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Noninvasive Tests for the Diagnostic Evaluation of Dyspnea Among Outpatients: the Multi-Ethnic Study of Atherosclerosis Lung Study

Elizabeth C Oelsner, MD MPH[a], **Joao AC Lima, MD**[b], **Steven M Kawut, MD MS**[c], **Kristin M Burkart, MD MSc**[a], **Paul L Enright, MD**[d], **Firas S Ahmed, MD**[a,e], and **R Graham Barr, MD DrPH**[a,f]

[a]Department of Medicine, College of Physicians and Surgeons, Columbia University Medical Center, 630 West 168th Street, PH9E-105, New York, NY 10032, USA.

[b]Department of Medicine, Johns Hopkins University, 600 N. Wolfe Street, Blalock 524D1, Baltimore, MD 21287, USA.

[c]Center for Clinical Epidemiology and Biostatistics, Perelman School of Medicine at the University of Pennsylvania, 718 Blockley Hall, 423 Guardian Drive, Philadelphia, PA, 19104-6021, USA.

[d]College of Public Health, University of Arizona, 1295 N. Martin, PO 245211, Drachman Hall, Tuscon, AZ 85724, USA.

[e]Department of Radiology, College of Physicians and Surgeons, Columbia University Medical Center, 630 West 168th Street, New York, NY 10032, USA.

[f]Department of Epidemiology, Mailman School of Public Health of Columbia University, 722 West 168th Street, New York, NY 10032, USA.

Abstract

Background—Dyspnea on exertion is a common and debilitating complaint, yet evidence for the relative value of cardiac and pulmonary tests for the evaluation of chronic dyspnea among adults without known cardiac or pulmonary disease is limited.

Methods—The Multi-Ethnic Study of Atherosclerosis (MESA) enrolled participants ages 45-84 years who were free of clinical cardiovascular disease from six communities; participants with clinical pulmonary disease were excluded from this report. Dyspnea on exertion was assessed via structured interview. Tests included electrocardiograms, cardiac computed tomography (CT) for coronary artery calcium, cardiac magnetic resonance imaging, spirometry, percent emphysema (percent of lung regions < -950 Hounsfield Units) on CT, inflammatory biomarkers and N-

Correspondence: Elizabeth Oelsner MD MPH Columbia University Medical Center 630 West 168th Street PH 9 East – Room 105 New York, NY 10032 Tel: 212 305 9056 Fax: 212 305 9349 eco7@cumc.columbia.edu.

Author Contributions

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terminal pro-Brain Natriuretic Peptide (NT-proBNP). Logistic regression was used to identify independent correlates of dyspnea after adjustment for age, sex, body mass index, physical activity, anxiety, and leg pain.

Results—Among 1,969 participants without known cardiopulmonary disease, 9% had dyspnea. The forced expiratory volume in one second (FEV_1) ($p < 0.001$), NT-proBNP ($p=0.004$), and percent emphysema on CT ($p=0.004$) provided independent information on the probability of self-reported dyspnea. Associations with the FEV_1 were stronger among smokers and participants with other recent respiratory symptoms or seasonal allergies; associations with NT-proBNP were present only among participants with coexisting symptoms of lower extremity edema. Only the FEV_1 provided a significant improvement in the receiver operating curve.

Conclusions—Among adults without known cardiac or pulmonary disease reporting dyspnea on exertion, spirometry, NT-proBNP, and CT imaging for pulmonary parenchymal disease were the most informative tests.

Keywords

dyspnea; spirometry; COPD; emphysema; heart failure; atherosclerosis; diagnostic tests

Introduction

Shortness of breath upon physical exertion affects almost one half of Americans.[1] Dyspnea represents an important patient-oriented outcome for cardiopulmonary diseases including chronic obstructive pulmonary disease (COPD), pulmonary fibrosis, and heart failure. Indeed, dyspnea may be interpreted as an integrated measure of pulmonary, cardiac, and vascular function, as well as conditioning.[2] Since dyspnea worsens with exertion, many patients will become sedentary, causing a downward spiral towards frailty and reduced quality of life.[3,4]

The optimal diagnostic work-up for adults with chronic dyspnea and no known cardiopulmonary disease remains unclear. Several algorithms have been proposed based upon the diagnostic yield of tests performed on dyspneic patients referred to specialty clinics,[5-11] yet no representative United States (US) population-based studies have been performed. Based on limited data, clinical guidelines recommend that a new complaint of dyspnea in adults warrants, in addition to a thorough history and physical, basic laboratory evaluation and preliminary diagnostic tests such as electrocardiogram (ECG), chest radiography, and possibly spirometry.[12]

We systematically assessed which diagnostic tests were associated with dyspnea among participants without diagnosed cardiac or pulmonary disease from a large panel of tests that were performed in a multiethnic, population-based cohort.

Methods

The Multi-Ethnic Study of Atherosclerosis (MESA) is a multi-center prospective cohort study designed to investigate the prevalence, correlates, and progression of sub-clinical cardiovascular disease.[13] MESA recruited 6814 adults ages 45-84 years of four race/

ethnicities from six communities in the US in 2000-2002. Exclusion criteria were clinical cardiovascular disease defined as a physician diagnosis of myocardial infarction, stroke, transient ischemic attack, heart failure, angina, any cardiovascular procedure or current atrial fibrillation; weight greater than 300 pounds; pregnancy; or impediment to long-term participation.

Additional exclusion criteria for the current report included cardiovascular event prior to dyspnea assessment; clinical pulmonary disease (physician diagnosis of asthma or emphysema); or not having performed diagnostic tests or missing relevant questionnaire items (**Figure 1**).

All tests were performed at the baseline examination, except as noted below. Protocols were approved by the Institutional Review Boards of all collaborating institutions and the National Heart Lung and Blood Institute.

Dyspnea

Dyspnea was assessed by trained interviewers in 2002-2004 and was defined as a positive response to either of the following: “When walking on level ground, do you get more breathless than people your own age?” and/or “Do you ever have to stop walking due to breathlessness?” This definition correspond to the modified Medical Research Council (mMRC) dyspnea scale grade 2.[14]

Coronary atherosclerosis

All participants underwent 12-lead ECGs on GE MAC 1200 electrocardiographs (GE Healthcare, Milwaukie, WI) with central quality control via visual inspection and automated classification according to the Minnesota ECG Code.[15]

Cardiac computed tomography (CT) was performed using standardized protocols on either electron-beam or multidetector CT scanners[16] for the assessment of phantom-adjusted Agatston score for coronary artery calcium, as previously described.[17,18]

Cardiac structure and function

All participants without MRI exclusions were asked to undergo cardiac MRI using a standard protocol.[19] Indices of left ventricular structure and function were determined by volumetric imaging.[19,20] Left ventricular ejection fraction was calculated as stroke volume divided by end-diastolic volume. Right ventricular parameters were measured similarly.[21] Measures of cardiac structure were indexed by body surface area.[22]

Lung function

Spirometry was performed in 2004-06 for 3965 participants in the MESA Lung Study out of 4483 randomly selected from those who consented to genetic analyses (99%), underwent baseline measures of endothelial function (89%), and attended an examination at that time (91%). Asian-Americans were oversampled. Spirometry was conducted using an automated dry rolling-seal spirometer according to American Thoracic Society guidelines.[23] Predicted

values were calculated using equations from the National Health and Nutrition Examination Survey III[24] with a 0.88 correction factor for Asians, as previously validated in MESA.[25]

Lung structure

Percentage of emphysema-like lung (hereafter referred to as percent emphysema) was measured as percentage of lung voxels with attenuation less than -950 Hounsfield units (HU), which has been validated on autopsy,[26] on the cardiac CT scans.[27,28]

Percentage of lung with features suggestive of interstitial lung abnormalities (hereafter referred to as percent high attenuation areas [HAA]) was defined as percent of lung voxels with attenuation between -600 and -250 HU.[29]

Both measures were previously validated against those obtained from full-lung scans (e.g., r=0.96 for percent emphysema on cardiac and full-lung scans on the same MESA scanners).[27,29]

Biomarkers of inflammation, renal function and fluid overload

Creatinine, fibrinogen, C-reactive protein (CRP), and N-Terminal pro-Brain Natriuretic Peptide (NT-proBNP) were measured using standard techniques.[29,30]

Other covariates

Body mass index (BMI) was defined as the weight in kilograms (kg) divided by the height in meters (m), squared, which were both measured via standard techniques. Race/ethnicity, educational attainment, leg pain, total intentional exercise per week, and tobacco use were self-reported. Never smoking was defined as a lifetime smoking history of less than 100 cigarettes. Current smoking was defined as cigarette use within the past 30 days. Pack-years were calculated as (cigarettes per day / 20) × years smoked. Hypertension and diabetes were defined by Joint National Committee VI and American Diabetes Association 2003 criteria, respectively. Symptoms of lower extremity swelling, orthopnea, respiratory infections, and seasonal allergies were elicited via structured interview.

Covariates were measured at the time of dyspnea assessment, with the exception of time-invariant covariates (e.g., race/ethnicity) and anxiety, which was assessed at baseline using the Spielberger State-Trait Anxiety Inventory.[31]

Statistical analysis

Differences in characteristics of participants with and without dyspnea were compared by chi-square, Wilcoxon, and Student's t-tests. Pearson partial correlations were computed for results of diagnostic tests, and variables with a p-value less than 0.50 were incorporated into a backwards-selection multivariable logistic regression model that also included age, BMI, gender, exercise, anxiety, and leg pain, since these were factors that showed strong univariate associations with dyspnea and have been associated with dyspnea in prior studies.[1,32-34]

The validity of the final model obtained via backwards selection was assessed in two ways. First, backwards selection was repeated using 100 bootstrap datasets constructed via random

sampling with replacement from the original set. Inclusion frequencies, defined as the number of times that a predictor was retained in backwards selection,[35] were evaluated. Second, model calibration was tested by comparing deciles of actual versus predicted probabilities of dyspnea.[36]

For each of the retained predictors, adjusting for the pre-specified covariates, receiver operating characteristic (ROC) curves were plotted and c-statistics were compared. Interactions between the retained predictors and age, gender, smoking status, diabetes, hypertension, and other clinical symptoms were tested via multiplicative interaction terms and stratified analyses. Analyses were repeated using clinically-relevant thresholds for diagnostic test results. The prevalence of test results exceeding these thresholds was compared among participants with and without dyspnea.

All analyses were performed in SAS version 9.3 (Cary, North Carolina).

Results

Of 6814 MESA participants, 6220 (91%) answered dyspnea items, of whom 5455 (88%) had no prevalent clinical cardiopulmonary diagnoses. Of these participants, 1969 (36%) completed all relevant tests; the largest decrements in sample size were due to participants not selected for spirometry and those unwilling or unable to undergo MRI (**Figure 1**). Included participants were somewhat younger and were less likely to be obese, smoke and report dyspnea than excluded participants (**Supplementary Table 1**).

The mean age of included participants was 62 +/− 10 years, 49% were women, and the race/ethnic distribution was 35% White, 22% African-American, 23% Hispanic and 20% Asian-American. Fifty percent had ever smoked cigarettes, 13% had diabetes, and 42% had hypertension.

Overall, 173 (9%) reported dyspnea. The group reporting dyspnea had significantly more women, higher BMI, greater anxiety, less intentional exercise, more leg pain, and greater smoking history, as well as more major ECG abnormalities, lower lung function, higher inflammatory markers, and higher NT-proBNP (**Table 1**).

After adjusting for age, sex, BMI, exercise, anxiety, and leg pain, the cardiopulmonary tests significantly associated with dyspnea were spirometry, NT-proBNP, percent emphysema, left ventricular ejection fraction and mass, and coronary artery calcium (**Table 2**). These variables were no more than modestly correlated with each other (**Supplementary Table 2**).

Only three of these diagnostic tests, however, provided independent information (**Table 3**). FEV_1 demonstrated the largest and strongest association with dyspnea: for each standard deviation (SD) reduction in FEV_1 (17%), there was a 38% increased odds of self-reported dyspnea (95% confidence interval [CI] 28-47%, p <0.001). NT-proBNP was associated with a 20% increase in the odds of dyspnea per SD (123 pg/mL) (95% CI 6-36%, p=0.004) and percent emphysema on CT was associated with a 27% increase per SD (4%) (95% CI 8-51%, p=0.004).

These three test results had the greatest inclusion frequencies in bootstrapped iterations of backward selection. FEV_1 was included in 95% of bootstrapped backward selection models, compared to 54% for NT-proBNP, and 35% for percent emphysema; the next most relevant predictor, race, was included in only 20% (**Supplementary Figure 1**). A calibration plot for the final model with the pre-specified covariates plus the three predictors demonstrated that predicted probabilities were similar to the observed probabilities (**Supplementary Figure 2**).

Compared to clinical factors alone, which were strongly predictive of dyspnea (c=0.744), only the FEV_1 provided a modest but statistically significant incremental improvement in prediction (c=0.768, p=0.047; **Figure 2**). Adjustment for NT-proBNP and percent emphysema yielded smaller and non-significant increases in the c-statistic (**Table 4**).

There were several instances of effect measure modification (**Supplementary Table 3**). FEV_1 was significantly associated with dyspnea among ever-smokers, and especially among current smokers, but not among never-smokers. The FEV_1 was also more strongly associated with dyspnea among participants who reported recent bronchitis, sinusitis, cold and flu symptoms, or seasonal allergies, however it remained significant among those without these symptoms. NT-proBNP was only significantly associated with dyspnea among those with self-reported lower extremity edema, however orthopnea did not significantly modify the associations for any of the retained diagnostic tests, and differences in effect estimates between participants with and without these symptoms were inconsistent. The association of percent emphysema with self-reported dyspnea was of greater magnitude in participants greater than 65 years old, but did not differ by smoking history. NT-proBNP was only significantly associated with dyspnea among non-hypertensive individuals, who had lower mean NT-proBNP levels compared to hypertensives (61 vs 110 pg/ml, p<0.001).

Analyses using thresholded test results found that the same three diagnostic tests provided independent information: FEV_1 below the lower limit of normal (OR 3.22, 95% CI 2.06-5.02); percent emphysema above the upper limit of normal (OR 1.75, 95% CI 1.05-2.92), and NT-proBNP above 300 pg/ml (OR 2.10, 95% CI 1.05-4.23).

Using clinically relevant thresholds, 36% of dyspneic participants demonstrated abnormal lung function, of which roughly-two thirds was consistent with airflow obstruction, defined as a ratio of the FEV_1 to the forced vital capacity (FVC) of less than 0.70 (**Figure 3**).[37] Using a more specific threshold of FEV_1/FVC ratio below the lower limit of normal,[24] 27% had abnormal lung function, of whom approximately one half met criteria for airflow obstruction. Abnormal levels of CT emphysema and NT-proBNP were present for an additional 6% of participants reporting dyspnea.

Among the 100 (57.8%) dyspneic participants for whom spirometry, percent emphysema, and NT-proBNP were within normal limits, 49% had abnormal results on another test. However, in most cases, the abnormal test result was equally common among patients with and without dyspnea (Supplementary Table 4). Thirty six percent had minor ECG abnormalities, 16% had major abnormalities, and 3% had Q waves, which was similar to, non-significantly higher, and significantly higher than nondyspneic participants

(Supplementary Table 4). Of the remaining participants with normal ECGs, 6% had elevated coronary artery calcium, similar to the non-dyspneic sample, and none had decreased left ventricular ejection fraction or increased left ventricular mass.

Discussion

In this multiethnic, population-based study, non-invasive diagnostic tests that provided independent diagnostic information for chronic dyspnea among patients without known cardiopulmonary disease included spirometry, NT-proBNP, and CT scanning for pulmonary emphysema. In contrast, measures of atherosclerosis and cardiac function, including ECGs and cardiac MRI, were not independently associated with dyspnea. These findings suggest that these tests of lung function and structure, in addition to NT-proBNP, may be suitable initial tests among outpatients reporting chronic dyspnea.

This is the first population-based study of which we are aware to evaluate the utility of a battery of cardiac and pulmonary tests for self-reported dyspnea in a community setting. Prior literature has examined the diagnostic yield of various tests among patients referred to specialty clinics for evaluation of shortness of breath.[6-11] These studies have shown spirometry to have the highest diagnostic yield, consistent with our results, as well as substantial benefit in chest imaging via X-ray or CT. For patients with normal spirometry and lung imaging, other tests such as diffusing capacity of the lung for carbon monoxide (DLCO), and exercise testing provided only incremental improvements in diagnostic accuracy.[6,7,11] No consistent approach to screening for cardiovascular causes has been presented in these prior studies, which were predominantly carried out in pulmonary clinics, and due to such problems of selection bias, the generalizability of their results remains unclear.

In our population-based sample, the prevalence of mMRC grade 2 dyspnea (9%) was similar to that observed in the US population-based Cardiovascular Health Study (CHS) and the multinational Burden of Obstructive Lung Diseases (BOLD) study (10% and 7%, respectively).[38,39] Consistent with these studies, self-reported dyspnea was associated with female sex, weight, smoking, anxiety, and physical exertion.[38-44]

Spirometry was the only test that significantly improved prediction of dyspnea after controlling for clinical factors. Among spirometric measurements, a reduction in FEV_1 was the strongest predictor of dyspnea, especially among smokers and those with recent bronchitis, sinusitis, “cold” or seasonal allergy symptoms. FEV_1/FVC ratio showed a strong bivariate association, however it was not retained in the final model, most likely due to its strong correlation with FEV_1. The FEV_1 was associated with a relatively modest (3%) incremental improvement in prediction of dyspnea compared to clinical factors alone; nonetheless, up to one in three participants with dyspnea had abnormal spirometry using standard cutoffs, consistent with a high diagnostic yield. These findings underscore the importance of spirometry in the evaluation of chronic dyspnea, a test that is a relatively simple and inexpensive test but which remains underutilized in clinical practice.[45,46]

Percent emphysema on CT was also significantly associated with dyspnea, particularly among participants over age 65 years, and this association was independent of spirometric airflow measures. These findings build upon previous studies showing associations of percent emphysema with lung cancer, cardiac function, hospitalizations, and all-cause mortality, all independent of lung function.[47-52] Furthermore, they highlight that emphysema, which is characterized by destruction of lung parenchyma,[53,54] is not infrequent in the absence of COPD.[48,55,56] Of note, the prognostic value of percent emphysema was not modified by smoking status, which may suggest detection of panlobular emphysema, which is not related to smoking[57] and has broader genetic predispositions than just alpha-1 antitrypsin deficiency.[58]

NT-proBNP, a biomarker of cardiac myocyte stress that is regularly used to screen for heart failure in the context of acute dyspnea,[59-62] also provided independent information regarding chronic dyspnea in this community-based setting. This result supports outpatient screening for heart failure via NT-proBNP, as also suggested by a recent systematic review.[63] The evidence of effect modification by hypertensive status, with stronger associations shown among non-hypertensives, indicates that NT-proBNP may be particularly useful in diagnosing dyspnea among patients who lack other known causes for elevations in this highly sensitive but relatively nonspecific test.

NT-proBNP was the only measure of cardiovascular disease which provided independent information despite only modest correlations between the various cardiac measures. Major ECG abnormalities were significantly more common among dyspneic participants, and in bivariate analyses adjusting for clinical factors, left ventricular ejection fraction and mass and coronary artery calcium, a measurement of subclinical atherosclerosis, were significantly associated with self-reported dyspnea. Nonetheless, the associations of these tests of cardiovascular health with prediction of dyspnea were not independent of lung measures and NT-proBNP. Although right ventricular measures have been shown to predict self-reported dyspnea in the MESA sample,[64] there were no significant associations observed in these cross-sectional data.

Strengths of this study include a well-characterized, population-based sample with gold standard measurements of subclinical heart and lung disease. Limitations include exclusion of a substantial number of participants who were missing either MRI or spirometry. This may have introduced selection bias, although presumably far less than prior pulmonary clinic-based studies, and refusals and exclusions are common in clinical practice. While most tests were performed at one exam, dyspnea was assessed 18 months later and spirometry about 4 years later. However, results from these tests are not expected to vary substantially over this period, except in the setting of acute decompensations, and therefore should remain relevant to chronic dyspnea, which was the outcome of interest. Duration of dyspnea was not specifically assessed in MESA, yet questionnaire items used to classify dyspnea were consistent with the mMRC scale, which has been interpreted as a measure of chronic dyspnea.

We lacked information on echocardiographic criteria for diastolic dysfunction, which is highly prevalent and predictive of heart failure symptoms, including dyspnea,[65]

notwithstanding evidence to suggest it is an uncommon cause of dyspnea in the elderly.[66] Nonetheless, NT-proBNP has shown to be strongly associated with severity of diastolic dysfunction.[67] Our findings pertain to automated quantitative emphysema measurements, yet radiologist-defined emphysema on CT has also been associated with dyspnea and reduced exercise tolerance in the presence and absence of COPD.[68] We were also unable to compare the performance of chest CT versus chest X-ray for the evaluation of pulmonary parenchymal diseases; X-ray is more commonly performed as an initial screening test, even though studies indicate that it is relatively low yield in the workup of dyspnea,[9,10] likely due to its lower sensitivity for emphysema and other parenchymal lung diseases.[69] Regardless, given that lung cancer screening is now recommended in smokers,[70] emphysema on CT may be increasingly available for clinical decision-making. We did not evaluate DLCO, which associates with dyspnea[71] and correlates modestly with emphysema on CT.[72] Bronchoprovocation, exercise testing and plethysmography were not performed. A measure of anemia was not available, however due to physiologic adaptations, anemia must be severe in order to cause dyspnea in otherwise healthy adults, such as those enrolled in MESA. Lastly, data on accompanying clinical symptoms was limited. Coexisting respiratory symptoms and lower extremity swelling modified the strength of the associations, however the FEV1 remained the most significant correlate of dyspnea in all symptom strata.

In conclusion, among adults without pre-existing clinical cardiopulmonary disease, dyspnea was most strongly associated with FEV_1, NT-proBNP, and percent emphysema on CT, and only FEV_1 significantly improved prediction of dyspnea versus clinical factors alone. Measures of cardiac structure and function on MRI were associated with dyspnea but did not provide information independent of these tests, and measures of atherosclerosis were less strongly associated. Thus, evaluation of dyspnea in the outpatient setting may benefit from prioritization of spirometry, followed by NT-proBNP assay and chest CT imaging for pulmonary parenchymal disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Clinical Significance

- This study evaluates associations between non-invasive diagnostic tests and self-reported dyspnea on exertion among community-dwelling adults without known cardiopulmonary disease.
- Spirometry, N-terminal Brain Natriuretic Peptide, and emphysema on computed tomography provided independent information regarding the likelihood of dyspnea, whereas measures of atherosclerosis and cardiac structure and function did not.
- These findings help fill an evidence gap on the prioritization of diagnostic tests for the outpatient work-up of dyspnea.

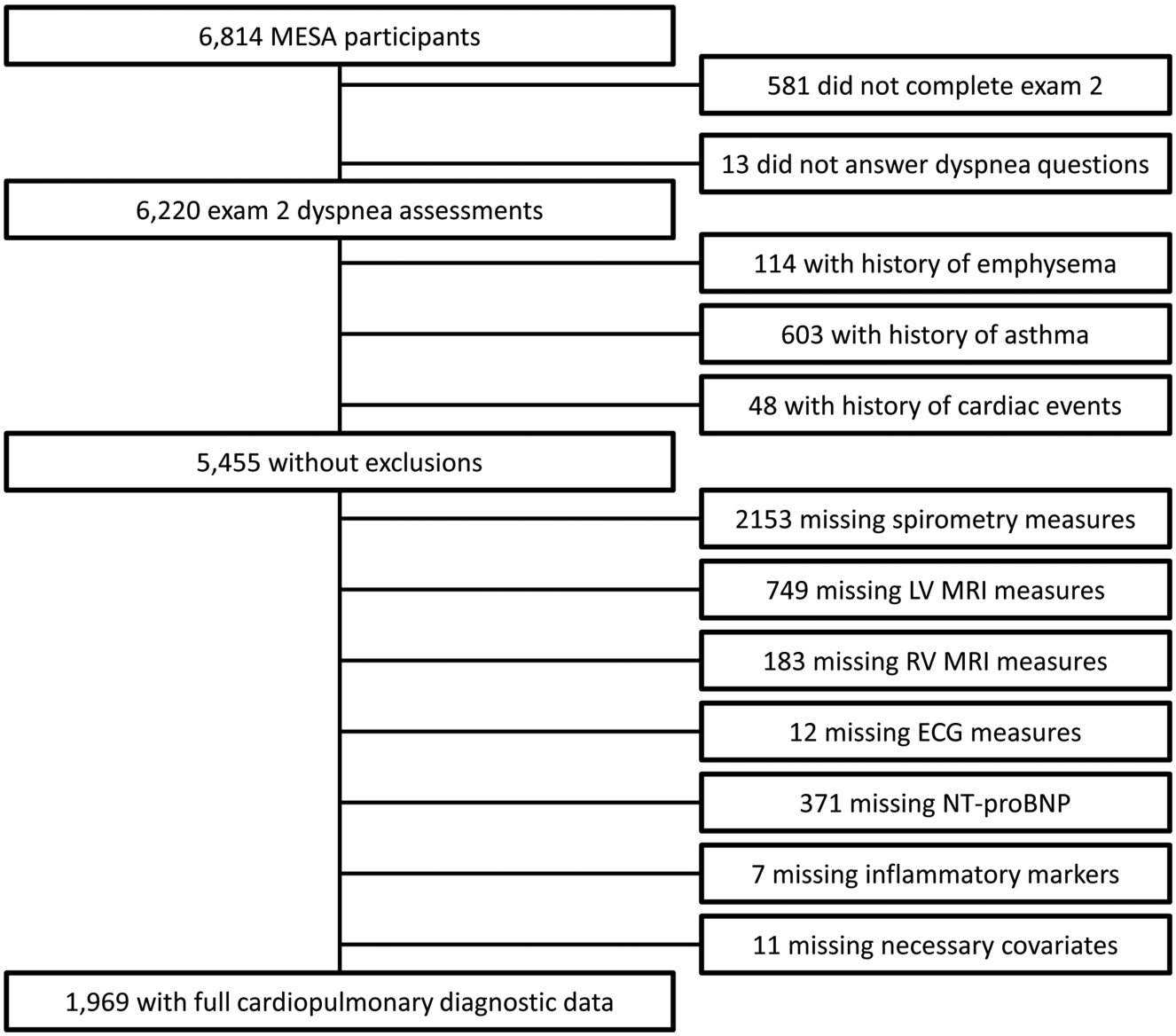

Figure 1.

Inclusion and exclusion criteria.

MESA=Multi-Ethnic Study of Atherosclerosis; MRI=magnetic resonance imaging; LV=left ventricle;

RV=right ventricle; ECG=electrocardiogram; NT-proBNP=N-terminal pro Brain Natriuretic Peptide.

Necessary covariates=age, sex, body mass index, exercise, leg pain, and anxiety.

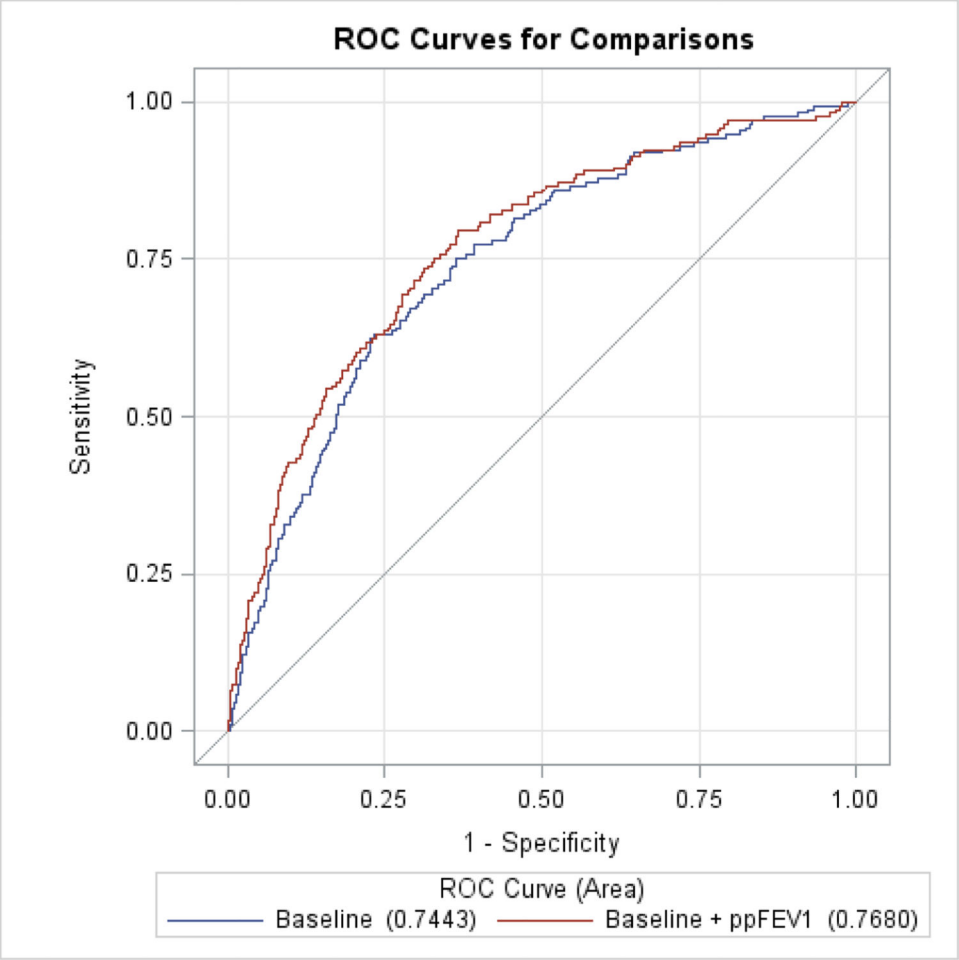

Figure 2.

Receiver Operating Curves (ROC) for baseline model versus baseline model plus the percent predicted forced expiratory volume in one second (FEV_1).

The baseline model includes age, body mass index, gender, exercise, anxiety, and leg pain.

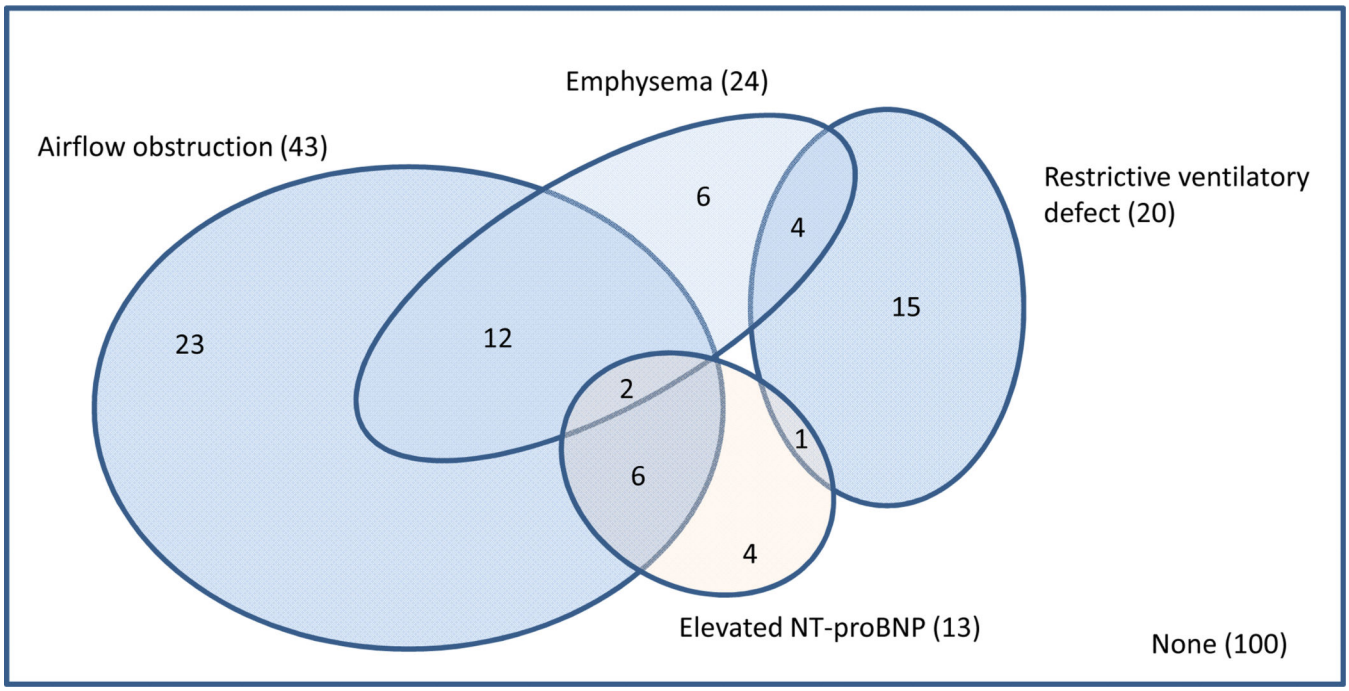

Figure 3.

Venn diagram for cardiopulmonary diagnoses, according to study test results, among participants with self-reported dyspnea (N=173).

Abnormal values were defined as follows: airflow obstruction as the ratio of forced expiratory volume in one second (FEV_1) to forced vital capacity (FVC) < 0.7; restrictive ventilatory defect as percent predicted FVC less than 80% with a normal FEV_1/FVC ratio; emphysema as percent emphysema > upper limit of normal; and elevated NT-proBNP as > 300 pg/ml.

Findings were similar when airflow obstruction was defined as FEV1/FVC < lower limit of normal, except the number of participants with airflow obstruction was smaller (N=26).

Table 1

Characteristics of participants in the Multi-Ethnic Study of Atherosclerosis without cardiopulmonary diagnoses, stratified by the self-report of dyspnea.[a]

Characteristics	No dyspnea (N=1796)	Dyspnea (N=173)	p-value
Age, years	62.3 (9.8)	63.4 (10.0)	0.162
Male gender	940 (52.3%)	65 (37.6%)	<0.001
Race			
White	619 (34.5%)	72 (41.6%)	0.118
Chinese	369 (20.6%)	24 (13.9%)	
Black	398 (22.2%)	37 (21.4%)	
Hispanic	410 (22.8%)	40 (23.1%)	
Education			0.098
No High School	179 (10.0%)	21 (12.1%)	
High School	423 (23.6%)	50 (28.9%)	
Some college or associate's degree	483 (26.9%)	52 (30.1%)	
Bachelor's Degree	347 (19.3%)	25 (14.5%)	
Graduate or Professional Degree	363 (20.2%)	25 (14.5%)	
Body Mass Index, kg/m^2	27.1 (4.7)	29.7 (5.5)	<0.001
Smoking status			0.150
Never	900 (50.1%)	78 (45.1%)	
Former	733 (40.8%)	72 (41.6%)	
Current	163 (9.1%)	23 (13.3%)	
Pack-years of smoking	0 (0, 14)	0.2 (0, 25)	0.023
Spielberger trait anxiety scale	15 (12, 18)	17 (14, 20)	<0.001
Total intentional exercise, MET-hr/wk	893 (160, 1890)	315 (0, 1238)	<0.001
Leg pain	212 (11.8%)	53 (30.6%)	<0.001
Arthritis	145 (8.1%)	24 (13.9%)	0.009
Cardiac MRI			
LV End-Diastolic Volume / BSA, ml/m^2	49 (43, 55)	47 (42, 52)	0.054
LV Ejection Fraction, percent	70 (65, 74)	69 (65, 75)	0.478
LV End-Diastolic Mass / BSA, g/m^2	55 (48, 62)	56 (49, 64)	0.312
RV Ejection Fraction, percent	71 (67, 75)	72 (67, 75)	0.350
RV End-Diastolic Mass / BSA, g/m^2	8 (7, 9)	8 (7, 9)	0.057
Coronary artery calcium, Agatston score	0 (0, 53)	3 (0, 109)	0.101
Electrocardiographic abnormalities			
Any major abnormalities	191 (10.6%)	27 (15.6%)	0.047
Any minor abnormalities	636 (35.4%)	59 (34.1%)	0.731
Spirometry			
Percent predicted FEV1	97.2 (16.1)	88.5 (19.7)	<0.001
FEV$_1$/FVC ratio	0.76 (0.07)	0.74 (0.10)	0.008
Chest CT			
Percent emphysema	3.08 (1.33, 5.90)	3.41 (1.05, 5.94)	0.570

Characteristics	No dyspnea (N=1796)	Dyspnea (N=173)	p-value
Percent high attenuation areas	4.20 (3.55, 5.24)	4.62 (3.67, 5.58)	0.163
Inflammatory markers			
CRP	1.52 (0.70, 3.46)	2.70 (1.09, 5.06)	0.002
Fibrinogen	329 (290, 377)	354 (309, 391)	0.002
Creatinine, mg/dl	0.95 (0.22)	0.93 (0.21)	0.308
NT-proBNP, pg/ml	47 (20, 92)	66 (34, 135)	0.001

Kg = kilogram. M = meter. MET = metabolic equivalent. Hr = hour. Wk = week. MRI = Magnetic Resonance Imaging. BSA = body-surface area. m = meters. LV = left ventricular. RV = right ventricular. ml = milliliter. g = grams. L = liter. Min = minute. FEV1 = forced expiratory volume in one second. FVC = forced vital capacity. CT = computed tomography. CRP = C-reactive protein. NT-proBNP = N-Terminal pro-Brain Natriuretic Peptide. Pg = picogram.

[a]Normally-distributed variables expressed as mean (standard deviation), and p-values pertain to two-sample T-tests. Non-normal variables expressed as median (interquartile range), and p-value derive from two-tailed Wilcoxon Two-Sample Tests with normal approximation. Categorical variables described as frequency (percent), and p-values pertain to chi-square tests.

Table 2

Multivariate associations of results of diagnostic tests and demographic factors with self-reported dyspnea.[a]

Potential predictor	Wald Chi-Square	p-value
Percent predicted FEV_1	37.33	<.0001
FEV_1/FVC ratio	23.38	<.0001
NT-proBNP	10.41	0.001
Percent emphysema	7.07	0.008
LV End-Diastolic Mass	5.13	0.024
LV Ejection Fraction	5.00	0.025
Smoking status	4.80	0.029
Pack years	4.35	0.037
Coronary artery calcium (Agatston score)	4.28	0.039
Race/ethnicity	4.21	0.040
Any Major ECG Abnormality	3.01	0.083
CRP	2.95	0.086
Fibrinogen	1.51	0.22
Arthritis	0.82	0.37
LV End-Diastolic Volume	0.74	0.39
Any Minor ECG Abnormality	0.32	0.57
Creatinine	0.21	0.65
RV Ejection Fraction	0.184	0.67
Percent high attenuation areas	0.019	0.89
RV End-Diastolic Mass	0.012	0.91
Educational Attainment	0.54	0.97

LV = left ventricular. RV = right ventricular. FEV_1 = forced expiratory volume in one second. FVC = forced vital capacity. CRP = C-reactive protein. NT-proBNP = N-Terminal pro-Brain Natriuretic Peptide. ECG = electrocardiogram.

[a]Models adjusted for age, body mass index, sex, exercise, anxiety, and leg pain.

Table 3

Results of diagnostic tests independently associated with self-reported dyspnea.[a]

Predictor	Odds ratio[b] (95% confidence interval)	Wald Chi-square	p-value
Percent predicted FEV_1	0.616 (0.525, 0.723)	35.22	<0.0001
NT-proBNP	1.202 (1.062, 1.361)	8.50	0.004
Percent emphysema	1.274 (1.079, 1.506)	8.14	0.004

FEV_1 = forced expiratory volume in one second. NT-proBNP = N-Terminal pro-Brain Natriuretic Peptide.

[a] Models adjusted for age, body mass index, gender, exercise, anxiety, and leg pain.

[b] Odds ratios reported per standard deviation of the predictor. Standard deviations were as follows: percent predicted FEV_1 = 17%; NT-proBNP = 123 pg/ml; percent emphysema = 4%.

Table 4

Comparison of Receiver Operating Curves (ROC) for baseline covariates plus selected cardiopulmonary diagnostic tests in prediction of self-reported dyspnea.

Model	Area Under Curve (95% CI)	Improvement over baseline model (95% CI)	Chi-Square	P-value
Baseline model[a]	0.744 (0.707, 0.782)	-	-	-
Baseline + percent predicted FEV_1	0.768 (0.731, 0.806)	0.024 (0.0003, 0.047)	3.95	0.047
Baseline + percent emphysema	0.752 (0.715, 0.789)	0.008 (−0.006, 0.021)	1.289	0.256
Baseline + NT-proBNP	0.752 (0.714, 0.789)	0.007 (−0.005, 0.019)	1.434	0.231
Baseline + all three tests	0.774 (0.737, 0.812)	0.030 (0.003, 0.057)	4.665	0.031

FEV_1 = forced expiratory volume in one second. NT-proBNP = N-Terminal pro-Brain Natriuretic Peptide.

[a]Baseline model includes age, body mass index, gender, exercise, anxiety, and leg pain.