Comparison between an Alternative and the Classic Definition of Chronic Bronchitis in COPDGene

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Abstract

Rationale: Previous studies on chronic bronchitis (CB) have used varying definitions.

Objectives: We sought to compare an alternative CB definition, using the St. George's Respiratory Questionnaire (SGRQ), a commonly used assessment tool, with the classic definition and to investigate if it had independent or additive value.

Methods: We analyzed data from 4,513 subjects from Global Initiative for Chronic Obstructive Lung Disease groups 1 to 4 in the COPDGene cohort. We compared the classic definition of CB with the SGRQ definition, defined by their answers to the questions about both cough and phlegm. We compared the Classic CB+ versus CB− groups, and the SGRQ CB+ and CB− groups. We also analyzed the cohort split into four groups: Classic CB+/SGRQ CB+, Classic CB+/SGRQ CB−, Classic CB−/SGRQ CB+, Classic CB−/SGRQ CB−.

Measurements and Main Results: A total of 26.1% subjects were Classic CB+, whereas 39.9% were SGRQ CB+. When the SGRQ definition was compared with the Classic CB definition, using this as the gold standard, the SGRQ CB definition had a sensitivity and specificity of 0.87 and 0.77, respectively. The SGRQ CB+ and Classic CB+ groups were strikingly similar, with more respiratory symptoms and exacerbations, worse lung function, and greater airway wall thickness. In addition, the Classic CB+/SGRQ CB+, Classic CB+/SGRQ CB−, and Classic CB−/SGRQ CB+ groups shared similar characteristics as well.

Conclusions: The SGRQ CB definition identifies more subjects with chronic cough and sputum who share a similar phenotype identified by the Classic CB definition. The addition of the SGRQ CB definition to the classic one can be used to identify more patients with chronic obstructive pulmonary disease at risk for poor outcomes.

Keywords: chronic obstructive pulmonary disease; chronic bronchitis; Saint George's Respiratory Questionnaire

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Chronic obstructive pulmonary disease (COPD) is a major public health problem that is projected to rank fifth worldwide in terms of disease burden and third in terms of mortality (1). According to recent statistics, chronic bronchitis (CB) affects approximately 10 million people in the United States (2). CB is classically defined as chronic cough and sputum production for 3 months a year for 2 consecutive years (3). However, the classic definition has infrequently been used in large studies. Although CB hastens lung function decline, increases the risk of exacerbations, reduces quality of life, and may increase mortality (4–7), the data on which these conclusions are based have used various definitions, including chronic phlegm, chronic mucus hypersecretion, bronchial hypersecretion, and chronic cough with phlegm (4, 8–12).

Because of its clinical sequelae, CB is important to identify. This is especially important now, as newer medical therapies such as phosphodiesterase-4 inhibitors can

reduce exacerbations in patients with CB. Unfortunately, the majority of studies on COPD have looked at the entire spectrum of COPD without separation into various clinical phenotypes, including recent large pharmaceutical trials (13, 14). There have been recent efforts, however, to identify this phenotype in newer studies. But even these studies have used different definitions of CB, including Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE, chronic cough), Azithromycin for Prevention of Exacerbations of COPD study (St. George's Respiratory Questionnaire [SGRQ] cough and phlegm), and Subpopulations and Intermediate Outcomes in COPD Study (SPIROMICS, chronic phlegm for 2 years) (15–17). Therefore, an acceptable uniform definition is needed to make prior, current, and future literature more consistent.

The SGRQ has been used extensively in large COPD clinical trials as a measure of health-related quality of life. Within the SGRQ are questions regarding short-term history of cough and phlegm production. Some studies have used a derived surrogate for CB based on the answers to the questions regarding cough and phlegm in the SGRQ (18–20). Although some have criticized this symptom assessment as not meeting criteria for the classic definition, clinical and radiographic characteristics have been identified that resemble prior literature on CB in terms of outcomes. We hypothesized that the SGRQ definition of CB would identify a similar phenotype described by the classic CB definition, and the addition of the SGRQ CB definition would have additive value in finding a group of patients with COPD at risk for poor outcomes.

Methods

Patient Selection and Division

The Genetic Epidemiology of COPD (COPDGene) study is a multicenter observational study that recruited more than 10,000 subjects. This study underwent institutional review board approval at all centers. Inclusion and exclusion criteria and protocol were described previously (21). We included subjects with COPD in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) groups 1–4 (4,513 subjects). We compared the classic definition of CB with a new definition derived from the SGRQ. Subjects were classified as Classic CB if they had chronic cough and phlegm for at least 3 months a year for at least 2 consecutive years, derived from separate questions about cough and phlegm using a modified form of the American Thoracic Society Division of Lung Disease Respiratory Epidemiology questionnaire (3). Subjects were classified as having SGRQ CB if they answered "almost every day" or "most days a week" to the following questions: "Over the last 4 weeks, I have coughed:" and "Over the last 4 weeks, I have brought up phlegm (sputum):." See Table 1 for description of both definitions and how they were derived. Subjects were divided into Classic CB+ or Classic CB−, and SGRQ CB+ or SGRQ CB−. We also divided the cohort in four mutually exclusive groups: Classic CB+/SGRQ CB+ (Group A), Classic CB+/SGRQ CB− (Group B), Classic CB−/SGRQ CB+ (Group C), and Classic CB−/SGRQ CB− (Group D).

Table 1. Definitions of Classic and SGRQ chronic bronchitis

Classic chronic bronchitis	
1. Do you usually have a cough? (Exclude clearing of throat.)	Yes No
If Yes, do you usually cough as much as 4 times a day, 4 or more days out of the week?	Yes No
2. Do you usually cough at all on getting up or first thing in the morning?	Yes No
3. Do you usually cough at all during the rest of the day or night?	Yes No
If Yes to any of the above (1–3), answer the following:	
Do you cough like this on most days, for 3 consecutive months or more during the year?	Yes No
For how many years have you had this cough?	Number of years___
4. Do you usually bring up phlegm from your chest?	Yes No
If Yes, do you usually bring up phlegm like this as much as twice a day, 4 or more days out of the week?	Yes No
5. Do you usually bring up phlegm from your chest on getting up, or first thing in the morning?	Yes No
6. Do you usually bring up phlegm from your chest during the rest of the day or at night?	Yes No
If Yes to any of the above (4–6), answer the following:	
Do you bring up phlegm like this on most days for 3 consecutive months or more during the year?	Yes No
For how many years have you had trouble with phlegm?	Number of years___
Chronic bronchitis = cough AND phlegm for at least 3 months a year for at least 2 consecutive years	
SGRQ chronic bronchitis	
1. Over the last 4 weeks, I have coughed:	Almost every day Several days a week A few days a month Only with lung/respiratory infections Not at all
2. Over the last 4 weeks, I have brought up phlegm (sputum):	Almost every day Several days a week A few days a month Only with lung/respiratory infections Not at all
Chronic bronchitis = cough AND phlegm almost every day or several times a week	

Definition of abbreviation: SGRQ = St. George's Respiratory Questionnaire.

Clinical, Physiologic, and Radiographic Characterization

Respiratory symptoms were collected using a modified form of the American Thoracic Society Division of Lung Disease questionnaire. Subjects were also asked if they experienced COPD exacerbations in the past year and to quantify the number of episodes, and if they have been to the emergency room or hospitalized for an exacerbation (the latter used to define severe exacerbations). Each subject underwent pre- and post-bronchodilator spirometry in the chronic stable state using an EasyOne spirometer (Zurich, Switzerland). Predicted values were obtained using National Health and Nutrition Examination Survey III data. Six-minute-walk distance was measured in standard fashion (22).

Volumetric chest CT acquisitions were obtained at full inspiration (200 mAs) and at the end of normal expiration (50 mAs). Quantitative image analysis to calculate percent emphysema and percent gas trapping was performed using 3D SLICER (http://www.slicer.org/). Percent emphysema was defined as the total percent with attenuation values less than −950 Hounsfield units on inspiratory images, and percent gas trapping was defined as the total percent with attenuation values less than −856 Hounsfield units on expiratory images. Airway disease was quantified as wall area percent (WA%: [wall area/total bronchial area] × 100]) using VIDA (http://www.vidadiagnostics.com) (23). The mean WA% was calculated as the average of the values for six segmental bronchi in each subject. Using 3D SLICER, airway wall thickness was also expressed as the square root of the wall area of a hypothetical 10-mm and 15-mm internal perimeter airway (Pi10 and Pi15, respectively) as previously described (24).

Statistics

Statistical analysis was performed using SPSS v 21.0 and SAS v 9.3 (Cary, NC). The Classic CB and SGRQ CB definitions were compared with Chi-square test and paired analyses such as kappa statistics and McNemar test, using the Classic CB definition as the gold standard. We compared clinical and radiologic measures between the Classic CB+ and Classic CB− groups using unpaired *t* test or Chi-square test. We compared the SGRQ CB+ and SGRQ CB− groups using similar techniques. We also analyzed the four mutually exclusive groups (Groups A, B, C, and D) with Chi-square test or one-way analysis of variance with Tukey test for *post hoc* analysis. We performed multivariate logistic and linear regressions to assess the risks conferred by SGRQ CB or Classic CB on severe exacerbations and exacerbation frequency. We used SGRQ CB and Classic CB in the same model as well as separately, with age, race, sex, current smoking, FEV_1 % predicted, and modified Medical Research Council scores as covariates. $P < 0.05$ was considered statistically significant.

More detailed methods can be found in the online supplement.

Results

A total of 1,179 of the 4,513 subjects were classified as Classic CB+ (26.1%), and 1,801 subjects were classified as SGRQ CB+ (39.9%). The numbers in the four mutually exclusive groups were 1,030 (22.8%) for Group A (Classic CB+/SGRQ CB+), 149 (3.3%) for Group B (Classic CB+/SGRQ CB−), 771 (17.1%) for Group C (Classic CB−/SGRQ CB+), and 2,562 (56.8%) for Group D (Classic CB−/SGRQ CB−), respectively. Figure 1 shows the breakdown of subjects according to SGRQ and Classic CB definitions. When the SGRQ definition was compared with the Classic CB definition, using the Classic CB definition as the gold standard, the SGRQ CB definition had a sensitivity and specificity of 0.87 and 0.77, respectively, to detect classically defined CB. Positive and negative predictive values were 0.57 and 0.95. The kappa statistic between the two tests was 0.55. Results were similar when the cohort was divided into individual GOLD stages (*see* Table E1 in the online supplement).

Table 2 summarizes the differences between the Classic CB+ and Classic CB− groups. The Classic CB+ group was younger, had a greater percentage of white subjects and men, had a greater pack-year history of smoking, was more likely to be current smokers, and had worse lung function and lower 6-minute-walk distance. Dyspnea was greater, there were more allergic ocular and nasal symptoms, more exposures to dusts and fumes, more nocturnal awakenings from cough or breathlessness, a greater history of gastroesophageal reflux disease, and a larger number of total and severe exacerbations in the Classic CB+ group. There were no differences in percent of emphysema or percent of gas trapping between groups, but airway wall thickness, measured as Pi10, Pi15, and WA% segmental, was greater in the Classic CB+ group. When the SGRQ CB+ group was compared with the SGRQ CB− group, the results were strikingly similar (Table 3). The SGRQ CB+ group had similar demographic characteristics to the Classic CB+ group and had greater symptoms, smoking, exposures, and exacerbations compared with the SGRQ CB− group. Similar trends were present in airway wall thickness measures between the SGRQ CB+ and SGRQ CB− groups. The only radiographic difference is that the SGRQ CB+ group had a greater degree of percent gas trapping compared with the SGRQ CB− group. Figure 2 demonstrates similarities between the Classic CB+ and SGRQ CB+ groups.

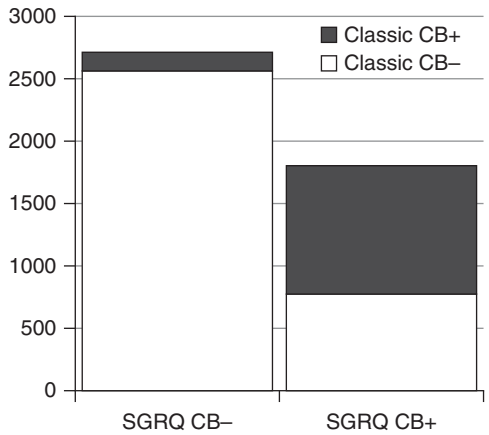

Figure 1. Breakdown of patients according to St. George's Respiratory Questionnaire (SGRQ) and Classic chronic bronchitis (CB) definitions in the entire cohort.

In addition, when the four mutually exclusive groups were compared, trends were also similar. Table 4 summarizes the results. There were statistically significantly different values across groups for most variables except for body mass index and percent emphysema, in concert with the results of the individual analyses between Classic CB+ versus Classic CB− and SGRQ CB+ versus SGRQ CB−. Subjects in Group A (subjects who were both SGRQ and Classic CB+) were more likely to be white, men, and current smokers compared with those in group D (subjects who were both SGRQ and Classic CB−). Group A had greater symptoms, more gastroesophageal reflux disease, more exposures to dusts and fumes, and more exacerbations compared with group D. Airway wall measures were also greater in group A compared with group D. Much like group A, groups B and C had greater symptoms, more upper airway symptoms, more exacerbations, and greater airway wall thickness on CT scan compared with group D. Figure 3 demonstrates differences between groups A, B, C, and D.

The results of the multivariate logistic and linear regression for SGRQ CB and Classic CB are shown in Table E2. For severe exacerbations, SGRQ CB+ had an odds ratio (OR) of 1.43 (95% confidence interval [CI], 1.21, 1.691) and Classic CB+ had an OR of 1.313 (95% CI, 1.098, 1.57). Using both SGRQ CB+ and Classic CB+ in the same model, SGRQ CB+ had an OR of 1.363 (95% CI, 1.22, 1.656) and Classic CB+ 1.107 (95% CI, 0.9, 1.363). For exacerbation frequency, SGRQ CB+ had a parameter estimate of 0.362 with SE of 0.036 ($P < 0.0001$), and Classic CB+ had a parameter estimate of 0.322 with SE of 0.040 ($P < 0.0001$). Using both in the same model, SGRQ CB+ had a parameter estimate of 0.289 and SE of 0.042 ($P < 0.0001$), and Classic CB+ had a parameter estimate of 0.156 with SE of 0.046 ($P = 0.0008$). These data suggest that SGRQ CB+ is more informative for predicting severe exacerbations than Classic CB+.

Table 2. Classic chronic bronchitis positive versus classic chronic bronchitis negative

Variable	Classic CB− (*n* = 3,333)	Classic CB+ (*n* = 1,179)	*P* Value
Race, white	75.7	81.4	<0.0001
Sex, male	53.8	62.1	<0.0001
BMI, kg/m^2	27.89 ± 6.01	27.86 ± 6.34	0.863
Age, yr	63.56 ± 8.62	63.10 ± 3.25	<0.0001
Smoking history, pack-years	50.18 ± 26.28	55.38 ± 28.18	<0.0001
Current smoking	37.8	58.9	<0.0001
FEV_1 % predicted	58.68 ± 23.34	53.59 ± 20.71	<0.0001
FVC % predicted	82.60 ± 20.49	79.69 ± 19.79	<0.0001
FEV_1/FVC	0.53 ± 0.13	0.50 ± 0.13	<0.0001
FEV_1 ch post-BD, L	0.100 ± 0.164	0.108 ± 0.174	0.075
FEV_1 % ch post-BD	8.03 ± 12.24	8.96 ± 13.23	0.006
6-min-walk distance, m	380 ± 126	363 ± 120	<0.0001
mMRC dyspnea score	1.74 ± 1.46	2.36 ± 1.40	<0.0001
GERD	27.9	32.8	0.002
Noct awake cough	22.1	53.6	<0.0001
Noct awake SOB	22.1	42.3	<0.0001
Allergic nasal symptoms	50.4	69.6	<0.0001
Allergic ocular symptoms	40.9	53.3	<0.0001
Dusty job ever	47.5	61.2	<0.0001
Fumes job ever	48.3	61.7	<0.0001
Exac freq, no./patient/yr	0.54 ± 1.06	0.98 ± 1.46	<0.0001
History of severe exac	17.6	25.4	<0.0001
Radiology			
% Emphysema	11.76 ± 12.32 (3,103)	11.20 ± 11.71 (1,095)	0.194
% Gas trapping	35.82 ± 21.01 (2,831)	36.53 ± 20.55 (995)	0.356
Pi10	3.693 ± 0.139 (3,080)	3.727 ± 0.154 (1,083)	<0.0001
Pi15	5.175 ± 0.201 (3,080)	5.247 ± 0.220 (1,083)	<0.0001
Wall area %, segmental	62.20 ± 3.13 (3,118)	63.10 ± 3.25 (1,100)	<0.0001

Definition of abbreviations: BD = bronchodilator; BMI = body mass index; CB = chronic bronchitis; ch = change; Exac = exacerbation; Freq = frequency; GERD = gastroesophageal reflux disease; mMRC = modified Medical Research Council; Noct awake cough = nocturnal awakenings secondary to cough; Noct awake SOB = nocturnal awakenings secondary to dyspnea; Pi10 = airway thickness of 10-mm airway; Pi15 = airway thickness of 15-mm airway.
Data expressed as mean ± SD or %. Radiographic data expressed as mean ± SD (n).

Discussion

Using the classic CB definition as the gold standard, we determined that the SGRQ CB definition had good sensitivity and specificity as well as very good negative predictive value, which held true in all subjects with COPD as well as in each GOLD stage. We found that the CB definition derived from the SGRQ identified a very similar population of subjects with COPD compared with the classic CB definition, both in clinical and radiographic phenotypes. When subjects were further divided into those that were both SGRQ and Classic CB positive or negative, and those in between, the subjects were similar to when they met criteria for either the SGRQ CB definition or Classic CB definition alone. We also reemphasize that those with cough and sputum, independently from how it is defined, are more dyspneic, have shorter 6-minute-walk distances, have more upper airway symptoms, are more prone to exacerbations, and have a more airway-predominant radiologic phenotype. Of note, those who were Classic CB− SGRQ CB+ or Classic CB+ SGRQ CB− also had worse symptoms, more exacerbations, and greater airway wall thickness compared with those who were Classic and SGRQ CB−. To our knowledge, this is the first study that has directly compared these two definitions of CB and has found similar results.

The search for a uniform method of reporting respiratory symptoms dates back more than 60 years. In the 1950s, the British Medical Research Council (MRC) committee on CB began a pioneering series of investigations into the epidemiology of CB and chronic airflow obstruction (25). They devised the MRC questionnaire based on the hypothesis that mucus hypersecretion leads to repeated lower respiratory infections and subsequently to airflow obstruction and emphysema (26). In a population-based survey conducted by the Royal College of General Practitioners (27), a report of chronic morning phlegm, winter bouts, and breathlessness discriminated those patients characterized by their physicians as having CB. Another

Table 3. St. George's Respiratory Questionnaire chronic bronchitis positive versus St. George's Respiratory Questionnaire chronic bronchitis negative

Variable	SGRQ CB− (*n* = 2,771)	SGRQ CB+ (*n* = 1,801)	*P* Value
Race, white	75.3	80.1	<0.0001
Sex, male	52.8	60.7	<0.0001
BMI, kg/m^2	27.83 ± 5.92	27.97 ± 6.36	0.456
Age, yr	63.64 ± 8.62	62.18 ± 8.55	<0.0001
Smoking history, pack-years	49.35 ± 25.81	54.83 ± 28.81	<0.0001
Current smoking	35.4	55	<0.0001
FEV_1 % predicted, %	59.77 ± 23.32	53.71 ± 21.48	<0.0001
FVC % predicted, %	83.61 ± 20.28	79.20 ± 20.16	<0.0001
FEV_1/FVC	0.53 ± 0.13	0.51 ± 0.13	<0.0001
FEV_1 ch post-BD, L	0.100 ± 0.168	0.100 ± 0.165	0.830
FEV_1 % ch, post-BD	7.97 ± 12.05	8.74 ± 13.18	0.015
6-min-walk distance, m	385 ± 124	361 ± 123	<0.0001
mMRC dyspnea score	1.65 ± 1.45	2.29 ± 1.41	<0.0001
GERD	27.6	31.7	0.003
Noct awake cough	18.2	48.6	<0.0001
Noct awake SOB	19.6	39.1	<0.0001
Allergic nasal symptoms	48.6	65.9	<0.0001
Allergic ocular symptoms	39.7	50.7	<0.0001
Dusty job ever	46.2	58.5	<0.0001
Fumes job ever	48	57.5	<0.0001
Exac freq, no./patient/yr	0.47 ± 0.96	0.94 ± 1.44	<0.0001
History of severe exac	15.9	25.2	<0.0001
Radiology			
% Emphysema	11.77 ± 12.48 (2,553)	11.36 ± 11.66 (1,665)	0.287
% Gas trapping	35.19 ± 21.14 (2,303)	37.23 ± 20.46 (1,523)	0.003
Pi10	3.687 ± 0.133 (2,509)	3.725 ± 0.155 (1,654)	<0.0001
Pi15	5.163 ± 0.199 (2,509)	5.241 ± 0.214 (1,654)	<0.0001
Wall area %, segmental	62.06 ± 3.15 (2,541)	63.00 ± 3.16 (1,677)	<0.0001

Data expressed as mean ± SD or %. Radiographic data expressed as mean ± SD (n).
Definition of abbreviations: BD = bronchodilator; BMI = body mass index; CB = chronic bronchitis; ch = change; Exac = exacerbation; Freq = frequency; GERD = gastroesophageal reflux disease; mMRC = modified Medical Research Council; Noct awake cough = nocturnal awakenings secondary to cough; Noct awake SOB = nocturnal awakenings secondary to dyspnea; Pi10 = airway thickness of 10-mm airway; Pi15 = airway thickness of 15-mm airway; SGRQ = St. George's Respiratory Questionnaire.

population-based survey in Great Britain showed that a diagnosis of CB was made less often by physicians than by questionnaire (28). In 1978, the American Thoracic Society subsequently derived its own questionnaire on lung diseases, which has remained the standard by which CB has been defined (3).

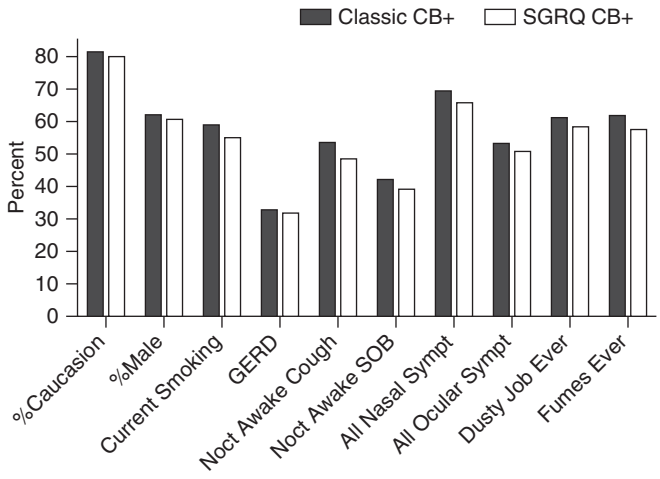

Figure 2. Clinical characteristics of each group. CB = chronic bronchitis; GERD = gastroesophageal reflux disease; SOB = shortness of breath; SGRQ = St. George's Respiratory Questionnaire.

Despite the standardization of the CB definition, many prior studies on CB have used variable definitions, including chronic phlegm, chronic mucus hypersecretion, chronic cough, and cough and sputum (4, 7, 15, 29). These studies have revealed different prevalences of CB and varying effects on outcomes, making the literature difficult to interpret. In the COPDGene study, classifying subjects with CB using the classic definition identified a group with more exacerbations, more respiratory symptoms, worse exercise capacity, and greater airway thickening (30). However, some recent large studies have used alternative definitions of CB, which clouds the picture (15, 16). This phenomenon is at least partially responsible for the variable and sometimes conflicting data on outcomes associated with CB.

In 1992, Jones and colleagues developed a self-completion questionnaire that measured health in chronic airflow obstruction called the St. George's Respiratory Questionnaire (30). Since that time, the SGRQ has been used in multiple studies as an outcome measure, whether from a medical or surgical intervention in COPD. Its widespread use has made it easy to compare interventions, so much so that a minimally clinical important difference has been determined for the SGRQ (31), much like other metrics of COPD care like 6-minute-walk distance and MRC dyspnea scale. This makes use of this questionnaire ideal for deriving a new definition for CB, as it could be applied to many studies in COPD throughout the years.

In this study we validate the use of the SGRQ CB definition as one that identifies subjects with similar clinical and radiographic phenotype as the classic definition. The division of subjects by either definition separated them into similar groups. We also showed that the SGRQ CB definition has excellent sensitivity and very good specificity compared with the classic definition. Specifically, not meeting criteria for the SGRQ CB definition makes it highly unlikely that someone would meet criteria for the classic one, but meeting criteria for the SGRQ CB definition makes it somewhat likely to have classically defined CB. We also emphasize that the population that was SGRQ CB+ Classic CB− or SGRQ CB− Classic CB+ also shared a similar

Table 4. Comparison of four groups

Variable	Classic CB+/SGRQ CB+ A (*n* = 1,030)	Classic CB+/SGRQ CB− B (*n* = 149)	Classic CB−/SGRQ CB+ C (*n* = 771)	Classic CB−/SGRQ CB− D (*n* = 2,562)	Overall *P* Value
Race, white	860 (83.5)*†‡	100 (67.11)†‡	583 (75.62)	1,942 (75.8)	<0.0001
Sex, male	641 (62.23)‡	91 (61.07)‡	452 (58.63)‡	1,340 (52.3)	<0.0001
BMI, kg/m^2	27.96 ± 6.43	27.14 ± 5.66	27.97 ± 6.26	27.87 ± 5.93	0.4638
Age, yr	61.84 ± 8.46†‡	60.4 ± 8.66†‡	62.64 ± 8.66‡	63.83 ± 8.59	<0.0001
Smoking history, pack-years	56.14 ± 28.29*‡	50.15 ± 26.89	53.08 ± 29.41‡	49.3 ± 25.75	<0.0001
Current smoking	610 (59.22)†‡	84 (56.38)‡	381 (49.42)‡	877 (34.23)	<0.0001
FEV_1 % predicted	53.29 ± 20.67‡	55.69 ± 20.96‡	54.26 ± 22.52‡	60.01 ± 23.43	<0.0001
FVC % predicted	79.57 ± 19.62‡	80.51 ± 20.99	78.69 ± 20.87‡	83.79 ± 20.23	<0.0001
FEV_1/FVC	0.502 ± 0.131‡	0.523 ± 0.120	0.513 ± 0.133‡	0.532 ± 0.135	<0.0001
FEV_1 ch post-BD, L	0.099 ± 0.168	0.108 ± 0.169	0.101 ± 0.151	0.102 ± 0.167	0.564
FEV_1 % ch post-BD	7.89 ± 12.00	9.41 ± 12.79	8.52 ± 13.02	8.90 ± 13.30	0.090
6-min-walk distance, m	362 ± 119‡	371 ± 125	360 ± 129‡	376 ± 124	<0.0001
Symptoms and exac					
mMRC dyspnea score	2.39 ± 1.39*†‡	2.12 ± 1.45‡	2.15 ± 1.44‡	1.62 ± 1.44	<0.0001
GERD	339 (32.94)‡	47 (31.54)	231 (29.96)	700 (27.32)	0.0075
Noct awake cough	560 (54.37)†‡	72 (48.32)‡	315 (40.91)‡	421 (16.43)	<0.0001
Noct awake SOB	438 (42.52)†‡	61 (40.94)‡	266 (34.5)‡	470 (18.35)	<0.0001
Allergic nasal symptoms	723 (70.19)†‡	98 (65.77)‡	463 (60.05)‡	1,219 (47.58)	<0.0001
Allergic ocular symptoms	551 (53.5)†‡	77 (51.68)‡	362 (46.95)‡	1,000 (39.03)	<0.0001
Dusty job ever	633 (61.46)†‡	89 (59.73)‡	420 (54.47)‡	1,162 (45.39)	<0.0001
Fumes job ever	637 (61.84)*†‡	90 (60.4)†‡	398 (51.62)	1,210 (47.27)	<0.0001
Exac freq, no./patient/yr	0.990 ± 1.483‡	0.886 ± 1.328‡	0.874 ± 1.375‡	0.443 ± 0.925	<0.0001
History of severe exac	255 (24.76)‡	44 (29.53)‡	198 (25.68)‡	388 (15.14)	<0.0001
Radiology					
% Emphysema	11.40 ± 11.72 (953)	9.80 ± 11.59 (142)	11.32 ± 11.60 (712)	11.89 ± 12.53 (2,391)	0.1865
% Gas trapping	37.17 ± 20.40*‡ (866)	32.24 ± 21.13† (129)	37.31 ± 20.55‡ (657)	35.37 ± 21.13 (2,174)	0.0096
Pi10	3.729 ± 0.155‡ (944)	3.715 ± 0.145‡ (139)	3.720 ± 0.156‡ (710)	3.685 ± 0.132 (2,370)	<0.0001
Pi15	5.250 ± 0.222†‡ (944)	5.228 ± 0.208‡ (139)	5.228 ± 0.203‡ (710)	5.159 ± 0.197 (2,370)	<0.0001
Wall area %, segmental	63.09 ± 3.23‡ (957)	63.19 ± 3.39‡ (143)	62.89 ± 3.07‡ (720)	62.00 ± 3.13 (2,398)	<0.0001

Data expressed as mean ± SD or %. Radiographic data expressed as mean ± SD (n). *P* value representative of analysis of variance or Chi-square test.
Definition of abbreviations: BD = bronchodilator; BMI = body mass index; CB = chronic bronchitis; ch = change; Exac = exacerbation; Freq = frequency; GERD = gastroesophageal reflux disease; mMRC = modified Medical Research Council; Noct awake cough = nocturnal awakenings secondary to cough; Noct awake SOB = nocturnal awakenings secondary to dyspnea; Pi10 = airway thickness of 10-mm airway; Pi15 = airway thickness of 15-mm airway; SGRQ = St. George's Respiratory Questionnaire.
*$P < 0.05$ compared to B.
†$P < 0.05$ compared to C.
‡$P < 0.05$ compared to D.

chronic bronchitic phenotype at risk for poor outcomes. This lends credence to the use of the SGRQ CB definition as an alternative to the classic definition.

Although this is the first direct comparison of the two definitions, other studies have used the SGRQ definition as a surrogate. For example, the Azithromycin for Prevention of Exacerbations of COPD study and SPIROMICS segregated subjects based on this definition and found similar trends in clinical phenotype (18, 19). We have shown that, using a novel definition of severe CB (cough, sputum, and chest trouble) identified subjects in the National Emphysema Treatment Trial at greater risk for mortality and hospitalizations (20). This again highlighted the prevalence of chronic bronchitic symptoms in those who had a predominantly hyperinflated and emphysematous clinical and radiographic phenotype and showed increased risk for poor outcomes.

Although the SGRQ CB definition seems like an adequate surrogate on some levels, it lacks good positive predictive value. We hypothesize that this is a result of the time course of 4 weeks dictated by the questions in the SGRQ, as opposed to the criteria of 2 consecutive years for the classic definition. Groups B (Classic CB+/SGRQ CB−) and C (Classic CB−/SGRQ CB+), which compose 3.3% and 17.1% of the cohort, respectively, exemplify this phenomenon. Indeed, these subjects had clinical and radiographic characteristics that were intermediate between Groups A (Classic CB+/SGRQ CB+) and D (Classic CB−/SGRQ CB−). It should be noted that group B is a distinct minority, again representing the significant negative predictive value of the SGRQ CB definition.

Although the results are compelling, this study has some limitations. As implied earlier, the SGRQ was designed to establish short-term history of symptoms and has been used to follow the clinical course of disease, whereas the classic CB definition has been used for diagnosis of a clinical syndrome and phenotype. Therefore, the purpose of each questionnaire differs. The currently available

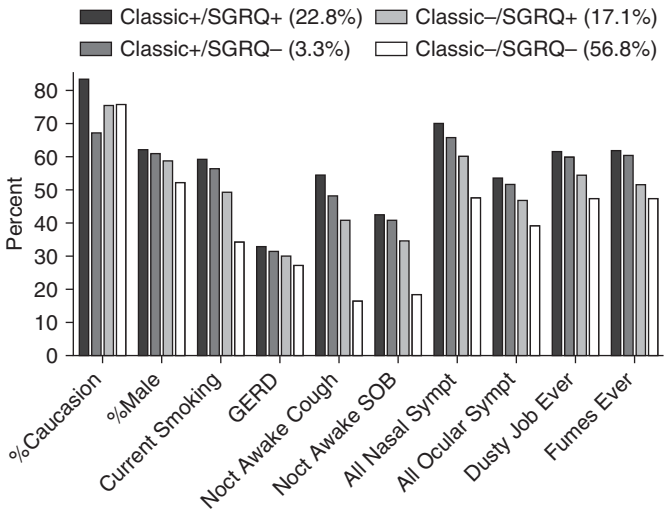

Figure 3. Clinical characteristics of groups A (SGRQ+/Classic CB+), B (Classic CB+/SGRQ CB−), C (Classic CB−/SGRQ CB+), and D (SGRQ-/Classic CB−). CB = chronic bronchitis; GERD = gastroesophageal reflux disease; SOB = shortness of breath; SGRQ = St. George's Respiratory Questionnaire.

respiratory symptom data in the COPDGene study is cross-sectional, thereby making the assessment of SGRQ only available at one time point. This makes changes in the SGRQ, and therefore possible changes in subjects' SGRQ CB status, unknown. Additionally, the ascertainment of exposures, allergic upper airway symptoms, and medical disorders were questionnaire-based and are therefore subject to recall bias. However, the large numbers of subjects, the differences in objective measures, such as 6-minute-walk distance and radiologic measures, and the highly significant *P* values suggest that the results are indeed real and not a result of chance.

Despite the inherent limitations of the study, we find convincing data that show the SGRQ CB definition, despite its short-term historical assessment of cough and phlegm, can act as an alternative for the classic CB definition or yield additive information, which has significant clinical implications. Significant cough and sputum, as ascertained by the SGRQ, suggests a clinical and radiologic phenotype strikingly similar to the chronic bronchitic phenotype as classically defined, and the addition of the SGRQ CB definition to the classic one identifies more subjects with a chronic bronchitic phenotype. Additionally, as the SGRQ is so commonly used in clinical trials, subgroups of subjects with COPD can be more accurately defined to better stratify clinical response to medical or surgical therapies. Performing subgroup analyses across studies can make data more comparable and can help lead the way to better understanding of this phenotype. Finally, change in SGRQ CB status may also help discern what therapies improve this constellation of symptoms. It will be interesting to see if and how the SGRQ CB definition is used prospectively and what implications can be derived from such analyses. ■

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