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Pulmonary Function, Muscle Strength and Mortality in Old Age

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Abstract

Numerous reports have linked extremity muscle strength with mortality but the mechanism underlying this association is not known. We used data from 960 older persons without dementia participating in the Rush Memory and Aging Project to test two sequential hypotheses: first, that extremity muscle strength is a surrogate for respiratory muscle strength, and second, that the association of respiratory muscle strength with mortality is mediated by pulmonary function. In a series of proportional hazards models, we first demonstrated that the association of extremity muscle strength with mortality was no longer significant after including a term for respiratory muscle strength, controlling for age, sex, education, and body mass index. Next, the association of respiratory muscle strength with mortality was attenuated by more than 50% and no longer significant after including a term for pulmonary function. The findings were unchanged after controlling for cognitive function, parkinsonian signs, physical frailty, balance, physical activity, possible COPD, use of pulmonary medications, vascular risk factors including smoking, chronic vascular diseases, musculoskeletal joint pain, and history of falls. Overall, these findings suggest that pulmonary function may partially account for the association of muscle strength and mortality.

Keywords

Muscle Strength; Respiratory Muscle Strength; Pulmonary Function; Mortality; Aging

1. Introduction

Numerous studies have reported that extremity muscle strength is associated with an increased risk of death in older persons (Al Snih, Markides, Ray, Ostir, & Goodwin, 2002; Laukkanen, Heikkinen, & Kauppinen, 1995; Metter, Talbot, Schrager, & Conwit, 2002; Newman et al., 2006; Phillips, 1986; Rantanen et al., 2000; Rantanen et al., 2003; Rolland et al., 2006).

However, the mechanisms underlying this association are not known. In some cases, loss of lower extremity muscle strength likely leads to mobility disability, falls, and death (de

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Rekeneire et al., 2003). However, it is possible that loss of extremity muscle strength may serve as an indicator of systemic disease and represent an early sign of physical frailty, which is associated with mortality (Buchman, Wilson, Bienias, & Bennett, 2008). A third possibility is that extremity muscle strength is a surrogate for weakness in other skeletal muscles such as respiratory muscles which may be more directly linked to mortality.

Respiratory muscle strength plays a key role in the respiratory network, which depends on intact neural circuitry which orchestrates the interplay between respiratory muscles and intrinsic pulmonary function to maintain adequate ventilation (Kim & Sapienza, 2005; Polkey & Moxham, 2001; Rantanen et al., 2003). In the absence of respiratory muscle activation, pressure gradients cannot be developed and air exchange at the alveolar surface cannot occur. Thus, impaired respiratory muscle strength can lead to pulmonary dysfunction, respiratory distress and even death. Therefore, we hypothesized that extremity muscle strength is a surrogate for respiratory muscle strength, and we also hypothesized that pulmonary function would mediate the association of respiratory muscle strength with mortality. While previous studies have examined the association of extremity muscle strength, respiratory muscle strength, and pulmonary function with mortality separately (Mannino, Buist, Petty, Enright, & Redd, 2003; Don D. Sin, Wu, & Man, 2005), we are unaware of any prior study that examined the joint effects of these three indices on risk of death.

We used data from more than 900 older persons without dementia participating in the Rush Memory and Aging Project, a longitudinal study of common chronic conditions of aging, to investigate the associations of extremity muscle strength, respiratory muscle strength and pulmonary function with mortality (Bennett, Schneider, Buchman et al., 2005). In a series of proportional hazards models, we first tested the hypothesis that extremity muscle strength is a surrogate for respiratory muscle strength. In subsequent models, we tested a second hypothesis that pulmonary function is a step in the causal chain linking respiratory muscle strength to death.

2. Methods

2.1 Participants

All participants are from the Rush Memory and Aging Project, a longitudinal investigation of common chronic conditions of old age (Bennett, Schneider, Buchman et al., 2005). 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. Clinical evaluations for the study commenced in 1997 but pulmonary function measures were not introduced into the study until 2001. Eligibility for these analyses required the absence of clinical dementia (see below) prior to or at the evaluation when pulmonary function was first obtained as well as a valid extremity muscle strength assessment. We excluded 74 of 1034 potentially eligible participants due to dementia; this resulted in a group of 960 persons eligible for these analyses. Their mean age at baseline was 80.7 years (SD, 7.4), the mean education was 14.4 years (SD, 3.0), and the mean Mini-Mental Status Exam score was 28.0 (SD, 2.1); 74.9% were women and 92.5% were white and non-Hispanic.

2.2 Clinical Diagnoses

Clinical diagnoses were made using a multi-step process, as previously described (Bennett et al., 2006). First, subjects underwent detailed annual cognitive function testing which included 21 cognitive performance tests. Second, the cognitive test data were reviewed by an experienced neuropsychologist who determined if cognitive impairment was present. Next, participants were evaluated in person by an experienced neurologist or geriatrician blinded to all previously collected data; this physician then used all available cognitive and clinical testing

results from the current years' evaluation to diagnose dementia. A composite measure of cognitive function based on 19 of the tests was used in these analyses. Detailed information about the individual cognitive tests and the construction of the composite cognitive measure are published elsewhere (Bennett, Schneider, Buchman et al., 2005; Wilson et al., 2005).

2.3 Assessment of Extremity Muscle Strength

Muscle strength was measured using portable hand-held dynamometers (Lafayette Manual Muscle Test System, Model 01163, Lafayette, IN). The hand-held dynamometer was used to assess seven muscle groups, including muscle strength in both arms (arm abduction, arm flexion, arm extension) and both lower extremities (hip flexion, knee extension, plantar flexion, and ankle dorsiflexion). In addition, grip and pinch strength were measured bilaterally using the Jamar hydraulic hand and pinch dynamometers (Lafayette Instruments, Lafayette, IN). The mean score for each of the nine muscle groups was converted to a z score, using the baseline mean and standard deviation of all study participants, and the z scores were averaged to yield a composite measure of extremity muscle strength as previously described (Buchman, Wilson, Boyle, Bienias, & Bennett, 2007).

2.4 Assessment of Respiratory Muscle Strength

Muscles needed for adequate respiration include the diaphragm and intercostal muscles which are innervated by cervical and thoracic root segments not involved in limb movements (Kim & Sapienza, 2005). One can isolate and estimate respiratory muscle strength by measuring the maximal pressures generated during inspiration [maximal inspiratory pressures, MIP] and expiration [maximal expiratory pressures, MEP] (Enright, Kronmal, Manolio, Schenker, & Hyatt, 1994; Kim & Sapienza, 2005). A hand-held device that contains a pressure sensitive transducer was used to assess MIP and MEP in cm H₂O [MicroMouth Pressure Meter MP01; MicroMedical Ltd., Kent, UK]. Two trials of both MIP and MEP were measured. The mean score for MIP and MEP were converted to z scores and averaged to yield an overall measure of respiratory muscle strength as previously described (Buchman, Wilson, Boyle, Bienias et al., 2007).

2.5 Assessment of Pulmonary Function

Pulmonary function was tested using a hand-held spirometer which measured vital capacity (VC), forced expiratory volume in one second (FEV1) and peak expiratory flow (PEF) [MicroPlus Spirometer MS03, MicroMedical Ltd. Kent, UK] (Otulana et al., 1990). 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 computing the average of the z scores for VC, FEV1, PEF as previously described (Buchman, Wilson, Boyle, Tang et al., 2007).

2.6 Mortality

Participation in the Memory and Aging Project includes agreeing to donation of brain, spinal cord, and selected muscles and nerve at the time of death and the study has an autopsy rate of more than 80%. Thus, determination of mortality is most commonly made at the time of death. In the event that autopsy was not successful, additional mechanisms for determining vital status include attempted contact by telephone. At the time of these analyses, 100% of the vital status data were complete and up to date.

2.7 Other Covariates

Gender and race were recorded at the baseline interview. Race and ethnicity questions and categories were the same as those used by the 1990 U.S. Census. Age in years was computed

from self-reported date of birth and date of the clinical examination at which the muscle strength measures were collected. Education (reported highest grade or years of education) was obtained at the time of the baseline cognitive testing. Weight and height were measured and recorded at each visit by a trained technician blinded to previously collected data. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. We included a term for BMI for linear associations and a quadratic term for BMI (BMI*BMI) because both low and high values of BMI can be associated with adverse health consequences. Physical activity was assessed with questions adapted from the 1985 Health Interview Survey (McPhillips, Pellettera, Barrett-Connor, Wingard, & Criqui, 1989). The times spent participating in each of five physical activities (e.g., walking for exercise), were combined across activities to provide an index of hours of physical activity per week, as previously reported (Bennett, Schneider, Buchman et al., 2005). Parkinsonian signs were based on a modified version of the motor portion of the Unified Parkinson's Disease Rating Scale (Boyle et al., 2005). Balance was based on three lower extremity performances including standing on each leg, standing on their toes and the number of steps off the line when asked to walk heel to toe as previously described (Buchman, Wilson, Boyle, Bienias et al., 2007). Frailty was based on five components including strength, timed walk, physical activity, BMI and fatigue as described previously (Buchman et al., 2008; Fried et al., 2001). To assess the influence of vascular risk factors and vascular disease burden on the association of motor function and mortality, the number of three vascular risk factors (i.e. the sum of hypertension, diabetes mellitus, and smoking), and four vascular diseases (myocardial infarction, congestive heart failure, claudication, and stroke) were used as covariates in the analyses (Boyle et al., 2005). Falls during the past year and the presence or absence of joint pain were based on participant report (Bennett, Schneider, Buchman et al., 2005). In addition, forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) were measured with a hand-held spirometer (MicroPlus® Spirometer MS03, MicroMedical Ltd.). In order to examine the possibility that participants with possible pulmonary disease influenced the results, we considered participants to have possible chronic obstructive pulmonary disease (COPD) if the ratio of FEV1/FVC was < 0.7, as suggested by previous literature (Iqbal, Schloss, George, & Isonaka, 2002). In addition, for these analyses, participants who were receiving one or more medications used to treat chronic pulmonary diseases including anticholinergics, beta-adrenergics, theophylline, steroid inhalants, and leukotrienes were considered to have possible pulmonary disease. Medications were inspected and coded using the Medi-Span® system [Medi-Span, Inc.] (Bennett, Schneider, Buchman et al., 2005).

2.8 Data Analysis

Pearson (r) correlations were used to assess the relationship of measures of extremity strength and respiratory function with age and education and t-tests to examine sex differences in motor function. We used t-tests or z value of Wilcoxon two sample test to compare the baseline characteristics of participants who did and did not die during the course of the study.

The first goal of the statistical analyses was to test the hypothesis that extremity muscle strength was a surrogate for respiratory muscle strength in its association with mortality. Therefore, we constructed a Cox proportional hazards model to estimate risk of death associated with extremity strength, controlling for the potential confounding effects of age, sex, education, and BMI. Because education entered as a continuous linear term violated the assumption of proportional hazards, we converted education into a trichotomous categorical measure (0–8 years, 9–12 years and 13 or more years of education) with 0–8 years as the reference category. Because there are known sex differences with respect to muscle strength, we also added an additional term to each of these three models to examine whether there was an interaction with sex. We then added a term for respiratory muscle strength to the model. In these models, losing

the effect of extremity muscle strength would suggest that it is a surrogate for respiratory muscle strength.

Next we tested the hypothesis that impaired respiratory muscle strength can lead to pulmonary dysfunction and subsequent death. To do this we conducted a form of mediation analysis. In this case, we first establish a relationship between respiratory muscle strength and mortality in a Cox proportional hazards model controlling for age, sex, and education. Next, we add a term for pulmonary function to the model and examine the effect of the new term to the association of respiratory muscle strength with mortality. If pulmonary function mediates the association (i.e., is a step in the causal chain linking respiratory muscle strength to mortality), then the effect of respiratory muscle strength on mortality should be markedly reduced. This type of analysis does not rule out other more complex interactions between pulmonary function and respiratory muscle strength. While mediation and confounding are identical statistically, they can be distinguished on conceptual grounds (MacKinnon, Krull, & Lockwood, 2000; Victora, Huttly, Fuchs, & Olinto, 1997). For example, there is no *a priori* conceptual basis to think that respiratory muscle strength would link extremity muscle strength to death while there is reason to think of extremity strength as a confounder. By contrast, there is a large body of literature to support the plausibility of a causal sequence such that loss of respiratory muscle strength will lead to pulmonary dysfunction and subsequent death. We subsequently added a number of terms to address the role of other potential confounding variables. The Cox proportional hazards models were validated graphically and analytically. Programming was done in SAS [SAS Institute Inc, Cary, NC] (SAS, 2000).

3. Results

3.1 Descriptive Properties of Extremity Muscle Strength and Respiratory Function

Extremity muscle strength ranged from -1.6 to 4.4 (mean= -0.005 ; SD= 0.73) with higher scores indicating greater muscle strength. Respiratory muscle strength ranged from -2.0 to 2.9 (mean= 0.022 ; SD= 0.89), with higher scores indicating greater muscle strength. Pulmonary function ranged from -2.3 to 3.3 (mean= 0.002 ; SD= 0.90) with higher scores indicating better performance.

Extremity muscle strength, respiratory muscle strength and pulmonary function were inversely related to age and positively associated with education, and men performed better than women on all three measures (Table 1). Extremity muscle strength was correlated with respiratory muscle strength ($r=0.49$, $p < 0.001$) and pulmonary function ($r=0.46$, $p < 0.001$). Respiratory muscle strength was also correlated with pulmonary function ($r=0.50$, $p < 0.001$); however, their correlation accounts for only about 25% of the shared variance, suggesting that while these variables are related, they measure different aspects of respiratory function

3.2 Extremity Muscle Strength and Risk of Death

We first examined the relation of extremity muscle strength to risk of death to confirm this well known association in this cohort. During a mean follow-up of more than two years (mean= 2.2 years, SD= 1.2 ; range 0 to 4.1 years), 114 persons died (11.9%). The mean time to death after the baseline evaluation was 1.4 years (SD= 1.1 ; range 0 to 4.0 years). Participants who died during the course of follow-up were older at baseline, performed more poorly on the Mini-Mental Status Test, had lower BMI and lower performance on each of the individual components used to construct the three composite measures used in these analyses (Table 2).

In a hazards model which controlled for age, sex, education and body mass index, higher levels of extremity muscle strength were associated with a reduced risk of death (Table 3, Model A). Because the effect size is not intuitively obvious from the composite measure, we compared

the effect size for strength to the effect size for age. The effect of a one unit increase of extremity muscle strength at baseline (Model A) was similar in magnitude to being 6 years younger at baseline (Age: HR, 1.11; 95% CI: 1.07, 1.14).

3.3 Extremity Muscle Strength, Respiratory Muscle Strength and Mortality

In a series of models, we examined the extent to which the association of extremity muscle strength with mortality was due to the fact that it serves as a surrogate for respiratory muscle strength. First we needed to show that both extremity muscle strength and respiratory muscle strength alone are associated with mortality. Above we showed that extremity muscle strength was associated with mortality. Next, we documented the association of respiratory muscle strength with mortality in a Cox proportional hazards model (Table 3, Model B). In this model, the effect of a one unit increase of respiratory muscle strength at baseline was associated with a reduced risk of death comparable to being about 7 years younger at baseline [Age: HR, 1.10; 95% CI: 1.07, 1.14).

Next, we examined both extremity and respiratory muscle strength in the same proportional hazards model. In this model, losing the association of extremity muscle strength with mortality when respiratory muscle strength was included, would suggest that extremity muscle strength is a surrogate for respiratory muscle strength. In this analysis, the association of extremity muscle strength with mortality was significantly reduced with only a trend for significance, whereas the association of respiratory muscle strength with mortality remained significant and was only marginally attenuated (Table 3, Model D). These data raise the possibility that the association of extremity muscle strength with mortality is at least partly due to the fact that extremity strength may be a partial surrogate for respiratory muscle strength.

3.4 Respiratory Muscle Strength, Pulmonary Function and Mortality

In the next series of models, we tested the hypothesis that respiratory muscle strength is at the beginning of a causal chain which can lead to pulmonary dysfunction and death. In other words, we examined the extent to which pulmonary function mediated the association of respiratory muscle strength with the risk of death.

We first documented the effect of pulmonary function on mortality in a Cox proportional hazards model, as above (Table 3, Model C). In this model, the effect of a one unit increase of pulmonary function at baseline was associated with a reduced risk of death comparable to being about 9 years younger at baseline (Age: HR, 1.09; 95% CI: 1.06, 1.13).

Next, we examined the extent to which the association of respiratory muscle strength with mortality was mediated by pulmonary function by including both terms in the same model. In this analysis, the association of respiratory muscle strength with mortality was attenuated by more than 50% and was no longer significant; by contrast, the association of pulmonary function with mortality was only marginally reduced and remained highly significant (Table 3, Model E).

In a final model, we added a term for extremity muscle strength, so that all three measures were included together. In this analysis, the findings were essentially unchanged (Table 3, Model F). These data are consistent with a pathway linking respiratory muscle strength with mortality through an effect on pulmonary function.

Two sets of survival curves in Figure 1 illustrate the analyses, which suggest that pulmonary function mediates the association of respiratory muscle strength and mortality. Each figure shows the estimated risk of death at low (25th percentile, solid line) and high (75th percentile, dotted line) levels of the predictor variable. Survival curves in the left column (Figure A and C) show the associations of pulmonary function and respiratory muscle strength alone and risk

of mortality estimated from separate analyses (Table 3, Models B and C), whereas the survival curves in the right hand column (Figures B and D) were estimated from a model including pulmonary function and respiratory muscle strength together (Table 3, Model E). Thus for example, when comparing figures A and B, the solid and dotted lines for low and high respiratory muscle strength in figure B are closer together than in figure A. This suggests that the association of respiratory muscle strength and mortality is reduced when pulmonary function is included together in the same model (Figure B). In contrast, when comparing figures C and D, the relative lack of change in the distance between the lines for low and high pulmonary function suggests that the association of pulmonary function and mortality is not dramatically affected by the inclusion of a term for respiratory muscle strength in the same model.

3.5 Muscle Strength, Pulmonary Function, Mortality and Potential Confounders

We repeated the last model (Table 3, Model F) several times adding a term for one of several covariates known to be associated with muscle strength, pulmonary function or mortality, to determine whether they might account for the associations of extremity and respiratory muscle strength and pulmonary function with mortality. These included: BMI, global cognition, parkinsonian signs, frailty, balance, physical activity, possible COPD, use of pulmonary medications, chronic vascular risk factors including smoking and vascular disease burden, musculoskeletal joint pain, history of falls. In these analyses, the results were unchanged, suggesting that the associations reported above were not due to the influence of these covariates (results not shown).

4. Discussion

In a cohort of 960 older persons without dementia, we examined the associations of extremity muscle strength, respiratory muscle strength and pulmonary function with mortality. Consistent with our first hypothesis, that extremity muscle strength is a surrogate for respiratory muscle strength and that respiratory muscle strength may account for the well-established association between extremity muscle strength and mortality, we found that the association of extremity muscle strength with mortality was attenuated by more than 30% and was no longer significant when considered together with respiratory muscle strength. Moreover, the association of respiratory muscle strength with mortality was attenuated by more than 50% and was no longer significant when respiratory muscle strength was considered together with pulmonary function, suggesting that the association of respiratory muscle strength and mortality is mediated through pulmonary function. In a final model in which we examined extremity muscle strength, respiratory muscle strength, and pulmonary function together, the associations of both extremity muscle strength and respiratory muscle strength with mortality were reduced to non-significance while pulmonary function remained highly significant. The findings were unchanged after controlling for several potential confounders. Overall, our findings suggest that respiratory muscle strength is at the beginning of a causal chain which can lead to reduced pulmonary function and death. Thus pulmonary function may partially account for the association between muscle strength and mortality. These findings underscore the importance of maintaining respiratory muscle strength in the elderly and of the need for interventions which focus on improving respiratory muscle strength and pulmonary function to decrease mortality.

Several previous studies have shown that extremity muscle strength declines with age and that lower levels of arm or leg strength are associated with increased risk of death (Al Snih et al., 2002; Laukkanen et al., 1995; Metter et al., 2002; Newman et al., 2006; Phillips, 1986; Rantanen et al., 2000; Rantanen et al., 2003; Rolland et al., 2006). While the association between extremity muscle strength and mortality is well-established, the biologic basis for this

association is poorly understood (Newman et al., 2006). It is unlikely that extremity muscle strength contributes directly to mortality; rather, it is more likely that extremity muscle strength is a proxy for other processes which lead to death, particularly those involving changes in skeletal muscle. The most extensively studied aspect of skeletal muscle is with respect to motor function. Skeletal muscle, controlled by spinal motor neurons, is the final effector of movement which is the output of an integrated set of motor control systems that reside throughout the central nervous system (Enoka & Fuglevand, 2001; Roos, Rice, & Vandervoort, 1997). Thus, impaired muscle function may reflect central nervous system dysfunction (e.g. stroke) that may lead to death. In addition, muscle plays a vital role in many metabolic processes (Vandervoort, 2002), and is known to be affected by a number of systemic disorders and common chronic diseases (Gosker, Wouters, van der Vusse, & Schols, 2000). Thus, the association of extremity muscle strength with mortality could be partially due to the fact that extremity muscle strength may serve as a surrogate for one of the many other essential roles of muscle that affect survival. This issue has not been examined in previous studies.

Impaired respiratory muscle strength has been studied extensively in patients with cardiac, pulmonary and neuromuscular disorders and is a widely recognized contributor to ventilatory failure and mortality in these conditions (Lyll, Donaldson, Polkey, Leigh, & Moxham, 2001; Meyer et al., 2001; Naeije, 2005). However, there are limited data on the association of respiratory muscle strength with mortality in older persons without known pulmonary disease (van der Palen et al., 2004). The present study expands upon findings from prior studies and shows that respiratory muscle strength is associated with mortality in older persons without known respiratory diseases. In addition, although previous studies have examined the separate associations of extremity muscle strength or respiratory function with mortality, they have not examined both of these measures of muscle strength together. When we examined extremity muscle strength and respiratory muscle strength together, the association of extremity muscle strength and mortality was reduced and no longer significant (Table 3, Models D). This suggests that extremity muscle strength may act as a surrogate for respiratory muscle strength, which to some extent accounts for the well-established association of extremity muscle strength with mortality.

While there are many causes for decreased pulmonary function, impaired respiratory muscle strength would be expected to lead to decreased ventilatory capacity (Naeije, 2005). However, there are few studies which have explicitly tested the degree to which respiratory muscle strength and other pulmonary function measures attenuate one another when considered together. One recent study reported that maximal inspiratory pressure was associated with cardiovascular disease outcomes (van der Palen et al., 2004). In that study, the association of maximal inspiratory pressure with disease outcomes was attenuated when FEV1 was included in the model and was no longer associated with disease outcomes (van der Palen et al., 2004). The attenuation of the association of MIP with disease when examined simultaneously with FEV1 is similar to the findings in the present study (Table 3, Model E). The results of the analyses in the previous study as well as the current study are in some measure consistent with a causal sequence of events in which impaired respiratory muscle strength leads to pulmonary dysfunction (i.e., pressure gradients cannot be developed and air exchange at the alveolar surface cannot occur leading to respiratory distress and death) (Kim & Sapienza, 2005; Polkey & Moxham, 2001). Thus, when pulmonary function is included in the same model as respiratory muscle strength, the latter is no longer associated with mortality since its association with mortality is mediated through pulmonary function and the latter is further along the chain of events leading to death.

Mediation analyses are increasingly being used in behavioral and epidemiological studies in an effort to move beyond simple associations and investigate potential intermediate steps in a causal chain that link risk factors to adverse clinical outcomes (MacKinnon et al., 2000; Victora

et al., 1997). In this case, mediation analyses address the extent to which pulmonary function represents a key step in the causal chain linking respiratory muscle strength with mortality. The approach is similar to identifying mediating factors that account for the association between hypertension and ischemic stroke. For example, one mechanism by which hypertension leads to stroke is cerebral atherosclerosis. It would be expected that a change in the relationship between hypertension and stroke would be observed after controlling for carotid atherosclerosis in an analysis, as atherosclerosis is an important link in the causal chain. We have used these types of analyses to investigate how postmortem indices work together and with a variety of risk factors to lead to cognitive impairment (Bennett, Schneider, Wilson et al., 2005). Although the findings from this study suggest that the association of muscle strength with mortality is mediated through pulmonary function, they do not preclude the possibility that muscle strength may be linked to mortality through other mechanisms. As noted above, muscle is multifunctional and may contribute or be associated with mortality via a variety of pathways.

Impaired ventilation may contribute to mortality most directly through its regulation of oxygenation and multisystem dysfunction secondary to hypoxia. Recent studies have reported that impaired ventilation is associated with subclinical changes in cerebral white matter and may increase the risk of stroke (Liao et al., 1999). Circulating inflammatory factors or hormones such as leptin also have been reported to be elevated with impaired ventilation, and these may accelerate atherothrombosis and vascular disease that may affect mortality secondary to cardiovascular events or stroke (D. D. Sin & Man, 2003; Yende et al., 2006). Impaired ventilation is associated with decreased exercise capacity, which may increase cardiovascular risk factors and the risk of ischemic heart disease and stroke. Lastly, oxidative stress with a variety of aberrations in oxidants, can cause a variety of respiratory diseases and may account in part for the association between impaired ventilation and mortality (Drost et al., 2005). The lung is a primary defense organ against environmental toxins, and impaired ventilation could lead to decreased tolerance of environmental toxins and thereby contribute to disease and death (Schunemann, Dorn, Grant, Winkelstein, & Trevisan, 2000).

This study has several limitations: first, our results are based on a selected group of participants more highly educated who agreed to organ donation at death, so replication of these results in population-based studies will be important. There also are limits to the measurements employed in this study. Hand-held dynamometry, which was used to measure muscle strength in the proximal arms and legs, does not measure all of the important aspects of muscle strength. Therefore, the use of a more sensitive measure of extremity muscle strength might have shown less attenuation when considered together with respiratory muscle strength. Thus, these findings will need to be replicated using more sensitive measures of muscle strength. Perhaps most importantly, a relative dichotomy was assumed between composite measures of respiratory muscle strength and pulmonary function. Composite respiratory muscle 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 which 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. Another limitation is that mediation models assume a causal chain without a recursive relationship between measures, and as noted above, hypoxia secondary to decreased pulmonary function from non-muscle diseases may also exacerbate impaired respiratory muscle strength.

Despite study limitations, several factors increase confidence in these findings. This study was based on a large number of community-based persons and those with dementia were excluded based on a uniform clinical evaluation and widely accepted diagnostic criteria; thus, we there was adequate statistical power to identify the associations of interest while controlling for potentially confounding variables. Multiple measures of muscle strength in arms and legs, spirometry and respiratory muscle strength were measured directly and summarized into composite measures that were used in these analyses. The use of composite measures with mediation analyses are useful for moving beyond simple associations to yield potential intermediate steps linking performance measures with mortality.

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Figure 1. Pulmonary Function, Respiratory Muscle Strength and Mortality

These figure shows the cumulative hazard for the risk of death during the study in two participants with moderately low (25th percentile) and high (75th percentile) respiratory muscle strength and pulmonary function. A shows the estimated risk of death for a person with low (25th percentile, solid line) and high (75th percentile, dotted line) levels of respiratory muscle strength and is contrasted with B when an additional term is added to control for pulmonary function. C shows the estimated risk of death for a person with low (25th percentile, solid line) and high (75th percentile, dotted line) levels of pulmonary function and is contrasted with D when an additional term is added to control for respiratory muscle strength. All models controlled for age, sex and education.

Table 1Intercorrelations of Extremity Muscle Strength and Respiratory Function Correlations^b

Variable	Sex ^a	Age	Education
Extremity Muscle Strength	-11.7 [354], p<0.001	-0.25	0.16
Respiratory Muscle Strength	-11.3 [361], p<0.001	-0.21	0.14
Pulmonary Function	-15.4 [320], p<0.001	-0.31	0.21

^aFrom t-tests comparing the means for women minus men for each variable. Degrees of freedom are based on Satterthwaite's approximation when the variances of the two groups were statistically unequal.

^bPearson correlation p<0.001 for all correlations.

Table 2

Characteristics of the Cohort at Baseline^a

Variable	Died (N=114)	Did Not Die (N=846)	Significance ^b
Age (years)	85.3 (5.7)	80.1 (7.3)	t[169]=-8.78, p<0.001
Education (years)	14.2 (3.1)	14.5 (3.0)	t[958]=-1.03, p=0.304
BMI	26.5 (5.7)	27.5 (5.4)	z = -2.18, p=0.029
Minimetal Status Exam	27.4 (2.5)	28.0 (2.1)	z = -2.48, p=0.013
Arm Abduction (lbs.)	3.0 (2.2)	4.0 (2.3)	t[941]=-4.20, p<0.001
Arm Flexion (lbs.)	10.9 (4.5)	12.8 (5.4)	t[158]=-4.14, p<0.001
Elbow Extension (lbs.)	9.6 (3.8)	10.6 (3.6)	t[953]=-2.58, p=0.010
Grip (lbs.)	45.9 (17.4)	48.0 (18.0)	t[957]=1.21, p=0.228
Pinch (lbs.)	9.4 (4.8)	10.7 (5.0)	t[954]=-2.53, p=0.012
Hip Flexion (lbs.)	9.1 (4.3)	10.6 (4.7)	t[946]=-3.11, p=0.002
Knee Extension (lbs.)	9.3 (3.1)	10.6 (4.0)	t[163]=-4.04, p<0.001
Plantar Flexion (lbs.)	13.9 (4.5)	15.3 (5.1)	t[950]=-2.66, p=0.008
Ankle Dorsiflexion (lbs.)	9.3 (4.0)	11.6 (4.9)	t[160]=-5.67, p<0.001
Maximal Expiratory Pressure (mm H ₂ O)	61.2(24.4)	66.5(24.2)	t[954]=-2.19, p=0.023
Maximal Inspiratory Pressure (mm H ₂ O)	34.6(21.9)	40.5(19.9)	t[954]=-2.93, p=0.004
Forced Expiratory Volume (Liter)	1.4 (0.6)	1.6 (0.5)	t[958]=-3.93, p<0.001
Vital Capacity (Liter)	1.7 (0.6)	1.9 (0.6)	t[958]=-2.88, p=0.004
Peak Expiratory Flow (Liter/minute)	237 (110)	268 (108)	t[958]=-4.00, p<0.001
Composite Extremity Muscle Strength	-0.28 (0.63)	0.31 (0.74)	t[159]=-4.81, p<0.001
Composite Respiratory Muscle Strength	-0.20 (0.95)	0.05 (0.88)	t[958]=-2.87, p<0.005
Composite Pulmonary Function	-0.30 (0.92)	0.04 (0.89)	t[958]=-3.89, p<0.001
Smoking History	37.7 %	40.0%	t[957]=-0.470, p=0.641
Possible Pulmonary Disease	12.7%	4.3%	t[958]=-3.30, p<0.001
Pulmonary Medications	18.4 %	7.2%	t[958]=-4.05, p<0.001

^aMean and standard deviation.

^bt-test or z value of Wilcoxon two sample test and p value; Satterthwaite-adjusted degrees of freedom as appropriate.

Table 3
Pulmonary Function Mediates the Association of Muscle Strength with Mortality ^a

	Extremity Muscle Strength	Respiratory Muscle Strength	Pulmonary Function
Model A	HR, 0.56; 95% CI: 0.38, 0.83 Est., -0.57; SE, 0.20; p=0.004		
Model B		HR, 0.63; 95% CI: 0.48, 0.83 Est., -0.46; SE, 0.14; p<0.001	
Model C			HR, 0.47; 95% CI: 0.36, 0.62 Est., -0.75; SE, 0.13; p<0.001
Model D	HR, 0.68 95% CI: 0.46, 1.01 Est., -0.39; SE, 0.20; p=0.06	HR, 0.69; 95% CI: 0.52, 0.92 Est., -0.37; SE, 0.15; p=0.01	
Model E		HR, 0.80; 95% CI: 0.60, 1.07 Est., -0.22; SE, 0.15; p=0.13	HR, 0.52; 95% CI: 0.39, 0.68 Est., -0.66; SE, 0.14; p<0.001
Model F	HR, 0.76; 95% CI: 0.50, 1.15 Est., -0.27; SE, 0.21; p=0.20	HR, 0.85; 95% CI: 0.63, 1.15 Est., -0.17; SE, 0.15; p=0.28	HR, 0.53; 95% CI: 0.40, 0.71 Est., -0.63; SE, 0.15; p<0.001

^aBased on Cox proportional hazards models with mortality as the outcome and all models adjusted for age, sex, education and BMI. Hazards Ratio (**HR**) and 95% confidence interval (**95% C.I.**) as well as estimates (**Est.**); standard error (**S.E.**) and significance (**p value**) are included for each of the predictors included in the different models examined.