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Dyspnea in Community-Dwelling Older Persons: A Multifactorial Geriatric Health Condition

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Abstract

Objectives—The evaluation of dyspnea in older persons is traditionally focused on cardiorespiratory diseases, rather than systematically evaluating the multiple impairments that often occur with advancing age and which may also contribute to dyspnea. Accordingly, we have evaluated the associations between a broad array of cardiorespiratory and non-cardiorespiratory impairments and dyspnea in older persons.

Design—Cross-sectional.

Setting—Cardiovascular Health Study.

Participants—4,413 community-dwelling persons; mean age was 72.6, 57.1% were female, 4.5% were African-American, 27.2% had less than a high school education, and 54.7% were ever-smokers.

Measurements—Dyspnea severity (American Thoracic Society grade ≥2 defined moderate-to-severe) and several impairments, including those established by: spirometry (forced expiratory volume in 1-second [FEV_1]), maximal inspiratory pressure (respiratory muscle strength), echocardiography, ankle-brachial index, blood pressure, whole-body muscle mass (bioelectrical impedance), single chair stand (lower extremity function), grip strength, serum hemoglobin and

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creatinine, Center for Epidemiologic Studies Depression Scale (CES-D), Mini Mental State Examination, medication use, and body mass index (BMI).

Results—In a multivariable logistic regression model, impairments having strong associations with moderate-to-severe dyspnea included: FEV_1 <lower limit of normal (adjusted odds ratios [adjOR] [95% confidence interval]=2.88 [2.37, 3.49]); left ventricular ejection fraction <45% (adjOR=2.12 [1.43, 3.16]); unable to perform a single chair stand (adjOR=2.10 [1.61, 2.73]), depressive symptoms (CES-D≥16; adjOR=2.02 [1.26, 3.23]); and obesity (BMI≥30; adjOR=2.07 [1.67, 2.55]). Impairments having modest but still statistically significant associations with moderate-to-severe dyspnea included respiratory muscle weakness, diastolic cardiac dysfunction, grip weakness, anxiety symptoms, and use of cardiovascular and psychoactive medications (adjORs ranged from 1.31-1.71).

Conclusion—In community-dwelling older persons, several cardiorespiratory and non-cardiorespiratory impairments were significantly associated with moderate-to-severe dyspnea, akin to a multifactorial geriatric health condition.

Keywords

dyspnea; aging; lung diseases; cardiovascular disease; geriatric syndromes

INTRODUCTION

Dyspnea in older persons merits strong consideration as a key public health concern. Across twenty study populations of older persons, for example, the prevalence of dyspnea at a moderate-to-severe level ranged from 17% to 62%,[1] with the highest rates in those aged ≥ 80.[2] Dyspnea at a moderate-to-severe level occurs at low exertional workloads, corresponding to activities of daily living, and is associated with decreased functional status and quality of life, and increased health care costs, hospitalization, and mortality.[1-6]

The evaluation of dyspnea in older persons is traditionally focused on cardiorespiratory diseases,[1,7] rather than systematically evaluating the multiple impairments that often occur with advancing age and which may also contribute to dyspnea.[3,8] The need for a comprehensive approach is informed by studies in older persons showing that a spirometric impairment has a poor positive predictive value for dyspnea (and vice versa),[9] and that cardiac dysfunction is an infrequent cause of dyspnea.[10] Importantly, even in persons with chronic obstructive pulmonary disease (COPD) and heart failure, the forced expiratory volume in 1 second (FEV_1) and left ventricular ejection fraction (LVEF) do not fully explain the experience of dyspnea.[11]

Accordingly, we propose a comprehensive approach when evaluating dyspnea in older persons, based on mechanisms that are both clinically and physiologically plausible. In particular, since an exertional component is a prominent clinical feature, a conceptual exercise model should be considered, including respiratory, cardiovascular, and musculoskeletal impairments.[12] In addition, since the ventilatory response is a prominent physiological factor, consideration should be given to a conceptual ventilatory model that describes dyspnea as a patient-perceived breathing discomfort arising from an imbalance

between ventilatory capacity and ventilatory demand.[12-15] In the latter model, additional impairments are identified, including neuropsychologic, medication related, hematologic (hemoglobin), renal, and nutritional. The diagnostic criteria for establishing the noted impairments, including corresponding pathways that lead to dyspnea, are described in the Methods section.

In the current study, using data from the Cardiovascular Health Study (CHS), a large, population-based sample of community-dwelling older persons,[16] we systematically evaluated the associations of a broad array of cardiorespiratory and non-cardiorespiratory impairments with dyspnea at a moderate-to-severe level.[17,18] In addition, as a secondary aim, we calculated the predicted probability of moderate-to-severe dyspnea in which key impairments were added cumulatively in a clinically meanigful sequence. We hypothesized that several impairments would be associated with moderate-to-severe dyspnea and that their multiple occurrence would substantially increase the predicted probability of having moderate-to-severe dyspnea, consistent with a multifactorial geriatric health condition as previously described for falls, dizziness, and delirium.[19-22]

METHODS

Study Population

The CHS is a population-based study of persons aged ≥65, identified from a random sample of Medicare eligibility lists in four U.S. communities.[16] Participants were community-dwelling, lacked mobility disability or severe cognitive impairment, and gave written informed consent. In the current study, the analytical sample included CHS participants who at baseline completed an American Thoracic Society (ATS) dyspnea questionnaire and at least two ATS-acceptable spirometric maneuvers (described below).[17,23-25] The rationale for these inclusion criteria was based on the outcome of interest being dyspnea and the high likelihood of CHS participants having a spirometric impairment (high prevalence of ever-smokers and of exposure to environmental tobacco smoke).[26] Hence, we evaluated the original CHS cohort that was recruited in 1989 and 1990 (N=5,201), of whom 4,413 participants met our inclusion criteria.

Demographic and Clinical Characteristics

Baseline characteristics included age, sex, race, education level, smoking status, and self-reported medical conditions. Exertional dyspnea was evaluated by the ATS questionnaire, graded in severity according to 5 questions that described everyday experiences — the more severe the dyspnea, the higher the ATS grade (range 0-5).[17] Dyspnea was classified as moderate-to-severe based on an ATS grade of at least 2, defined by a Yes response to: “Do you have to walk slower than people of your age on the level because of breathlessness?” ATS dyspnea grades ≥2 are associated with adverse health outcomes and establish dyspnea as occurring at low exertional workloads.[17,18] None and mild dyspnea were defined by ATS grades 0 and 1, based on the absence vs. presence of dyspnea when hurrying on the level or up a slight hill, respectively.[17]

Impairments

The cardiorespiratory and non-cardiorespiratory impairments of interest are described below, including corresponding dyspnea pathways[12-15] and diagnostic criteria.

Respiratory—Respiratory impairments decrease the ventilatory capacity and may lead to dyspnea at low exertional workloads. In addition, dead space ventilation may be increased in respiratory conditions (e.g. COPD), further exacerbating dyspnea through an increased ventilatory demand.

Spirometry was performed using ATS protocols,[23] and included the ratio of forced expiratory volume in 1-second (FEV_1) to forced vital capacity (FVC), as well as FEV_1 and FVC alone. Reference equations from the Global Lung Initiative (GLI) were used to establish the spirometric lower limit of normal (LLN).[27] Normal spirometry was then defined by both the FEV_1/FVC and FVC ≥LLN, whereas spirometric impairment was defined as airflow-obstruction if FEV_1/FVC<LLN (e.g. COPD or asthma) and as restrictive-pattern if FEV_1/FVC≥LLN but FVC<LLN (e.g., interstitial lung disease, heart failure, respiratory muscle weakness, and osteoporotic thoracic kyphosis).[25,27-29] The FEV_1 alone was also evaluated because it strongly predicts the maximal attainable ventilation during exercise.[12,14] A decreased FEV_1 was established if Z-score values were <LLN.[25,27-29]

The maximal inspiratory pressure (MIP) in cm H_2O was measured through a mouthpiece connected to a pressure transducer. The highest value was recorded, if a second MIP of at least 90% of the highest value was obtained during three to five attempts.[30,31] Based on reference equations from the CHS, a decreased MIP (<LLN) established respiratory muscle weakness.[31]

Cardiovascular—Cardiovascular impairments decrease the delivery and distribution of oxygen to the exercising muscle. This, in turn, reduces the aerobic capacity of the exercising muscle, leading to an exercise-induced lactic acidosis at low exertional workloads. The subsequent buffering of lactate by bicarbonate increases CO2 flux to the lung, thus increasing ventilatory demand and leading to dyspnea. In addition, a cardiovascular disease such as heart failure can decrease ventilatory capacity (e.g. spirometric restrictive-pattern), further exacerbating dyspnea.

Measures included the LVEF, diastolic dysfunction, peripheral artery disease (PAD), orthostasis, and hypertension. LVEF thresholds were as follows: normal (>55%) and decreased (45-54% and <45%).[32] Diastolic dysfunction was defined by echocardiography, based on peak E to A velocity >1.5 (decreased compliance) or <0.7 (decreased relaxation).[10,32] PAD was defined by an ankle-brachial index (ABI) <0.90.[33] Orthostasis was defined by a decrease in systolic blood pressure ≥20 mmHg from supine to standing, or inability to complete a standing blood pressure measurement due to orthostatic symptoms.[34] Hypertension was defined by a blood pressure ≥150/90 mmHg or antihypertensive use with a physician diagnosis of hypertension.[35]

Musculoskeletal—Musculoskeletal impairments decrease oxygen utilization at the level of the exercising muscle, thus reducing its aerobic capacity and leading to an exercise-

induced lactic acidosis at low exertional workloads. As discussed earlier, an exercise-induced lactic acidosis can lead to dyspnea through an increase in ventilatory demand.

Measures included skeletal muscle index, grip strength, and single chair stand. Whole-body muscle mass was estimated using bioelectrical impedance analysis, normalized for height, and termed the skeletal muscle index (SMI).[36] The SMI was reported as low if ≤8.50 kg/m^2 in men, and if ≤5.75 kg/m^2 in women.[37] Grip strength was reported as the average of 3 sex- and BMI-adjusted dynamometer readings. A decreased grip strength, defined as falling in the lowest quintile for this measure, established grip weakness.[38] The single chair stand required participants to stand up from a seated position without using their arms.[3,16] Participants were classified as "able" if successful or "unable" if they either used their arms or were unable to stand.

Neuropsychological—Neuropsychological impairments may affect the experience of dyspnea by altering the perception of breathing discomfort or by leading to a sedentary state that adversely affects the aerobic capacity of the exercising muscle. Depressive and anxiety symptoms were evaluated by the Center for Epidemiologic Studies Depression Scale (CES-D).[39] Depressive symptoms corresponded to a score of ≥16 on the CES-D,[40] and anxiety corresponded to a Yes answer for the CES-D item "did you feel fearful?"[41] Cognitive impairment was established by a Mini Mental State Examination (MMSE) score <24.[42]

Medications—Impairments related to the use of medications may also affect the experience of dyspnea by altering the perception of breathing discomfort or through adverse effects on respiratory, cardiovascular, and musculoskeletal function.[43] Medications were classified as cardiovascular, if including a statin or antihypertensive, or classified as psychoactive, if including an antipsychotic, benzodiazepine, or antidepressant.

Hematologic—Anemia decreases arterial oxygen content and can thus lead to exertional dyspnea as a consequence of a reduction in the delivery of oxygen to the exercising muscle. Anemia may also exacerbate coexisting cardiorespiratory impairments. Anemia was established by age-appropriate cut-offs for persons aged ≥65,[44] namely a serum hemoglobin (g/dL) below the following ranges: <13.2 for white men, <12.2 for white women, <12.7 for black men, and <11.5 for black women.

Renal—Impaired renal function may lead to dyspnea as a result of increased ventilatory demand from the bicarbonate buffering of an underlying metabolic acidosis. Chronic kidney disease may also exacerbate respiratory, cardiovascular, and musculoskeletal impairments. Kidney disease was defined by a serum creatinine >1.5 mg/dL.

Nutritional—Obesity and weight loss may lead to sarcopenia and, in turn, to dyspnea, including as a result of impairments of the muscles of ambulation and breathing.[3,12-15,36] Obesity was established by a body mass index (BMI) ≥30kg/m^2 and unintentional weight loss by ≥10 lbs in the prior year.[38] There were no underweight participants in this cohort (none had a BMI <18.5).

Statistical Analysis

Demographic and clinical characteristics were first summarized as means and standard deviations, or counts and percentages. Next, using categorical variables, frequency distributions of cardiorespiratory and non-cardiorespiratory impairments were cross-tabulated with the dyspnea outcome, stratified as none or mild vs. moderate-to-severe.

Logistic regression models evaluated the associations between impairments (represented by binary indicator variables) and moderate-to-severe dyspnea (vs. none or mild dyspnea). In unadjusted analyses, separate logistic regression models were used for each impairment. In adjusted analyses, a multivariable logistic regression model was used, including all impairments and additionally adjusted for age, sex, race, education, and smoking status. In addition, to evaluate the impact of having multiple impairments, a logistic regression model was used to calculate the predicted probabilities of moderate-to-severe dyspnea. Results are reported for combinations of four key impairments proceeding from none to all four impairments being present in a clinically meaningful sequence. The selected impairments were FEV_1<LLN, LVEF<45%, unable to perform a single chair stand (lower extremity impairment), and depressive symptoms, as these commonly coexist in patients with multimorbidity, especially when including an older age group and complex diseases such as COPD and heart failure.[3,8,43]

Baseline data for diastolic cardiac dysfunction, grip weakness and unintentional weight loss) had ≥5% missing, whereas other variables had <5% missing data. The pattern, nature, and mechanism of missing data were assessed for all variables and found to be plausibly missing at random. Multiple imputation was then used to account for missing data. Ten datasets were imputed, using fully conditional specification methods. Multiple imputation was performed using PROC MI (SAS 9.4), and PROC MIANALYZE (SAS 9.4).

SAS version 9.4 software (SAS Institute Inc. 2011; Cary, NC) was used in the analyses. P values <0.05 were interpreted to be statistically significant.

RESULTS

Table 1 summarizes baseline characteristics of the analytical sample. Mean age was 72.6, 57.1% were female, 4.5% were African-American, 27.2% had less than a high school education, and 54.7% were ever-smokers. The five most prevalent medical conditions included high blood pressure (35.0%), coronary artery disease (20.0%), diabetes mellitus (9.5%), COPD (9.3%), and cancer (15.2%); the number of medical conditions averaged 1.1 ± 1.1. Moderate-to-severe dyspnea was established in 17.5% of participants. Table 1 also summarizes characteristics of excluded participants, showing results similar to the analytical sample.

Table 2 reports the frequency of cardiorespiratory impairments, according to dyspnea severity and for the entire analytical sample. Relative to participants who had none or mild dyspnea, those with moderate-to-severe dyspnea had a 2-fold or greater prevalence of having a spirometric restrictive-pattern (5.0% vs. 10.9%), spirometric airflow-obstruction (15.7% vs. 30.7%), FEV_1<LLN (17.0% vs. 41.8%), MIP<LLN (6.4% vs. 13.2%), and LVEF<45%

(2.8% vs. 7.2%). Similarly, Table 3 reports the frequency of non-cardiorespiratory impairments. Relative to participants who had none or mild dyspnea, those with moderate-to-severe dyspnea had an approximate 2-fold or greater prevalence of unable to perform a single chair stand (6.6% vs. 19.1%), depressive symptoms (1.7% vs. 6.1%), use of psychoactive medications (11.3% vs. 21.2%), and unintentional weight loss (4.4% vs. 9.3%), respectively.

Table 4 reports odds ratios with 95% confidence intervals (CIs) for having moderate-to-severe dyspnea, based on the presence vs. absence of impairments. In the multivariable model, the strongest associations with moderate-to-severe dyspnea, namely having an adjusted OR (adjOR) ≥ 2.00, included the impairments of FEV_1<LLN (adjOR=2.88 [2.37, 3.49]), LVEF<45% (adjOR=2.12 [1.43, 3.16]), unable to perform a single chair stand (adjOR=2.10 [1.61, 2.73]), depressive symptoms (adjOR=2.02 [1.26, 3.23]), and obesity (adjOR=2.07 [1.67, 2.55]). Impairments having more modest but still statistically significant associations with moderate-to-severe dyspnea (adjORs ranging from 1.31-1.71) included respiratory muscle weakness, LVEF 45%-54%, diastolic cardiac dysfunction, grip weakness, anxiety symptoms, and medication use.

To further inform the analyses in Table 4, the unadjusted odds ratios (unadjOR) with 95% CIs for having moderate-to-severe dyspnea are also reported for each covariate, using logistic regression models that evaluated separately each covariate and were unadjusted for other variables: age 71-80 (unadjOR=1.41 [1.19, 1.67]) and age >80 (unadjOR=1.88 [1.45, 2.44]), versus age 65-70; female sex (unadjOR=1.21 [1.03, 1.41]); African-American (unadjOR=1.29 [0.91, 1.82]); less than high school education (unadjOR=1.77 [1.50, 2.08]); and ever-smoker (unadjOR=1.23 [1.04, 1.45]) and current-smoker (unadjOR=1.49 [1.17, 1.90]), versus never-smoker.

Table 5 reports the predicted probabilities of moderate-to-severe dyspnea, according to four key cardiorespiratory and non-cardiorespiratory impairments. The results showed that the predicted probability of moderate-to-severe dyspnea increased from 0.50 to 0.92 when two non-cardiorespiratory impairments (unable to perform a single chair stand and depressive symptoms) were added to two cardiorespiratory impairments (FEV_1<LLN and LVEF<45%).

DISCUSSION

Among 4,413 community-dwelling older persons, we found that a substantial proportion had cardiorespiratory and non-cardiorespiratory impairments, as well as moderate-to-severe dyspnea (ATS grade ≥2). We also found that cardiorespiratory impairments, including FEV_1<LLN and LVEF<45%, were strongly associated with moderate-to-severe dyspnea, yielding adjORs >2.00. Similarly, non-cardiorespiratory impairments, including being unable to perform a single chair stand, depressive symptoms, and obesity were strongly associated with moderate-to-severe dyspnea, also yielding adjORs >2.00. Impairments having modest but still significant associations with moderate-to-severe dyspnea included respiratory muscle weakness, diastolic cardiac dysfunction, grip weakness, anxiety symptoms, and medication use, yielding adjORs ranging from 1.31-1.71.

Our results reaffirm the importance of cardiorespiratory impairments in the evaluation of dyspnea in older persons.[1,7,12-15] In particular, cardiorespiratory impairments were strongly associated with moderate-to-severe dyspnea, a level of dyspnea that is likely to occur at low exertional workloads as during performance of activities of daily living.[12-15,17,18] As described earlier, cardiorespiratory impairments can lead to dyspnea through adverse effects on exercise performance, including an imbalance between ventilatory capacity and ventilatory demand.[12-15]

Non-cardiorespiratory impairments are likewise important in the evaluation of moderate-to-severe dyspnea in older persons. For example, being unable to perform a single chair stand, a measure of impaired lower extremity function (especially proximal muscle function),[3,45,46] had a magnitude of association with moderate-to-severe dyspnea (adjOR=2.10 [1.61, 2.73]) that was comparable with FEV_1<LLN (adjOR=2.88 [2.37, 3.49]) and LVEF<45% (adjOR=2.12 [1.43, 3.16]). In addition, grip weakness, depressive and anxiety symptoms, obesity, and medication use were all significantly associated with moderate-to-severe dyspnea. As described earlier, these non-cardiorespiratory impairments can lead to dyspnea through adverse effects on exercise performance, including altering the perception of breathing discomfort and through an imbalance between ventilatory capacity and ventilatory demand.[3,12-15,43]

We also calculated the predicted probability of moderate-to-severe dyspnea by adding four key impairments in a clinically meaningful sequence (i.e., proceeding from none to all four impairments being present). The selected impairments are known to commonly coexist in patients with multimorbidity, especially when including an older age group and complex diseases such as COPD and heart failure.[3,8,43] As shown in Table 5, the predicted probability of moderate-to-severe dyspnea increased from 0.50 to 0.92 when two non-cardiorespiratory impairments (unable to perform single chair stand and depressive symptoms) were added to two cardiorespiratory impairments (FEV_1<LLN and LVEF<45%).

Hence, our results suggest that dyspnea in older persons represents a multifactorial geriatric health condition, defined by having multiple causes in multiple domains and occurring in a manner analogous to falls, dizziness, and delirium.[19,20-22] The evaluation of dyspnea as a multifactorial geriatric health condition is clinically meaningful. Older persons experience multimorbidity and adverse effects related to polypharmacy,[8,43,47] highlighting the importance of considering a broad array of impairments. Beyond those already discussed in the current study, other potential impairments could have been identified through an expanded medication review and gait assessment (including foot problems). In addition, environmental barriers (stairs and clutter at home) and coexisting symptoms such as fatigue and pain may have further modified the experience of dyspnea.[43,48] Accordingly, future work should evaluate whether managing dyspnea as a multifactorial geriatric health condition improves outcomes, in a manner similar to that previously shown for falls and delirium.[20,22]

Importantly, the evaluation and management of dyspnea as a multifactorial geriatric health condition should additionally consider the experience of breathlessness as occurring in multiple dimensions, including sensory–perceptual (what breathing feels like), affective

distress (how distressing breathing feels), and symptom impact or burden (functional status).[15] These dimensions further define the appropriate diagnostic instrument for measuring dyspnea (Borg and visual analog scales, multi-item scales of emotional responses, multidimensional scales of quality of life/health status),[15] as well as further define therapeutic endpoints (e.g. management of affective distress), including expanded use of non-pharmacologic [behavioral] interventions that are applicable across multiple diseases (and impairments).[15,49] In the current study, for example, our use of the ATS dyspnea questionnaire largely measured symptom impact (activity limitation due to breathlessness) and, hence, our results are more specific to that dimension.

Unexpectedly, we found that skeletal muscle mass, as measured by the SMI, was not associated with moderate-to-severe dyspnea. Our evaluation of SMI considered alternative diagnostic thresholds, including tertiles and published[36] sex-specific quartiles and disability-related thresholds — these were not associated with moderate-to-severe dyspnea (data not shown). Our results therefore suggest that impaired skeletal muscle function, as reflected by poor performance on the single chair stand, grip weakness, and respiratory muscle weakness, is the more relevant factor in the development of dyspnea, rather than skeletal muscle mass. Future work, however, should evaluate the association between SMI and measures of skeletal muscle function, as this approach will potentially identify diagnostic thresholds for SMI that are more likely to be significantly associated with dyspnea.

Consistent with prior work,[33] the current study additionally found that, in the multivariable model, PAD was not associated significantly with dyspnea. Because it impairs walking endurance, we posit that PAD may limit exercise to workloads that are insufficient to increase ventilatory demand to levels that lead to dyspnea.[33]

The current study has several strengths, including a large sample of community-dwelling older persons and the concurrent assessment of a broad array of impairments that are clinically and physiologically meaningful to the experience of dyspnea. We acknowledge, however, several potential limitations. First, as the associations between impairments and dyspnea were cross-sectional, we cannot infer causality. Nonetheless, prior work has established that the selected impairments have a strong clinical and physiological basis as causal factors in the development of dyspnea.[12-15] Second, the CHS respiratory evaluation was limited to spirometry, lacking assessments such as diffusing capacity of the lung for carbon monoxide (a measure of gas exchange at the alveolar-capillary interface) and static lung volumes (a measure of impaired respiratory mechanics manifested as restriction, hyperinflation, and air trapping).[29] In particular, this limited our capacity to assess pulmonary vascular disease and more comprehensive impairments in respiratory mechanics. However, because idiopathic pulmonary arterial hypertension has a low prevalence (15-50 cases per one million persons),[50] and because abnormalities in diffusing capacity or static lung volumes are often due to cardiorespiratory diseases that also cause abnormalities in spirometry (COPD, interstitial lung disease, and heart failure),[29] it is unlikely that a more extensive respiratory evaluation would have changed appreciably the results of the current study. Third, anxiety symptoms were evaluated based on a single item from the CES-D.[39-41] Fourth, CHS had underrepresentation of persons aged >80 (mean age was 72.6) and no representation from Hispanics, thus limiting generalizability of our results for those

particular populations. Lastly, the assembly of the CHS cohort in 1989-1990 may raise concerns regarding “timeliness” of data, but this is unlikely to be a major limitation as the same impairments remain relevant to the current generation of older persons.[6,33,49]

In conclusion, in a large sample of community-dwelling older persons, we found that several cardiorespiratory and non-cardiorespiratory impairments were strongly associated with moderate-to-severe dyspnea, akin to a multifactorial geriatric health condition. Because many of these impairments are modifiable, this approach could inform a comprehensive strategy designed to prevent or ameliorate a prevalent and clinically meaningful symptom in older persons.

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Table 1

Demographic and clinical characteristics

Characteristic	Analytical Sample [a]		Excluded Participants [a]	
	N [b]	Mean ± SD or n (%)	N [b]	Mean ± SD or n (%)
Age (years)	4413	72.6 ± 5.3	712	73.9 ± 6.7
Females		2518 (57.1)		390 (54.8%)
African-American		199 (4.5)		41 (5.8)
Education: < High School	4403	1199 (27.2)	708	220 (31.1)
Smoking status				
Never	4411	2001 (45.4)	711	360 (50.6)
Former		1895 (43.0)		267 (37.6)
Current		515 (11.7)		84 (11.8)
Medical conditions [c]				
High blood pressure	4371	1529 (35.0)	702	256 (36.5)
Coronary artery disease [d]	4156	831 (20.0)	653	133 (20.4)
Diabetes mellitus	4387	416 (9.5)	707	71 (10.0)
COPD [e]	4388	409 (9.3)	706	71 (10.1)
Asthma	4400	285 (6.5)	703	63 (9.0)
Heart failure	4250	118 (2.8)	677	21 (3.1)
Kidney disease	4385	111 (2.5)	705	22 (3.1)
Stroke	4382	93 (2.1)	705	15 (2.1)
Cancer (ever)	4406	670 (15.2)	710	99 (13.9)
Number of medical conditions	4413	1.1 ± 1.1 [f]	712	1.2 ± 1.1
Dyspnea				
None or mild dyspnea [g]	4413	3640 (82.5)	686	552 (80.5)
Moderate-to-severe dyspnea [h]		773 (17.5)		134 (19.5)

Abbreviations: ATS (American Thoracic Society), COPD (chronic obstructive pulmonary disease).

[a] Of the 5,201 participants in the original cohort, 4,413 met inclusion criteria, including completion of the ATS Adult Questionnaire and at least two ATS acceptable spirometric maneuvers, both at the baseline visit (analytical sample, N=4,413). Of the remaining 788 participants, 76 did not grant permission for data analysis and 712 did not meet our inclusion criteria (excluded participants, N=712).

[b] Varies by missing data.

[c] Self-reported, physician-diagnosed.

[d] Angina or myocardial infarction.

[e] Chronic bronchitis or emphysema.

[f] Median 1 (interquartile range: 0-2).

[g] Grade 0 or 1 on the ATS Adult Questionnaire.

[h] Grade ≥2 on the ATS Adult Questionnaire.

Table 2

Frequency distributions of cardiorespiratory impairments, according to dyspnea severity and for the entire study sample

Impairments	Dyspnea		ALL
	None or Mild [a]	Moderate-to-Severe [b]	
	n/N (%) [c]		
Spirometry [d]			
Normal	2885/3640 (79.3)	452/773 (58.5)	3337/4413 (75.6)
Restrictive-pattern	183/3640 (5.0)	84/773 (10.9)	267/4413 (6.1)
Airflow-obstruction	572/3640 (15.7)	237/773 (30.7)	809/4413 (18.3)
FEV_1 [e]			
Normal: ≥LLN	3022/3640 (83.0)	450/773 (58.2)	3472/4413 (78.7)
Decreased: <LLN	618/3640 (17.0)	323/773 (41.8)	941/4413 (21.3)
MIP [f]			
Normal: ≥LLN	3295/3519 (93.6)	640/737 (86.8)	3935/4256 (92.5)
Decreased: <LLN	224/3519 (6.4)	97/737 (13.2)	321/4256 (7.5)
LVEF			
Normal: ≥55%	3344/3615 (92.5)	642/761 (84.4)	3986/4376 (91.1)
Decreased: 45-54%	171/3615 (4.7)	64/761 (8.4)	235/4376 (5.4)
<45%	100/3615 (2.8)	55/761 (7.2)	155/4376 (3.5)
Diastolic cardiac function [g]			
Normal	2706/3472 (77.9)	480/719 (66.8)	3186/4191 (76.0)
Impaired	766/3472 (22.1)	239/719 (33.2)	1005/4191 (24.0)
Peripheral artery disease [h]			
No	3144/3539 (88.8)	603/739 (81.6)	3747/4278 (87.6)
Yes	395/3539 (11.2)	136/739 (18.4)	531/4278 (12.4)
Orthostasis [i]			
No	3000/3603 (83.3)	606/765 (79.2)	3606/4368 (82.6)
Yes	603/3603 (16.7)	159/765 (20.8)	762/4368 (17.5)
Hypertension [j]			
No	2070/3640 (56.9)	363/773 (47.0)	2433/4413 (55.1)
Yes	1570/3640 (43.1)	410/773 (53.0)	1980/4413 (44.9)

Abbreviations: ATS (American Thoracic Society), FEV_1 (forced expiratory volume in 1-second), FVC (forced vital capacity), LLN (lower limit of normal), LVEF (left ventricular ejection fraction), MIP (maximal inspiratory pressure).

[a] Grade 0 or 1 on the ATS Adult Questionnaire.

[b] Grade ≥2 on the ATS Adult Questionnaire.

[c] N varies due to missing data.

[d] Normal spirometry was defined by FEV_1/FVC and FVC, both ≥LLN; airflow-obstruction by FEV_1/FVC<LLN; and restrictive-pattern by FEV_1/FVC≥LLN and FVC<LLN.

[e] FEV_1 was evaluated because it predicts the maximal attainable ventilation during exercise.

[f] A decreased MIP <LLN defined respiratory muscle weakness.

[g] Diastolic dysfunction defined by peak E/A velocity >1.5 (decreased compliance) or <0.7 (decreased relaxation).

[h] Defined by an ankle-brachial index (ABI) <0.90. ABIs >1.4 were excluded from analysis (n=50) as these were likely due to underlying calcinosis.

[i] Defined as a drop in systolic blood pressure ≥20mmHg from supine to standing position or inability to do a standing blood pressure due to orthostatic symptoms.

[j] Defined as a blood pressure ≥150/90mmHg or use of antihypertensive medications with a physician's diagnosis of hypertension.

Table 3

Frequency distributions of non-cardiorespiratory impairments, according to dyspnea severity and for the entire study sample

Impairments	Dyspnea		ALL
	None or Mild [a]	Moderate-to-Severe [b]	
	n/N (%) [c]		
Musculoskeletal			
Low SMI [d]			
No	3140/3584 (87.6)	662/763 (86.8)	3802/4347 (87.5)
Yes	444/3584 (12.4)	101/763 (13.2)	545/4347 (12.5)
Grip weakness [e]			
No	2676/3405 (78.6)	459/699 (65.7)	3135/4104 (76.4)
Yes	729/3405 (21.4)	240/699 (34.3)	969/4104 (23.6)
Single chair stand [f]			
Able	3361/3597 (93.4)	617/763 (80.9)	3978/4360 (91.2)
Unable	236/3597 (6.6)	146/763 (19.1)	382/4360 (8.8)
Neuropsychologic			
Depressive symptoms [g]			
No	3576/3636 (98.4)	725/772 (93.9)	4301/4408 (97.6)
Yes	60/3636 (1.7)	47/772 (6.1)	107/4408 (2.4)
Anxiety symptoms [h]			
No	3153/3637 (86.7)	592/771 (76.8)	3745/4408 (85.0)
Yes	484/3637 (13.3)	179/771 (23.2)	663/4408 (15.0)
Cognitive impairment			
MMSE ≥ 24	3474/3637 (95.5)	711/772 (92.1)	4185/4409 (94.9)
MMSE < 24	163/3637 (4.5)	61/772 (7.9)	224/4409 (5.1)
Medications			
Cardiovascular [i]			
No	2216/3640 (60.9)	328/773 (42.4)	2544/4413 (57.7)
Yes	1424/3640 (39.1)	445/773 (57.6)	1869/4413 (42.4)
Psychoactive [j]			
No	3226/3638 (88.7)	609/773 (78.8)	3835/4411 (86.9)
Yes	412/3638 (11.3)	164/773 (21.2)	576/4411 (13.1)
Hematologic			
Anemia [k]			
No	3277/3615 (90.7)	671/764 (87.8)	3948/4379 (90.2)
Yes	338/3615 (9.4)	93/764 (12.2)	431/4379 (9.8)

Impairments	Dyspnea		ALL
	None or Mild [a]	Moderate-to-Severe [b]	
	n/N (%) [c]		
Renal			
Kidney disease [l]			
No	3437/3623 (94.9)	699/765 (91.4)	4136/4388 (94.3)
Yes	186/3623 (5.1)	66/765 (8.6)	252/4388 (5.7)
Nutritional			
BMI [m]			
<30	3072/3636 (84.5)	547/771 (71.0)	3619/4407 (82.1)
≥30	564/3636 (15.5)	224/771 (29.1)	788/4407 (17.9)
Weight loss >10 lbs [n]			
No	3284/3436 (95.6)	633/698 (90.7)	3917/4134 (94.8)
Yes	152/3436 (4.4)	65/698 (9.3)	217/4134 (5.3)

Abbreviations: ATS (American Thoracic Society), BMI (body mass index, kg/m^2), CES-D (Center for Epidemiologic Studies Depression Scale), MMSE (Mini Mental State Examination), SMI (skeletal muscle index).

[a] Grade 0 or 1 on the ATS Adult Questionnaire.

[b] Grade ≥2 on the ATS Adult Questionnaire.

[c] N varies due to missing data.

[d] Low SMI was established by SMI ≤ 8.50 kg/m2 in men and ≤5.75 kg/m2 in women.

[e] Weakness was defined by the lowest quintile of the average of 3 dynamometer readings (sex and BMI adjusted).

[f] Participants were asked to stand up from a seated position in a chair without using their arms. Based on their performance, participants were classified as able to stand up without using arms or as unable to stand up without using arms (i.e., used their arms or unable to stand).

[g] CES-D score of ≥16.

[h] CES-D item of “did you feel fearful”: Yes vs. No.

[i] Any statin or antihypertensive.

[j] Any antipsychotic, benzodiazepine, or antidepressant.

[k] Hemoglobin established anemia if below the following ranges: < 13.2 g/dL for white men aged ≥65, < 12.2 g/dL for white women aged ≥65, < 12.7 g/dL for black men aged ≥65, and < 11.5 g/dL for black women aged ≥65.

[l] Creatinine < 1.5 mg/dl defined normal kidney function, whereas ≥1.5 defined kidney disease.

[m] None had a BMI <18.5 kg/m^2.

[n] Unintentional weight loss in the prior year.

Table 4

Unadjusted and adjusted odds ratios (OR) for having moderate-to-severe dyspnea, according to cardiorespiratory and non-cardiorespiratory impairments

Impairment [a]	Moderate-to-severe dyspnea [b]	
	Unadjusted OR (95% CI) [c]	Adjusted OR (95% CI) [d]
Cardiorespiratory		
Restrictive-pattern	2.65 (2.21, 3.17)	See footnote [e]
Airflow-obstruction	2.94 (2.23, 3.87)	
FEV_1<LLN	3.51 (2.97, 4.15)	2.88 (2.37, 3.49)
Respiratory muscle weakness (MIP<LLN)	2.39 (1.86, 3.07)	1.60 (1.20, 2.14)
LVEF 45-54%	1.97 (1.46, 2.67)	1.71 (1.22, 2.40)
LVEF<45%	2.83 (2.02, 3.97)	2.12 (1.43, 3.16)
Diastolic dysfunction	1.79 (1.51, 2.12)	1.32 (1.08, 1.61)
Peripheral artery disease	1.79 (1.45, 2.21)	1.19, (0.93, 1.53)
Orthostasis	1.31 (1.08, 1.59)	1.18 (0.95, 1.47)
Hypertension	1.49 (1.27, 1.74)	0.91 (0.74, 1.11)
Non-cardiorespiratory		
Low SMI	1.07 (0.85, 1.35)	0.95 (0.73, 1.25)
Grip weakness	1.99 (1.67, 2.36)	1.31 (1.06, 1.61)
Single chair stand	3.42 (2.74, 4.27)	2.10 (1.61, 2.73)
Depressive symptoms	3.89 (2.63, 5.74)	2.02 (1.26, 3.23)
Anxiety symptoms	1.97 (1.63, 2.39)	1.54 (1.22, 1.93)
Cognitive impairment	1.83 (1.35, 2.49)	1.00 (0.69, 1.45)
Cardiovascular medication	2.11 (1.80, 2.47)	1.65 (1.35, 2.01)
Psychoactive medication	2.11 (1.73, 2.58)	1.71 (1.35, 2.15)
Anemia	1.35 (1.06, 1.72)	1.03 (0.78, 1.38)
Kidney disease	1.75 (1.31, 2.34)	1.18 (0.82, 1.68)
Obesity	2.23 (1.86, 2.67)	2.07 (1.67, 2.55)
Unintentional weight loss	2.20 (1.63, 2.97)	1.31 (0.91, 1.87)

Abbreviations: ATS (American Thoracic Society), CI (confidence interval), FEV_1 (forced expiratory volume in 1-second), LLN (lower limit of normal), LVEF (left ventricular ejection fraction), OR (odds ratios), SMI (skeletal muscle index).

[a] See footnotes to Tables 2 and 3, regarding diagnostic criteria for establishing the presence vs. absence of an impairment.

[b] Grade ≥2 on ATS Adult Questionnaire.

[c] From logistic regression models that evaluated separately each impairment.

[d] From a multivariable logistic regression model that included all impairments and was additionally adjusted for age, sex, race, education, and smoking status.

[e] Restrictive-pattern and airflow-obstruction were highly correlated with FEV_1<LLN; the magnitude of the correlation was 0.66 and 0.68, respectively. Accordingly, because exertional dyspnea was the outcome of interest and because FEV_1 is associated with the maximal attainable

ventilation during exercise,[12,14] FEV_1<LLN was entered into the adjusted multivariable analysis, but not restrictive-pattern and airflow-obstruction.

Table 5

Predicted probability of moderate-to-severe dyspnea, according to four key impairments [a]

Impairments	Predicted Probability[b] Moderate-to-Severe Dyspnea [c]
All four impairments absent	0.11
FEV_1<LLN	0.29
+ LVEF<45%	0.50
+ Single chair stand (unable)	0.76
+ Depressive symptoms (CES-D ≥16)	0.92

Abbreviations: ATS (American Thoracic Society), CES-D (Center for Epidemiologic Studies Depression Scale), FEV_1 (forced expiratory volume in 1-second), LLN (lower limit of normal), LVEF (left ventricular ejection fraction).

[a] The four key impairments commonly coexist in patients with multimorbidity, especially in an older age group and complex diseases such as COPD and heart failure.[3,8,43]

[b] From a logistic regression model with four key impairments reported in a clinically meaningful sequence, proceeding from none to all four impairments being present. The predicted probabilities represent the means of ten imputation samples (see Methods).

[c] Grade ≥2 on ATS Adult Questionnaire.