Clinical and Radiographic Predictors of GOLD–Unclassified Smokers in the COPDGene Study

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Rationale: A significant proportion of smokers have lung function impairment characterized by a reduced FEV₁ with a preserved FEV₁/FVC ratio. These smokers are a poorly characterized group due to their systematic exclusion from chronic obstructive pulmonary disease (COPD) studies.

Objectives: To characterize the clinical, functional, and radiographic features of Global Initiative for Chronic Obstructive Lung Disease (GOLD)–Unclassified (FEV₁/FVC ≥ 0.7 and FEV₁ < 80% predicted) and lower limits of normal (LLN)–unclassified (FEV₁/FVC ≥ LLN and FEV₁ < LLN) subjects compared to smokers with normal lung function and subjects with COPD.

Methods: Data from the first 2,500 subjects enrolled in the COPDGene study were analyzed. All subjects had 10 or more pack-years of smoking and were between the ages of 45 and 80 years. Multivariate regression models were constructed to determine the clinical and radiological variables associated with GOLD–Unclassified (GOLD–U) and LLN–Unclassified status. Separate multivariate regressions were performed in the subgroups of subjects with complete radiologic measurement variables available.

Measurements and Main Results: GOLD–U smokers account for 9% of smokers in COPDGene and have increased body mass index (BMI), a disproportionately reduced total lung capacity, and a higher proportion of nonwhite subjects and subjects with diabetes. GOLD–U subjects exhibit increased airway wall thickness compared to smoking control subjects and decreased gas trapping and bronchodilator responsiveness compared to subjects with COPD. When LLN criteria were used to define the “unclassified” group, African American subjects were no longer overrepresented. Both GOLD–U and LLN–Unclassified subjects demonstrated a wide range of lung function impairment, BMI, and percentage of total lung emphysema.

Conclusions: Subjects with reduced FEV₁ and a preserved FEV₁/FVC ratio are a heterogeneous group with significant symptoms and functional limitation who likely have a variety of underlying etiologies beyond increased BMI.

Clinical trial registered with www.clinicaltrials.gov (NCT000608764).

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Smokers with reduced FEV₁ or FVC in the setting of preserved FEV₁/FVC ratio are a poorly characterized group due to their exclusion from most COPD studies.

What This Study Adds to the Field

Our study characterizes the clinical and radiographic features of these GOLD (Global Initiative for Obstructive Lung Disease)–unclassified smokers.

Keywords: lung diseases, classification; lung diseases, diagnosis; lung diseases, epidemiology

The heterogeneity of chronic obstructive lung disease (COPD) in clinical care has been compounded by, paradoxically, both underdiagnosis and over- or misdiagnosis. On the population level, massive underdiagnosis of obstructive lung disease exists and may contribute to undertreatment (1). However, among patients receiving medical care, the diagnosis of COPD is often made clinically, with only one-third of patients ever receiving confirmatory spirometry (2–5). Among patients who undergo spirometry, 8 to 14% (2, 4, 6) have evidence of impaired lung function that cannot be classified under current Global Initiative for Chronic Obstructive Lung Disease (GOLD) diagnostic and staging criteria (7). These GOLD–Unclassified (GOLD–U) subjects, who exhibit reduced FEV₁ but maintain an FEV₁/FVC ratio greater than or equal to 0.7, are a poorly characterized group due to their systematic exclusion from COPD studies.

Reduced FEV₁ or FVC in the setting of a preserved FEV₁/FVC ratio is often described as a restrictive pattern. However, substantial evidence has shown that this pattern on spirometry has poor predictive value for true restriction as assessed by reduced total lung capacity (TLC) (8–10). Despite lack of true restrictive disease, multiple studies have demonstrated that this pattern on spirometry is stable in the majority of subjects (11, 12) and is associated with increased mortality (13–15) and decreased functional status (16). Smokers with this spirometric pattern have been studied as subgroups in population-based studies, but extensive characterization of these subjects with regard to clinical and radiographic features has not been made previously. We hypothesized that subjects with the GOLD–U pattern of spirometry will have distinct clinical, functional, and radiographic characteristics when compared to smokers with normal lung function and subjects with COPD (GOLD stages 2–4).

Some of the results in the current manuscript have been previously reported in the form of an abstract (17).

(Received in original form January 5, 2011; accepted in final form April 14, 2011)

Supported by National Institutes of Health grants U01 HL089856 (to E.K.S.), U01 HL089897 (to J.D.C.), and T32HL007427 (to S.T.W.).

Author contributions: E.S.W. participated in data analysis and manuscript writing. J.E.H. participated in data collection, statistical support, and manuscript review. E.A.R. participated in data collection and manuscript editing. J.R.M. and B.J.M. participated in concept and design, data collection, and manuscript review. D.A.L. participated in data analysis and manuscript editing. J.D.C. and E.K.S. participated in funding support, concept and design, data collection, and manuscript review.

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This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

Am J Respir Crit Care Med Vol 184, pp 57–63, 2011

Originally Published in Press as DOI: 10.1164/rccm.201101-0021OC on April 14, 2011

Internet address: www.atsjournals.org

METHODS

COPDGene is an ongoing study that enrolled subjects from 21 clinical centers throughout the United States (clinicaltrials.gov identifier NCT000608764). Institutional review board approval was obtained at each participating clinical center, and all subjects provided informed consent. Details regarding the study design have been previously published (18). Subjects are self-identified non-Hispanic whites or African Americans with 10 or more pack-years of smoking, between the ages of 45 and 80 years. Subjects completed a modified American Thoracic Society Respiratory Epidemiology questionnaire, St. George's Respiratory Questionnaire, and 6-minute walk test. Pre- and post-bronchodilator spirometry was performed using an EasyOne spirometer (nidd, Zurich, Switzerland) according to the American Thoracic Society guidelines (19). Volumetric inspiratory and expiratory chest computed tomography (CT) scans using multidetector CT scanners were completed on all subjects per protocol (18).

Variable Definitions

FEV₁ and FVC % predicted values and the lower limits of normal were calculated according to the prediction equations by Hankinson and colleagues (20). GOLD-U subjects have a post-bronchodilator FEV₁ less than 80% predicted and FEV₁/FVC greater than or equal to 0.7. Smoking control subjects have a post-bronchodilator FEV₁/FVC greater than or equal to 0.7 and FEV₁ greater than or equal to 80% predicted. Subjects with COPD have a post-bronchodilator FEV₁/FVC less than 0.7 and FEV₁ less than 80% predicted (GOLD stages 2–4). Bronchodilator response was considered positive if the subject had greater than or equal to 0.2-L increase in FEV₁ or FVC and greater than or equal to 12% change in FEV₁ or FVC above baseline (pre-bronchodilator) measurements. Additional variable definitions are provided in the online data supplement.

Quantitative CT measurements of total lung capacity (TLC_{CT}), emphysema, and gas trapping percentages were performed using Slicer (Version 2, www.slicer.org). Percent emphysema was quantified as the percentage of lung volume on inspiratory CT with an attenuation less than –950 Hounsfield Units (HU). Gas trapping was quantified as the percentage of lung volume on expiratory CT (taken at functional residual capacity [FRC]) with an attenuation less than –856 HU. Airway analysis was performed using the Pulmonary Workstation Plus (VIDA Diagnostics, Inc., Coralville, IA) (21, 22). Details are provided in the online data supplement. The square root of wall area for a hypothetical airway with an internal perimeter of 10 mm (Pi10) was derived (23).

Statistical Analysis

All analyses were performed using SAS (v9.1; Cary, NC). Comparisons between the GOLD-U group and smoking control subjects and between the GOLD-U group and subjects with COPD (GOLD stages 2–4) were made separately. Univariate comparisons were made using Fisher's exact test for dichotomous variables and a Student's *t* test or Wilcoxon rank sum test for normal and nonnormal continuous variables, respectively. Variables with a univariate *P* value less than 0.05 were considered as candidates in the multivariable regression model. Logistic regression with GOLD-U status as the dependent variable was performed using stepwise selection; all variables with a *P* value less than or equal to 0.05 were retained in the final model. Variables not retained as covariates in the final model were tested as confounders and retained in the model if greater than or equal to 10% change in the effect estimate was observed. Because radiographic variables were missing in some subjects due to technical limitations, a separate multivariable analysis was conducted in individuals with complete radiographic data. Selected analyses were repeated using lower limits of normal (LLN) (20) to define the smoking control subjects (LLN-control), COPD (LLN-COPD), and Unclassified (LLN-Unclassified) groups. Details are outlined in the online data supplement.

RESULTS

GOLD-U subjects represent 9.1% of the first 2,500 subjects recruited in COPDGene. Univariate comparisons between

GOLD-U and smoking control subjects and GOLD-U and subjects with COPD are summarized in Table 1. Compared to smoking control subjects, GOLD-U subjects have greater pack-years of smoking, decreased 6-minute-walk distance (6MWD), lower resting oxygen saturation, greater subsegmental airway wall area, and increased rates of respiratory medication use and comorbid cardiovascular disease (such as congestive heart failure [CHF], hypertension, stroke, and transient ischemic attacks). Compared to subjects with COPD, GOLD-U subjects have fewer pack-years of smoking, higher rates of current smoking, greater 6MWD, reduced subsegmental airway wall area, and lower rates of bronchodilator responsiveness and respiratory medication use. Compared with both groups, GOLD-U subjects have higher body mass index (BMI), reduced TLC and emphysema, and a higher proportion of subjects with diabetes and who are of nonwhite race.

Because the spirometric pattern of reduced FEV₁ in the setting of a preserved FEV₁/FVC ratio is often described as being a restrictive pattern, we applied the prediction equations of Stocks and Quanjer (24) to the TLC_{CT} (Table 2). Previous studies have demonstrated excellent correlation between CT-derived estimates of TLC and measurements obtained through helium dilution (25) and body plethysmography (26). Approximately one-half of the GOLD-U cohort was found to have restrictive lung disease as defined by a reduced TLC_{CT}. Although the prevalence of restrictive lung disease is significantly higher in GOLD-U subjects, a substantial proportion of smoking control subjects and a small minority of subjects with COPD also have reduced TLC_{CT}.

The results of the multivariable analyses to determine the predictors of GOLD-U status are summarized in Table 3. In the models comparing GOLD-U to smoking control subjects, increased BMI, decreased 6MWD and resting oxygen saturation, higher subsegmental airway wall area, and history of CHF were significant and independent predictors of GOLD-U status. In the multivariate models comparing GOLD-U to patients with COPD, increased BMI and resting oxygen saturation, less emphysema, lower subsegmental airway wall area, and decreased rates of bronchodilator responsiveness were significant predictors. Decreased TLC_{CT} was a significant predictor even after adjusting for BMI in analyses comparing GOLD-U subjects to smoking control subjects and subjects with COPD.

GOLD-U subjects are a heterogeneous group; the range of values of FEV₁ % predicted, BMI, and percent emphysema is illustrated in Table 4. Subgroup analyses within the GOLD-U cohort by racial group and sex were conducted. There were no significant differences in age, current smoking status, or FEV₁ % predicted by sex. Women with GOLD-U spirometry had reduced exercise capacity, significantly more dyspnea, and worse quality of life. Men with GOLD-U spirometry had significantly more pack-years of smoking and emphysema but reduced subsegmental airway wall area. Univariate comparisons by racial group are summarized in Table 5. African-American GOLD-U subjects were younger and had fewer pack-years of smoking, a higher proportion of current smokers, reduced exercise capacity, and a lower mean FEV₁ % predicted than white subjects. African-American GOLD-U subjects also had less emphysema and thicker subsegmental airway wall measurements than white subjects. There were no differences in BMI by racial group or by sex.

To further examine the role of BMI in GOLD-U subjects, univariate comparisons were made between obese (BMI ≥ 30) and nonobese (BMI < 30) subjects (Table 6). Obese GOLD-U subjects had significantly more dyspnea, reduced functional capacity as assessed by 6MWD, and lower resting oxygen saturation. BMI was significantly correlated with FEV₁ % predicted (Rho = –0.21,

TABLE 1. UNIVARIATE COMPARISONS BETWEEN GLOBAL INITIATIVE FOR OBSTRUCTIVE LUNG DISEASE–UNCLASSIFIED SUBJECTS, SMOKING CONTROL SUBJECTS, AND SUBJECTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (GLOBAL INITIATIVE FOR OBSTRUCTIVE LUNG DISEASE STAGES 2–4)

	GOLD-U Subjects	Smoking Control Subjects	Subjects with COPD
N	227	1,001	1,059
Age, yr	58.5 (8.7)	57.8 (8.9)	64.1 (8.4)*
Male	48.0	49.2	51.8
Non-white race	40.5	32.5*	18.8*
Pack-years	43.7 (26.8)	37.5 (20.6)*	53.3 (26.7)*
Current smoking	52.9	51.9	33.2*
Heart rate	76.8 (13.1)	74.3 (12.7)*	77.8 (13.1)
BMI	31.9 (7.2)	28.8 (5.9)*	28.0 (6.2)*
6-min walk distance, ft	1,251.7 (405.4)	1,491.8 (405.2)*	1,136.6 (429.1)*
Resting O ₂ saturation	96.3 (2.4)	97.0 (1.8)*	94.5 (3.6)*
FEV ₁ , % predicted	70.4 (7.4)	97.9 (12)*	48.9 (18.1)*
FVC, % predicted	71.7 (8.3)	96.7 (12.1)*	76.3 (17.7)*
% Emphysema [†]	1.8 (2)	2.7 (3.0)*	15.5 (13.3)*
% Gas trapping [‡]	11.8 (8.5)	11.7 (9.5)	42.3 (20.3)*
Pi10 [§]	3.8 (0.1)	3.7 (0.1)*	3.8 (0.1)
Subsegmental wall area %	65.0 (2.4)	63.0 (2.2)*	65.7 (2.4)*
TLC, % predicted	79.4 (13)	93.3 (15.1)*	102.6 (16.8)*
Functional residual capacity, % predicted	87.0 (18)	89.9 (20.1)	128.9 (33.4)*
Long-acting β -agonist, % of users	13.7	3.7*	51.7*
Long-acting muscarinic antagonist, % of users	8.4	2.3*	44.2*
Inhaled corticosteroids, % of users	15.9	4.7*	53.6*
Oral steroids, % of users	2.6	0.4*	6.2*
St. George's Respiratory Questionnaire	27.6 (23.0)	15.5 (17.4)*	40.3 (21.1)*
MMRC	1.4 (1.5)	0.7 (1.1)*	2.2 (1.4)*
Chronic cough	30	21.6*	38.2*
Chronic sputum	22.9	17.9	35.9*
Chronic bronchitis	17.6	13.3	27.3*
Asthma, ever	16.7	10.9*	24.1*
Asthma, current	9.7	5.4*	17.1*
Positive bronchodilator response	13.6	9.5	36.1*
History of CHF	5.3	0.8*	5.1
Diabetes	22.5	12*	11.9*
Hypertension	48.5	35.5*	47.5
Stroke	3.1	1.6	3.5
TIA	3.5	1.4*	2.7
Obstructive sleep apnea	20.7	12*	16.6

Definition of abbreviations: BMI = body mass index; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; GOLD-U = Global Initiative for Obstructive Lung Disease–Unclassified; MMRC = modified Medical Research Council dyspnea score; Pi10 = square root of wall area for a hypothetical airway with an internal perimeter of 10 mm; TIA = transient ischemic attack; TLC = total lung capacity.

Data are presented as percent or mean (SD). Bronchodilator response was considered positive if the subject had ≥ 0.2 -L increase in FEV₁ or FVC and $\geq 12\%$ change in FEV₁ or FVC above baseline (prebronchodilator) measurements.

* Denotes P value < 0.05 when compared to GOLD-U subjects.

[†] For emphysema and TLC, $n = 224$ (GOLD-U), 993 (control subjects), 1,047 (COPD).

[‡] For functional residual capacity and gas trapping, $n = 202$ (GOLD-U), 908 (control subjects), 991 (COPD).

[§] For Pi10, $n = 217$ (GOLD-U), 975 (control subjects), 991 (COPD).

^{||} For subsegmental wall area, $n = 217$ (GOLD-U), 974 (control subjects), 990 (COPD).

P value = 0.0015) and subsegmental wall area measurements ($Rho = 0.17$, P value = 0.01) but was not significantly correlated with the percent of emphysema (P value = 0.13) or TLC_{CT} (P value = 0.32).

To examine the effects of multiple covariates on subsegmental airway wall area percentage in GOLD-U subjects, univariate analyses and multivariable regression were performed. Subsegmental airway wall area percentage demonstrated a significant negative correlation with FEV₁ % predicted ($Rho = -0.29$, P value < 0.0001); the association remained significant after adjustment for age, sex, race, and pack-years smoked, as well as with and without adjustment for BMI. Subsegmental wall area percentage did not vary significantly by the presence or absence of bronchodilator response or chronic bronchitis.

Selected analyses were repeated using the LLN to define unclassified (LLN-Unclassified), smoking control (LLN-control), and COPD (LLN-COPD) groups. There were 13% fewer unclassified subjects, 16% more control subjects, and 10% fewer subjects with COPD in the LLN analysis. The concordance rate

between GOLD-U and LLN-Unclassified groups was moderate ($kappa = 0.72$) (Table 7). LLN-Unclassified subjects are also a heterogeneous group (see Table E1 in the online supplement). Univariate comparisons between the LLN groups are summarized in Table E2. African American subjects account for a smaller proportion of LLN-Unclassified subjects compared to GOLD-U subjects. However, African American subjects in the LLN-Unclassified group continue to have lower FEV₁ % predicted than white subjects despite being significantly younger and having fewer pack-years of smoking (Table E3). Differences by race in TLC, emphysema, and airway wall area percentage also persist. The prevalence of restrictive abnormalities in each of the LLN groups is similar to the prevalence when GOLD criteria are used (Table E4). In the multivariate models predicting LLN-Unclassified status, similar predictors were identified (Table E5). Increased BMI, resting oxygen saturation, and subsegmental airway wall area percentage are again identified as significant predictors. However, CHF and race are no longer significant predictors in any of the multivariate analyses.

TABLE 2. PREVALENCE OF RESTRICTIVE ABNORMALITIES IN GLOBAL INITIATIVE FOR OBSTRUCTIVE LUNG DISEASE–UNCLASSIFIED SUBJECTS, SMOKING CONTROL SUBJECTS, AND SUBJECTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

	GOLD-U Subjects	Smoking Control Subjects	Subjects with COPD
TLC,* L	4.5 (1.1)	5.3 (1.3) [†]	6.0 (1.4) [†]
TLC, % predicted	79.4 (13)	93.3 (15.1) [†]	102.6 (16.8) [†]
FVC < 80% predicted, % of subjects	88.6	6.0 [†]	57.9 [†]
TLC < 80% predicted, % of subjects	56.3	17.8 [†]	9.0 [†]
TLC < LLN, % of subjects	45.5	13.8 [†]	7.2 [†]

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; GOLD-U = Global Initiative for Obstructive Lung Disease–Unclassified; TLC = total lung capacity.

Data are presented as mean (SD) or percent.

* Based on chest CT measurements.

[†] Denotes *P* value < 0.05 when compared with GOLD-U subjects.

DISCUSSION

Our study is the first to extensively characterize smokers with the GOLD-Unclassified pattern on spirometry with respect to clinical and radiographic variables. Although a considerable degree of heterogeneity within the GOLD-U group was noted, several distinguishing characteristics were identified.

The association of increased BMI in GOLD-U subjects relative to both smoking control subjects and subjects with COPD is consistent with previous reports in the literature (27). Increased body mass and adiposity are known to impact spirometry and lung volume measurements (28–30). Proportionately decreased FEV₁ and FVC with resultant preservation of the FEV₁/FVC ratio has been observed in overweight and obese subjects. However, the reductions in FEV₁ and FVC, although statistically significant, are typically small, and FEV₁ and FVC values usually remain well within the range of normal predicted values even in extreme obesity (29, 30). Thus, obesity alone is unlikely to account for the FEV₁ impairment observed in GOLD-U subjects.

Moderate reductions in TLC have likewise been associated with increasing BMI, although once again, values typically remain within the range of normal (28). Among obese (BMI > 30) smoking control subjects in our cohort, the mean TLC % predicted was 91.3% (data not shown); thus we believe the degree to which TLC is reduced in the GOLD-U group is out of proportion to what would be expected from obesity alone. Interestingly, reduced FRC, which is often the most dramatic effect of obesity on lung function (28), is not observed in GOLD-U subjects relative to smoking control subjects. It should be noted that FRC measurements were acquired from CT data obtained in the supine position. FRC can be reduced significantly in normal subjects on assuming a recumbent position, whereas obese subjects, despite having a reduced FRC at baseline, typically experience no further reduction in FRC (31, 32). Despite these caveats, the FRC % predicted values for both groups remain within the normal range. Thus, although increased BMI clearly contributes to the respiratory impairment observed in some GOLD-U subjects, its role is neither comprehensive nor straightforward.

The association of low BMI with increased emphysema measured by quantitative CT has been well established in subjects with COPD (33, 34). The finding of reduced emphysema estimates in GOLD-U subjects who, on average, have higher BMI, would appear congruent with previous observations, although the mechanism behind this observation remains obscure. Reduced emphysema seems unlikely to be related to artifact from increased soft tissue mass, since this should cause increased image noise with resultant increase in the numbers of voxels below the −950 HU threshold. It is possible that this results from the relatively decreased TLC_{CT} in these individuals,

resulting in a relatively increased mean lung attenuation and a relative decrease in the percentage of voxels below the threshold value. In addition, the direction of causation between low BMI and increased emphysema has not been firmly established; severe emphysema can feasibly cause wasting, but it is less clear whether increased body mass would be protective against the development of emphysema.

Independent of BMI, an interesting feature of our GOLD-U cohort is the high proportion of African American subjects. The relative enrichment of African Americans in the GOLD-U cohort may represent an artifact caused by a combination of the spirometric prediction equations used for African American subjects and the fixed thresholds used to define GOLD-U subjects. The proportion of African American subjects relative to smoking control subjects is reduced when LLN criteria are applied. However, the consistently decreased proportion of African American subjects in the COPD cohort may reflect racial differences in the response to tobacco smoke. Analogous to studies in COPD populations (35), African Americans in the GOLD-U cohort were younger, had decreased cumulative exposure to tobacco smoke, and had lower FEV₁ % predicted than white GOLD-U subjects.

Comorbid conditions identified as significant predictors of GOLD-U status include diabetes and CHF. Consistent with previous reports, diabetes appears to be a risk factor for impaired lung function independent of BMI (36, 37). Although the mechanism behind this association remains obscure, at least one study has demonstrated that pulmonary abnormalities may antedate the diagnosis of diabetes and suggests the two disorders may share a common origin (13, 36). Reduced FEV₁ and FVC have also been associated with and may antedate the diagnosis of CHF (38–40). Interestingly, the self-reported rates of CHF were comparable in GOLD-U and subjects with COPD, even though obstruction is a relatively rare finding in CHF. This may reflect the diagnostic uncertainty frequently encountered in the clinical management of a dyspneic patient.

Increased subsegmental wall area percentage in GOLD-U subjects relative to smoking control subjects was an unexpected but consistent finding. In our analyses, subsegmental wall area percentage varied significantly by sex and race and was significantly associated with BMI. The literature regarding the association of wall area thickness and BMI has been inconsistent (33, 34); however, a positive correlation with segmental airway wall area percentage and BMI in subjects with COPD has been previously reported (33). Likewise, conflicting reports regarding differences in airway wall thickness by sex also exist. Several studies based on radiologic data have found increased wall area percentage in male subjects with COPD (41–43), whereas histological examination of lung tissue from subjects from the National Emphysema Treatment Trial found increased wall area

TABLE 3. MULTIVARIABLE MODELS OF GLOBAL INITIATIVE FOR OBSTRUCTIVE LUNG DISEASE—UNCLASSIFIED STATUS

	OR	95% CI
GOLD-U versus Smoking Control Subjects		
Clinical variables*		
Resting O ₂ saturation	0.867	0.803–0.935
BMI	1.041	1.016–1.065
History CHF	5.016	1.877–13.409
6MWD (per 100 ft)	0.890	0.857–0.924
Clinical + radiographic variables†		
Diabetes mellitus	1.579	1.016–2.452
Pack-years	1.010	1.003–1.018
Resting O ₂ saturation	0.882	0.809–0.960
BMI	1.030	1.004–1.057
6MWD (per 100 ft)	0.948	0.905–0.993
History of CHF	3.460	1.107–10.817
TLC, ‡ L	0.767	0.651–0.904
Subsegmental wall area %	1.302	1.202–1.409
GOLD-U versus subjects with COPD (GOLD stages 2–4)		
Clinical variables§		
Age (per 10 yr)	0.630	0.490–0.810
BMI	1.121	1.089–1.154
Resting O ₂ saturation	1.244	1.149–1.347
Bronchodilator response	0.266	0.167–0.424
6MWD (per 100 ft)	1.098	1.047–1.150
Asthma (current)	0.407	0.235–0.705
Nonwhite race	1.458	0.926–2.295
Diabetes mellitus	2.317	1.427–3.761
Chronic bronchitis	0.533	0.339–0.838
Clinical + radiographic variables¶		
Bronchodilator response	0.321	0.180–0.572
Resting O ₂ saturation	1.159	1.048–1.283
BMI	1.066	1.028–1.105
% Emphysema	0.752	0.661–0.856
% Gas trapping	0.926	0.899–0.954
TLC, ‡ L	0.670	0.527–0.851
Subsegmental wall area %	0.774	0.693–0.865

Definition of abbreviations: BMI = body mass index; CHF = congestive heart failure; CI = confidence interval; COPD = chronic obstructive pulmonary disease; GOLD-U = Global Initiative for Obstructive Lung Disease—Unclassified; TLC = total lung capacity; 6MWD = 6-min walk distance.

* Variables tested but not retained in the final model include: nonwhite race, pack-years, chronic cough, physician-diagnosed asthma (ever), resting heart rate, history of diabetes, hypertension, transient ischemic attack, and obstructive sleep apnea.

† Final model includes race as nonsignificant confounder. Additional variables tested but not retained in the final model include: chronic cough, physician-diagnosed asthma (ever), resting heart rate, history of hypertension, transient ischemic attack, obstructive sleep apnea, and % emphysema.

‡ TLC based on chest computed tomography measurements

§ Final model includes current smoking and pack-years as nonsignificant confounders. No additional variables were tested.

|| Becomes nonsignificant after addition of confounders.

¶ Final model includes race as a nonsignificant confounder. Additional variables tested but not retained in the final model include: age, diabetes, 6MWD, current smoking, pack-years, chronic bronchitis, and physician-diagnosed asthma (current).

percentage in female subjects (44). The increased subsegmental wall area percentage in female GOLD-U subjects may be due to processes distinct from those involved in obstructive lung disease. The lack of concurrent significant gas trapping and emphysema is consistent with this hypothesis. Whether increased subsegmental

TABLE 4. RANGES OF VALUES FOR KEY VARIABLES IN GLOBAL INITIATIVE FOR OBSTRUCTIVE LUNG DISEASE—UNCLASSIFIED SUBJECTS

Variable	Range
BMI	17.2–53.75
FEV ₁ , % predicted	44–79
% Emphysema	0.01–11.43

Definition of abbreviation: BMI = body mass index.

TABLE 5. DIFFERENCES BY RACE IN GLOBAL INITIATIVE FOR OBSTRUCTIVE LUNG DISEASE—UNCLASSIFIED SUBJECTS

	White	African American
N	135	92
Age, yr	61.9 (8.8)	53.5 (5.6)*
Pack-years	48.4 (29.6)	36.9 (20.3)*
BMI	31.6 (6.9)	32.3 (7.8)
Current smoking, % of subjects	37.8	75.0*
FEV ₁ % predicted	71.3 (7.2)	69.2 (7.7)*
FEV ₁ /FVC ratio	0.76 (0.05)	0.77 (0.05)
6MWD	1,333.1 (398.2)	1,132.1 (387.9)*
TLC, L (liters)	4.8 (1.1)	4.2 (1)*
% Emphysema	2.0 (2.2)	1.4 (1.5)*
% Gas trapping	11.5 (7.6)	12.1 (9.8)
Subsegmental wall area %	64.5 (2.1)	65.8 (2.4)*
Pi10	3.77 (0.10)	3.85 (0.14)*
Resting O ₂ saturation	95.9 (2.5)	96.9 (2.0)*
MMRC	1.2 (1.4)	1.6 (1.6)
SGRQ	26 (22.5)	29.9 (23.8)

Definition of abbreviations: BMI = body mass index; MMRC = Modified Medical Research Council dyspnea score; Pi10 = wall thickness for a hypothetical airway with an internal perimeter of 10 mm; SGRQ = St. George's Respiratory Questionnaire; TLC = total lung capacity; 6MWD = 6-min walk distance.

Data are presented as mean (SD) or percent.

* Denotes *P* value < 0.05 when compared to white subjects.

airway wall thickness represents a differential response to cigarette smoke in African Americans is unknown—to date, there have been no studies reporting airway wall thickness in African American subjects in either COPD or asthma.

Although aggregate measures are useful in characterizing GOLD-U subjects as a group, the heterogeneity of GOLD-U subjects becomes evident when the ranges of variables such as BMI, FEV₁ % predicted, and % emphysema are examined. Multiple disease processes can be associated with the pulmonary function impairment observed in GOLD-U subjects and include interstitial lung disease (45), thoracic cage abnormalities, or functional impairments, such as diaphragmatic paralysis. It is also evident that a subset of GOLD-U subjects have processes typically associated with obstructive lung disease, such as emphysema.

TABLE 6. CHARACTERISTICS OF OBESE VERSUS NONOBESE GLOBAL INITIATIVE FOR OBSTRUCTIVE LUNG DISEASE—UNCLASSIFIED SUBJECTS

	Obese	Nonobese
N	133	94
Age, yr	58.0 (8.8)	59.3 (8.6)
Sex, % male	46.6	50.0
Race, % African American	39.9	41.5
Pack-years	44.5 (27.7)	42.5 (25.7)
Current smoking (%)	49.6	57.5
FEV ₁ % predicted	70.0 (7.5)	71.0 (7.4)
FEV ₁ /FVC ratio	0.77 (0.05)	0.76 (0.05)
6MWD	1,190.4 (412.1)	1,338.4 (381.3)*
% Emphysema	1.7 (1.7)	1.8 (2.3)
% Gas trapping	10.9 (6.2)	13.2 (11.0)
Subsegmental wall area %	65.1 (2.3)	64.9 (2.4)
Pi10	3.82 (0.13)	3.78 (0.11)*
Resting O ₂ saturation	95.8 (2.5)	96.9 (1.9)*
MMRC	1.7 (1.5)	1.0 (1.3)*
SGRQ	31.9 (24.2)	21.5 (19.9)*

Definition of abbreviations: BMI = body mass index; MMRC = Modified Medical Research Council dyspnea score; Pi10 = wall thickness for a hypothetical airway with an internal perimeter of 10 mm; SGRQ = St. George's Respiratory Questionnaire; 6MWD = 6-min walk distance.

Data are presented as mean (SD) or percent. "Obese" is defined as BMI ≥ 30, and "nonobese" as BMI < 30.

* Denotes *P* < 0.05 when compared with obese subjects.

TABLE 7. GLOBAL INITIATIVE FOR OBSTRUCTIVE LUNG DISEASE—UNCLASSIFIED VERSUS LOWER LIMIT OF NORMAL UNCLASSIFIED SUBJECTS IN COPD_{GENE}

LLN-Unclassified			
GOLD-Unclassified	Yes	No	Total
Yes	158	69	227
No	40	2,233	2,273
Total	198	2,302	2,500

Definition of abbreviations: GOLD = Global Initiative for Obstructive Lung Disease; LLN = lower limit of normal.

Longitudinal studies have demonstrated that approximately one-third of subjects with the GOLD-U pattern of respiratory impairment will develop obstructive lung disease (11). This group may benefit from early diagnosis and treatment. This is, however, contingent upon the ability to accurately diagnose these processes; although 21.6% of GOLD-U subjects and 28.3% of LLN-Unclassified subjects currently report a history of physician-diagnosed COPD (data not shown), the correlation with actual percent emphysema is poor and suggests considerable misclassification.

The current diagnostic and staging criteria systems for COPD, which are based solely on spirometry, do not address the overlap in underlying disease processes between GOLD-U, COPD, and smoking control subjects that likely exists. Many GOLD-U subjects have nontrivial amounts of emphysema, and a significant minority of smoking control subjects and subjects with COPD have evidence of reduced TLC. This diagnostic imprecision persists even when the groups are defined by LLN thresholds. Ideally, a diagnostic and staging system would allow for the identification of subjects with more than one concurrent disease process (46); such a system would necessarily be based on information from multiple arenas.

The strengths of the current study include the wealth of radiographic and epidemiological data on this previously poorly characterized group of smokers with GOLD-U spirometry. The limitations of our study include the possibility of spirometric artifacts, such as incomplete inspiration, which could theoretically account for the reduced FVC observed in GOLD-U subjects. And although COPD_{GENE} is more inclusive than most COPD studies, it is not a population-based study, and subjects are limited to former and current smokers; this may impact the generalizability of our findings. Although the sample size used in the current study has allowed for the identification of a considerable number of risk factors for the GOLD-U pattern of respiratory impairment, characterization of the subgroups within the GOLD-U population remains challenging. Subgroups of interest, which may represent differing pathophysiological processes, include subjects with emphysema versus subjects who are of African American race with increased airway wall thickness. Additional analyses on the remainder of the COPD_{GENE} cohort, as well as longitudinal and genetic analyses, will allow for more detailed studies in the future.

Author Disclosure: E.S.W. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. J.E.H. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. E.A.R. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. B.J.M. received support for travel from the COPD Foundation. He was on the Advisory Board for Forest, AstraZeneca (AZ), Novartis, Dey, Nycomed, Respironics, Schering, Johnson & Johnson, Sequal, and Embryon. He was a consultant for Astellas, Talecris, and Chiesi. He received institutional grant support from AZ, GlaxoSmithKline (GSK), Pfizer, NABI Biopharmaceuticals, Boehringer Ingelheim (BI), and Sepracor. He received lecture fees from GSK, BI, and Pfizer. He received institutional compensation for the review of documents related to a clinical trial from Spiration and received compensation for video presentations from BI and Pfizer. D.A.L. received institutional grant support from Siemens, Inc. and was on

the Advisory Board for Actelion, Inc. He was a consultant for Intermune, Gilead, Perceptive, Novartis, Actelion, and Centocor. J.D.C. is employed by National Jewish Health and received travel accommodations from AZ. E.K.S. received institutional grant support from the COPD Foundation and GSK. He received travel accommodations from the COPD Foundation. He was a consultant for and received lecture fees from GSK and AZ.

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