). In a final model, we added possible confounders to the previous model including BMI, physical activity, vascular risk factors, and vascular diseases. The association of respiratory muscle strength and incident loss of the ability to ambulate was unchanged, but the associations of pulmonary function and leg strength with loss of the ability to ambulate were both attenuated (Table 5, *Model H*).

DISCUSSION

In a cohort of more than 800 ambulatory community-dwelling older persons without dementia, we found that, when considered separately and together, pulmonary function, respiratory muscle strength, and leg strength were relatively independently associated with incident mobility disability. These findings were unchanged when we considered a number of potential confounders including body composition, physical activity, and vascular risk factors including smoking and vascular diseases. In secondary analyses using the onset of the inability to ambulate as a complementary outcome, pulmonary function, respiratory muscle strength, and leg strength were also independently associated with the loss of the ability to ambulate. These findings do not support the hypothesis that pulmonary function mediates the association of muscle strength with mobility disability. However, these results do suggest that there are other factors and pathways that link pulmonary function, respiratory muscle strength, and leg

TABLE 5. PULMONARY FUNCTION, MUSCLE STRENGTH, AND LOSS OF THE ABILITY TO AMBULATE

Model	Pulmonary Function (HR [95% CI] P Value)	Respiratory Muscle Strength (HR [95% CI] P Value)	Leg Strength (HR [95% CI] P Value)
Model A	0.600 (0.454, 0.793) P < 0.001		
Model B		0.513 (0.391, 0.672) P < 0.001	
Model C			0.618 (0.464, 0.821) P < 0.001
Model D	0.724 (0.540, 0.971) P = 0.031	0.561 (0.422, 0.745) P < 0.001	
Model E	0.648 (0.490, 0.857) P = 0.002		0.656 (0.491, 0.877) P = 0.004
Model F		0.567 (0.429, 0.749) P < 0.001	0.725 (0.542, 0.968) P = 0.029
Model G	0.748 (0.558, 1.003) P = 0.053	0.612 (0.457, 0.820) P = 0.001	0.741 (0.552, 0.993) P = 0.045
Model H	0.827 (0.608, 1.125) P = 0.227	0.568 (0.417, 0.774) P < 0.001	0.761 (0.564, 1.027) P = 0.074

The hazard ratios for the one unit difference in pulmonary function, respiratory muscle strength and leg strength are summarized for a series of discrete-time proportional hazards models for the time to becoming unable to ambulate and which were all adjusted for age, sex and education. Each model includes additional terms for various combinations of pulmonary function, respiratory muscle strength and leg strength as follows. Model A included a term for pulmonary function alone; Model B included a term for respiratory muscle strength alone; Model C included a term for leg strength alone; Model D included terms for pulmonary function and respiratory muscle strength; Model E included terms for pulmonary function and leg strength; Model F included terms for respiratory muscle strength and leg strength; and Model G included terms for pulmonary function, respiratory muscle strength, and leg strength. Model H includes all the terms in Model G as well as terms for body mass index (BMI), BMI*BMI, physical activity, vascular risk factors, and vascular diseases.

strength with the development of mobility disability in the elderly.

Mobility decline in the elderly is common and associated with adverse health outcomes including death and disability (1, 2). Increased awareness and understanding of the growing burden of mobility disability in elders underscores the need to identify risk factors for its development to facilitate new intervention strategies. Prior studies have focused on leg strength and its relationship with mobility disability in the elderly (23–25). Recent work in this cohort has shown that both leg strength and respiratory muscle strength are independently associated with the rate of mobility decline in the elderly, but the factors which link muscle strength with mobility remain unclear (4, 18). While some previous studies have reported an association between pulmonary function and mobility disability in elders even after controlling for leg strength, none have also controlled for respiratory muscle strength (9, 26). The current study builds on previous studies by including all three factors (pulmonary function, respiratory muscle strength, and leg strength) in the same analyses. Results from the primary analyses showed that even when both leg strength and respiratory muscle strength were considered together with pulmonary function, all three factors were relatively independently associated with incident mobility disability. These findings were confirmed in secondary analyses using a complementary outcome, the loss of the ability to ambulate. We acknowledge that in the final model the *P* value for pulmonary function goes from being significant to a trend (Table 5, *Model A* vs. *Model G*); however, examination of the hazard ratios suggests that there is a similar magnitude of attenuation of the hazard ratio for respiratory muscle strength (Table 5, *Model B* vs. *Model G*). Nevertheless, further studies are needed to replicate these findings in other cohorts and to examine if consistent findings are obtained when other adverse health outcomes are considered.

The factors that link pulmonary function and muscle strength with mobility disability are not clear. Pulmonary dysfunction with impaired ventilation not only may cause muscle dysfunction, but may also affect multiple organ systems that contribute to mobility. For instance, impaired ventilation is also associated with increased circulating inflammatory markers and serum leptin, which may affect systemic metabolism as well as accelerate atherosclerosis and cardiovascular disease (27). This may explain recent reports that impaired ventilation is associated with subclinical cerebral white matter changes (28). Skeletal muscle plays a crucial role as the final effector of motor unit output controlling a wide range of motor functions including respiration, ambulation, and postural control (29). However, in addition to its integral role in motor function, muscle has pivotal roles in other nonmotor functions such as thermoregulation and systemic metabolism (30). Thus, respiratory muscle strength might be associated with mobility disability not only because of its role as part of the respiratory network but because of one its other essential nonmotor roles. Since muscle is located outside the blood-brain barrier, both respiratory and leg muscles are vulnerable to a wide range of systemic disorders and chronic diseases that can lead to impaired strength and mobility disability (31). Finally, both respiration and mobility are controlled by distinct distributed neural networks that begin in the brain and extend beyond the nervous system to the muscle in the periphery (6, 32–35). Thus, subclinical neuropathology at multiple levels of the neuroaxis may cause dysfunction of respiration or mobility. These findings extend previous work in this cohort by suggesting that respiratory muscle strength, leg strength, and physical activity make relatively independent contributions to mobility decline in elders and that these associations persist even when

pulmonary function is considered. Thus, physical activity and pulmonary function are likely to contribute to the development of mobility disability through mechanisms apart from their known effects on muscle strength and that a focus on a single physiologic system in older persons is insufficient for clarifying the biology of age-related mobility decline. Further work is needed to identify the factors that link pulmonary function and muscle strength with mobility disability in the elderly.

Our study has several limitations. First, the participants in this study are a selected group having agreed to post-mortem donation, so these results will need to be replicated in the general population. Respiratory muscle strength was measured with a hand-held device in the community and, in contrast to laboratory testing, data from only two trials were collected. In addition, hand-held dynamometry was used to measure lower extremity strength, which does not measure all of the important aspects of strength. Therefore, although respiratory and leg strength were both associated with mobility decline, the use of a more sensitive measure of strength might have shown attenuation of their association with mobility disability. Perhaps most importantly, a relative dichotomy was assumed between composite measures of respiratory muscle strength and pulmonary function. Strength was based on the assessment of inspiratory and expiratory muscle strength, both which derive from different muscles but are related. Similarly, the composite measure of pulmonary function was constructed from several measures that depend on varying degrees of both respiratory muscle strength and intrinsic lung function. Peak expiratory flow reflects mostly intrinsic pulmonary function characteristics, while vital capacity results from both pulmonary function and respiratory muscle strength. Consequently, composite pulmonary function is not a pure measure of lung function but, to some degree, reflects lung as well as some respiratory muscle contributions.

Despite these limitations, several factors increase confidence in the findings from this study. Perhaps most importantly, pulmonary function, respiratory muscle strength, and leg strength were evaluated as part of a uniform structured clinical evaluation and incorporated many widely accepted and reliable performance measures; objective gait performance was used to define end-points for mobility disability. Based on a uniform clinical evaluation and widely accepted diagnostic criteria, persons with dementia were excluded from analyses and a relatively large number of older persons were studied, resulting in adequate statistical power to identify the associations of interest while controlling for potentially confounding variables.

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