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Spirometric impairments, cardiovascular outcomes, and noncardiovascular death in older persons

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ABSTRACT

Background: In prior work involving older persons, the reported associations of spirometric impairments with cardiovascular outcomes may have been confounded by age-related changes in lung function. Hence, using more age-appropriate spirometric criteria from the Global Lung Function Initiative (GLI), we have evaluated the associations of spirometric impairments, specifically restrictive-pattern and airflow-obstruction, with cardiovascular death (CV-death) and hospitalization (CV-hospitalization). In these analyses, we also evaluated the competing outcome of noncardiovascular death (nonCV-death) and calculated measures of relative and absolute risk.

Methods: Our study sample was drawn from the Cardiovascular Health Study (CHS), including 4232 community-dwelling white persons aged ≥65 years. Multivariable regression models included the following baseline predictors: GLI-defined restrictive-pattern and airflow-obstruction, age, male gender, obesity, waist circumference, current smoker status, ≥10 pack-years of smoking, hypertension, dyslipidemia, diabetes, and cardiovascular and cerebrovascular disease. Outcomes included adjudicated CV-death, CV-hospitalization, and nonCV-death, ascertained over 10 years of follow-up. Measures of association included hazard ratios (HRs), rate ratios (RRs), and average attributable fraction (AAF), each with 95% confidence intervals.

Results: Restrictive-pattern and airflow-obstruction were associated with CV-death (adjusted HRs: 1.57 [1.18, 2.09] and 1.29 [1.04, 1.60]) and with nonCV-death (adjusted HRs: 2.10 [1.63, 2.69] and 1.79 [1.51, 2.12]), respectively. Airflow-obstruction, but not restrictive-pattern, was also associated with CV-hospitalization (adjusted RRs: 1.18 [1.02, 1.36] and 1.20 [0.96, 1.50], respectively). The adjusted AAFs of restrictive-pattern and airflow-obstruction were 1.68% (0.46, 3.06) and 2.35% (0.22, 4.72) for CV-death, and 3.44% (1.97, 5.08) and 7.77% (5.15, 10.60) for nonCV-death, respectively.

Conclusion: Assessment of GLI-defined spirometric impairments contributes to broad geriatric risk stratifications for both cardiovascular and non-cardiovascular outcomes.

1. Introduction

In prior work involving older persons, the reported associations of spirometric impairments with cardiovascular outcomes may have been confounded by age-related changes in lung function [1–8]. Specifically, prior work defined spirometric impairments based on percentile distributions within a study sample, e.g., quintiles, or on percent predicted (%Pred) values, i.e., [measured/predicted] x 100% [1–8]. We note that, to distinguish spirometric impairments from normal-for-age spirometry, percentile distributions should be based on comparisons with a reference population of healthy never-smokers [9,10]. We also note that %Pred assumes incorrectly that a given value is equivalent for all persons [11]. To illustrate the effect of age in a white male of average height, the same value of 80%Pred for the forced expiratory volume in 1 s (FEV_1) will correspond to the 6th and 14th percentile distribution of the reference population at ages 40 and 70 years, respectively [11].

To better establish age-appropriate spirometric impairments, an alternative approach was introduced in 2008, termed Lambda-Mu-Sigma (LMS) [9]. The LMS approach uses spirometric Z-scores to rigorously account for age-related changes in lung function, with a Z-score of −1.64 defining the lower limit of normal (LLN) as the 5th percentile distribution of the reference population [9]. In 2012, using data from large populations of asymptomatic lifelong nonsmokers and the LMS approach, the Global Lung Function Initiative (GLI) published reference

Abbreviations: AAF, average attributable fraction; BMI, body mass index; CV, cardiovascular; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; GLI, Global Lung Function Initiative; HR, hazard ratio; nonCV, noncardiovascular; RR, rate ratio

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equations that expanded the availability of spirometric Z-scores, additionally including an age range of up to 95 years [10]. However, spirometric impairments as defined by GLI-calculated Z-scores have not yet been evaluated as risk factors for cardiovascular outcomes.

Accordingly, the aim of the current study is to evaluate the associations between GLI-defined spirometric impairments and cardiovascular outcomes, wherein we additionally account for the competing outcome of noncardiovascular death (nonCV-death) and a broad array of potential confounders. Specifically, using multivariable regression models, we have evaluated the associations of GLI-defined restrictive-pattern and airflow-obstruction with cardiovascular death (CV-death), cardiovascular hospitalization (CV-hospitalization), and nonCV-death, respectively, over 10 years of follow-up. In these analyses, we have calculated measures of relative risk (e.g., hazard ratios) and absolute risk (i.e., average attributable fraction [AAF]) [12]. Our study sample is drawn from the Cardiovascular Health Study (CHS), including persons aged ≥65 years (as older age is associated with reduced lung function and adverse outcomes) [9,10,13,14]. Because the current study provides a more age-appropriate and comprehensive evaluation, our results may further inform the role of spirometry in geriatric risk stratification, including both cardiovascular and noncardiovascular outcomes.

2. Materials and methods

2.1. Study population

CHS is a longitudinal study of persons aged ≥65 years, identified from a random sample of Medicare eligibility lists in four communities in the United States [14]. For our analytical sample, we included participants from the initial 1989–1990 CHS cohort, as only this group completed clinical and spirometric evaluations at the same visit (study entry). Moreover, consistent with prior work from CHS and other cohorts involving older persons [15–18], we required that participants achieve a spirometric quality control (QC) grade C or higher, i.e., having at least two acceptable forced vital capacity (FVC) maneuvers and $FEV1_1$ values matching within 200 mL [15].

We note that mandating only two acceptable FVC maneuvers for inclusion in our analytical sample is not consistent with the 2005 spirometric guidelines from the American Thoracic Society (ATS) and European Respiratory Society (ERS) [19], wherein the requirement was for at least three acceptable FVC maneuvers and more stringent repeatability criteria. However, the ATS/ERS guidelines also state that: “no spirogram or test result should be rejected solely on the basis of its poor repeatability.” [19] Therefore, although greater spirometric repeatability is recommended, the ATS/ERS criteria allow for clinical judgment, as otherwise older persons who are physically frail and at increased risk of adverse health outcomes would be potentially excluded from the current analyses (despite achieving two acceptable FVC maneuvers) [15,20,21]. Importantly, the CHS criteria that defined the performance of an FVC maneuver as acceptable are consistent with ATS/ERS guidelines [19].

Lastly, since the proportion of African-Americans was too small to support our analyses (5.3%), we selected only white participants. Based on our inclusion criteria, the final analytical sample thus included 4232 white participants, representing 81.4% of the 1989–1990 cohort.

The institutional review boards from the Veterans Affairs Connecticut Healthcare System and Yale University approved the current study. We note that the CHS dataset used in the current study had been previously deidentified and was publicly available.

2.2. Baseline demographic and clinical characteristics

Baseline characteristics included age, gender, body mass index (BMI), waist circumference, smoking history (current smoker status and pack-years), and cardiovascular conditions and risk factors. A BMI ≥30 kg/m^2 (including measured weight and standing height) defined obesity [14], and a waist circumference ≥110 cm in males and ≥95 cm in females defined high risk values [22], based on previously published associations with mortality (adjusted hazard ratios of 1.52 [1.45, 1.59] and 1.79 [1.70, 1.89], respectively, in a pooled analysis of 11 studies [age range 25–83 years]) [22]. In a supplemental analysis, we evaluated the alternative waist circumference thresholds of > 100 cm in males and > 90 cm in females as intermediate risk values, based on previously published associations with mortality (adjusted hazard ratios of 1.19 [1.15, 1.24] and 1.50 [1.42, 1.58], respectively, in a pooled analysis of 11 studies [age range 25–83 years]) [22].

Cardiovascular conditions and risk factors were defined according to CHS criteria, as follows [14]: hypertension (systolic ≥160 mm Hg, diastolic ≥95 mm Hg, or history of hypertension requiring antihypertensive medication); dyslipidemia (low-density lipoprotein cholesterol ≥160 mg/dL or high-density lipoprotein cholesterol < 40 mg/dL); diabetes mellitus (taking insulin or oral hypoglycemic, or fasting glucose ≥126 mg/dL); and adjudicated coronary heart disease (myocardial infarction or angina), heart failure, claudication, and cerebrovascular disease (stroke or transient ischemic attack).

2.3. Spirometric impairment

Participants underwent spirometry in the seated position, using a water-sealed, Collins Survey II spirometer [14,15]. The testing protocol included FVC maneuvers, repeated up to eight times, with the goal of achieving at least three acceptable and two repeatable FVC maneuvers (as per contemporary ATS criteria) [15]. For reasons discussed earlier, we established our spirometric analytical sample based on a QC grade C or higher, defined by participants having at least two acceptable FVC maneuvers and $FEV1_1$ values matching within 200 mL [14,15]. Notably, CHS did not specifically evaluate spirometry after administering a bronchodilator [14,15].

Spirometric results were reviewed at the CHS Pulmonary Function Reading Center [15], which included flow and volume grades for the forced expiratory volume in 1 s (FEV_1) and FVC, respectively. The largest FEV_1 and FVC values from acceptable FVC maneuvers were reported, with FEV_1/FVC calculated from the largest FEV_1 and FVC values.

Using GLI-2012 reference equations for whites (Caucasians) [10], which included the predictor variables of age, gender, and the measured standing height, we calculated Z-scores for FEV_1/FVC and FVC. With the LLN set at a Z-score of −1.64,[10] and applying spirometric categories as described by the ATS/ERS [23], we defined normal spirometry by FEV_1/FVC and FVC ≥ LLN, restrictive-pattern by FEV_1/FVC ≥ LLN but FVC < LLN, and airflow-obstruction by FEV_1/FVC < LLN [16–18]. For those with airflow-obstruction, we also calculated the average FEV1 Z-score and interpreted as follows [17]: FEV_1 Z-scores ≥ −1.64 denote mild, < −1.64 but ≥ −2.55 denote moderate, and < −2.55 denote severe airflow-obstruction.

Prior work has established a strong mathematical, clinical, and physiological rationale for GLI-defined spirometric impairments in aging populations [9,10,16–18,24], including restrictive-pattern as representing a restrictive ventilatory defect [24]. In addition, prior work has shown that applying a minimum spirometric QC grade C is clinically meaningful when evaluating the phenotypes of normal spirometry and spirometric impairments in aging populations [16–18].

2.4. Longitudinal outcomes

Our outcomes of interest were vital status and hospitalization. These were adjudicated centrally by CHS committees through the use of standardized diagnostic criteria, ICD-9-CM codes (International Classification of Diseases, 9th revision, clinical modification), medical records, proxy interviews, obituaries, and death certificates [14,25].

Vital status was available on all participants, ascertained over a 10-