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Chronic Bronchitis Is Associated With Worse Symptoms and Quality of Life Than Chronic Airflow Obstruction

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BACKGROUND: COPD includes the chronic bronchitis (CB) and emphysema phenotypes. Although it is generally assumed that emphysema or chronic airflow obstruction (CAO) is associated with worse quality of life (QOL) than is CB, this assumption has not been tested.

METHODS: The current study's analyses from the Lovelace Smokers' Cohort (LSC) were validated in the COPD Gene Cohort (COPDGene). CB without CAO (CB only) was defined as self-reported cough productive of phlegm for ≥ 3 mo/y for 2 consecutive years and postbronchodilator $FEV_1/FVC \geq 70\%$. CAO without CB (CAO only) was defined as a postbronchodilator $FEV_1/FVC < 70\%$ with no evidence of CB. QOL outcomes were obtained from the St. George's Respiratory Questionnaire (SGRQ) and the 36-Item Short Form Health Survey (SF-36) questionnaires. A priori covariates included age, sex, pack-years of smoking, current smoking, and FEV_1.

RESULTS: Smokers with CB without CAO (LSC = 341; COPDGene = 523) were younger and had a greater BMI and less smoking exposure than did those with CAO only (LSC = 302; COPDGene = 2,208). Compared with the latter group, QOL scores were worse for those with CB only. Despite similar SGRQ Activity and SF-36 Role Physical and Physical Functioning, SGRQ Symptoms and Impact scores and SF-36 emotional and social measures were worse in the CB-only group, in both cohorts. After adjustment for covariates, the CB-only group remained a significant predictor for "worse" symptoms and emotional and social measures.

CONCLUSIONS: To our knowledge, this analysis is the first to suggest that among subjects with COPD, those with CB only present worse QOL symptoms and mental well-being than do those with CAO only.

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ABBREVIATIONS: CAO = chronic airway obstruction; CAT = COPD Assessment Test; CB = chronic bronchitis; COPDGene = COPD Gene Cohort; GOLD = Global Initiative for Chronic Obstructive Lung Disease; LSC = Lovelace Smokers' Cohort; QOL = quality of life; SF-36 = 36-Item Short Form Health Survey; SGRQ = St. George's Respiratory Questionnaire

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COPD, which limits airflow and gas exchange, is one of the leading causes of morbidity, disability, and death worldwide,[1] and is the third most common cause of death in United States.[2] COPD is characterized by two phenotypes involving hypersecreted mucus and occlusion of the conducting airways (chronic bronchitis [CB]) and an enlargement, destruction, or both of the walls of peripheral airspaces with the presence of chronic airflow obstruction (CAO). CB was depicted classically as the "blue bloater" with greater mucus and cough but less shortness of breath than the "pink puffer" with primarily emphysema. Over the past several years, it has become clear that the line between classic major symptoms may be blurred, and careful examination of symptoms with characterization of physiologic changes is needed.[3,4]

Previous studies reported that patients with CB in the COPD Gene Cohort (COPDGene) had worse respiratory symptoms and a higher risk of exacerbations compared with those without CB.[3] Further, male sex, white race, lower FEV_1 %, allergic rhinitis, history of acute bronchitis, current smoking, and increased airway wall thickness as measured by quantitative CT scan increased the odds for CB.[5] Another study compared subjects with CB but normal lung function ($FEV_1/FVC \geq 0.70$) with nonobstructed subjects without CB.[6] Although these studies compared patients with and without CB, comparison of the overall quality of life (QOL) among patients with CB and those with CAO has not been tested rigorously. There has been some assertion that those with CAO have worse disease impact than do those with CB.[7] Based on findings from initial analyses of the QOL in smokers with and without CB and those without CAO, we noticed a dramatic effect of symptoms in patients with CB. Therefore, we analyzed the QOL relationships between smokers with CB without CAO (CB only) and those with CAO without CB (CAO only) in the Lovelace Smokers' Cohort (LSC) and validated our findings in the COPDGene.

Materials and Methods

Study Population

Our study population was drawn from eligible participants, primarily women, from a cohort of current and former smokers in New Mexico (LSC) recruited since March 2001 with a median follow-up period of approximately 6 years. At initial and follow-up examination visits that occurred at 18-month intervals, subjects completed questionnaires (including and in particular, the Medical Outcomes Study 36-Item Short Form Health Survey [SF-36] and the St. George's Respiratory Questionnaire [SGRQ]) and underwent phlebotomy, anthropometry, and spirometry by trained study personnel, as published previously.[8,9]

Validation Population

Our study validation population was drawn from eligible participants from the multicenter COPDGene cohort (www.COPDGene.org), and none of the subjects was represented in both cohorts.

Inclusion and Exclusion Criteria

Participants were included if they were aged 40 to 75 years and were former or current smokers with ≥ 20 pack-years of smoking history at baseline examination for the LSC and ≥ 10 pack-years for the COPDGene. Subjects with a self-reported history of asthma at baseline examination were excluded, because asthma is an established confounder for QOL measures and may coexist with either CAO or CB.[10-14] Exclusion of subjects with a history of asthma reduced the eligible population for the LSC and the COPDGene to 1,895 and 7,341, respectively.

Questionnaires

Demographic information such as age, smoking history, environmental exposure history, and history of respiratory disease were obtained using the adult American Thoracic Society Division of Lung Disease-78 questionnaire.[15] The SGRQ and SF-36 questionnaires were used to evaluate QOL and symptoms, the SGRQ to evaluate respiratory-specific health status, with higher scores indicating worse health status,[16] and the SF-36 to evaluate general physical and mental function, with lower scores indicating worse health status.

Dependent (Outcome) Variables

Dimension scores from the SGRQ and the SF-36 were used as outcome variables for the analysis. In the LSC, individual items of the SGRQ Symptom dimension and the sleep question from the Impacts dimension were used in the univariate and multivariate analysis to explore differences in the symptom expression. In addition, individual items from the SF-36 that were characteristic of depressive mood changes were examined for differences. These specific items and derived scores are described in e-Appendix 1. In the COPDGene, only the SGRQ and SF-36 dimension scores were used as dependent variables.

Group Definition

In the first analysis, all participants with CB were compared with those without CB (Fig 1). CB was defined as self-reported cough productive of phlegm for ≥ 3 mo/y for at least 2 consecutive years. The second analysis also compared those with CB with those without CB, but was restricted to those participants who had no CAO. CAO was defined as a baseline ratio of postbronchodilator $FEV_1/FVC < 70\%$. The third analysis compared participants with CB but no CAO (CB only) with participants with CAO without CB (CAO only) (Fig 1). This third analysis involved a total of 634 LSC subjects with about equal numbers of those with CB only ($n = 341$) and those with CAO only ($n = 302$). To further test the hypothesis that individuals with CB only present with worse QOL than do patients with CAO only, the multivariate analysis focused on the third analysis and examined individuals with CB only and those with CAO only. This third analysis is the only one that is discussed further; however, the findings of analyses 1 and 2 are available in e-Appendix 1.

Statistical Approach

Summary statistics including means, SDs, and SEs for continuous variables and proportions for categorical variables were determined. Cross-sectional analyses used logistic and linear regression techniques for categorical and continuous dependent variables, respectively. The analyses were performed overall and after stratification into the two baseline disease categories. All statistical analyses were done using SAS software, version 9.3 (SAS Institute Inc). A two-sided P value of $< .05$ was considered statistically significant. Multivariable analysis was carried out with the covariates of self-reported age, sex, pack-years of smoking, current

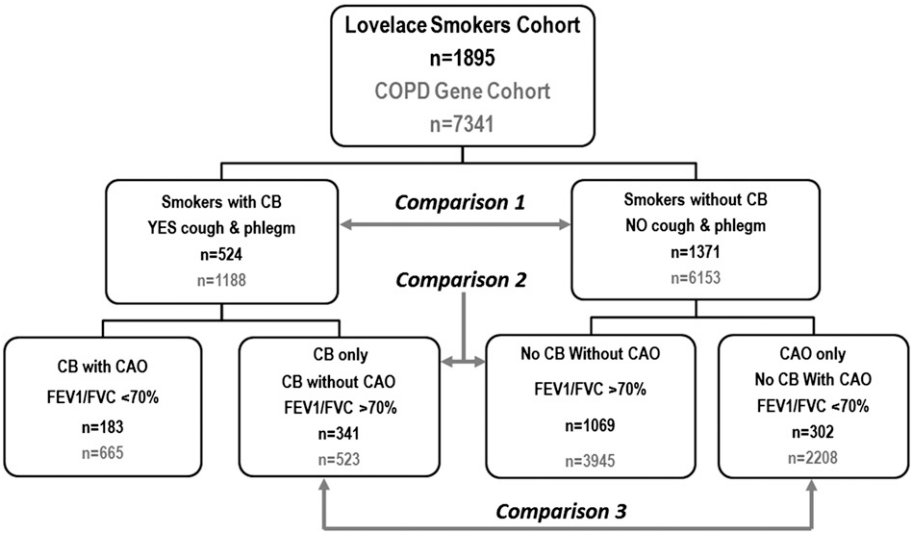

Figure 1 – *Flow diagram of sample comparisons from the Lovelace Smokers' (primary) cohort and the COPD Gene (validating) cohort. Numbers in gray represent those present in validating cohort. CAO = chronic airway obstruction; CB = chronic bronchitis.*

smoking status, and baseline FEV_1 % predicted, and Hispanic ethnicity (available in LSC). The minimal set of covariates was determined based on biologic relevance to be appropriate for all models and was chosen a priori. Accordingly, in each analysis, the covariates do not necessarily reflect those variables with a corresponding significant result within the univariate tests.

Institutional Review Board Approval

The study in the LSC was approved by the Western Institutional Review Board (No. 20031684), and all subjects gave informed consent for their participation. The multicenter study on the COPDGene was approved by the appropriate institutional review boards and by the ancillary study oversight committee.

Results

Because the observed differences in SGRQ- and SF-36-derived scores between smokers with and without CB among participants with or without CAO were striking (e-Tables 1-3), we compared the QOL between smokers with CB only (n = 341) and those with CAO only (n = 302) (Table 1).[17] Chest CT scans in the COPDGene demonstrated significantly higher emphysema and gas trapping in the CAO-only group, confirming the validity of our phenotype definition (e-Table 4). However, the CT scan measure of wall area does not reflect the known pathologic findings in CB.

In both cohorts, compared with those with CAO only, smokers with CB only were younger, more were Hispanic (LSC only), and they had a greater BMI (Table 1). Smokers with CB only also reported fewer pack-years of smoking, although they were more likely to be current smokers. Although the CB-only group reported a history of congestive heart failure and diabetes mellitus similar to that of the CAO-only group in the LSC, they reported a greater prevalence of congestive heart failure in the COPDGene.

More importantly, the total and dimension scores on the SGRQ were greater (implying worse QOL) in the CB-only than in the CAO-only group subjects in both cohorts (Table 2). With respect to individual symptom items, CB-only group subjects in the LSC reported more cough, phlegm, and wheezing in general and morning wheeze with similar levels of shortness of breath but fewer good days and more severe breathing attacks. Also in the LSC cohort, CB-only subjects were more frequently troubled by sleep interruptions and reported SF-36-derived depressive mood. In both cohorts, the CB-only group had lower (ie, worse) SF-36-derived General Health, Role Emotional, Mental Health, Bodily Pain, Vitality, and Social Functioning scores than did the CAO-only group, but they had similar SF-36-derived Physical Functioning and Role Physical scores. Figure 2 presents the differences in the SF-36 and SGRQ averaged (between the LSC and the COPDGene) dimension scores. The observation that the CB-only group had overall worse symptoms did not change after excluding smokers with GOLD (Global Initiative for Chronic Obstructive Lung Disease)-unclassified preserved ratio impaired spirometry ($FEV_1/FVC \geq 0.7$ and $FEV_1 < 80\%$ predicted).

In parallel multivariable analyses in the two cohorts, the CB-only group demonstrated greater odds for higher (ie, worse) SGRQ total and dimension scores than did the CAO-only group (Table 3). Examining individual SGRQ symptom items in the LSC, the CB-only group

TABLE 1] Cross-sectional Comparison of Characteristics Between CB-Only Group and CAO-Only Group (Univariate Analysis)

Characteristic	LSC			COPDGene		
	CB Only (n = 341)	CAO Only (n = 302)	*P* Value[a]	CB Only (n = 523)	CAO Only (n = 2,208)	*P* Value
Female	256 (75.1)	211 (69.9)	.14	220 (42.1)	934 (42.3)	.92
Age, y	52.5 ± 9	61.6 ± 8.8	< .001	55.7 ± 7.8	64 ± 8.6	< .001
Hispanic ethnicity	80 (23.5)	25 (8.3)	< .001	…	…	…
Black	…	…	…	204 (39.0)	453 (20.5)	< .001
Smoking, pack-y	37.2 ± 17	46.9 ± 26.5	< .001	42.6 ± 22.5	51.3 ± 26.5	< .001
Current smoking	273 (80.1)	150 (49.7)	< .001	414 (79.2)	869 (39.4)	< .001
BMI, kg/m^2	28.7 ± 6	26.6 ± 5.8	< .001	29.7 ± 6.6	27.4 ± 5.7	< .001
COPD stage I	…	118 (39.1)	…	…	521 (23.6)	…
COPD stage II	…	149 (49.3)	…	…	946 (42.8)	…
COPD stage III	…	25 (8.3)	…	…	484 (21.9)	…
COPD stage IV	…	10 (3.3)	…	…	257 (11.6)	…
FEV_1	2.8 ± 0.7	2.1 ± 0.8	< .001	2.8 ± 0.8	1.8 ± 0.8	< .001
FEV_1/FVC	78 ± 4.6	60 ± 9.2	< .001	78 ± 9.1	54 ± 9.5	< .001
NHANES FEV_1 % predicted	93.2 ± 13.6	73.8 ± 19.1	< .001	90.2 ± 16.6	61.2 ± 23.5	< .001
History of CHF	3 (0.9)	2 (0.8)	.91	97 (18.5)	318 (14.4)	.02
History of diabetes	27 (7.9)	15 (5.9)	.34	17 (3.3)	76 (3.4)	.83
% Emphysema	…	…	…	2.2 ± 3	13.5 ± 13.2	< .001
% Emphysema lower lobes	…	…	…	1.8 ± 2.3	11.1 ± 12.2	< .001
% Emphysema lower third slicer	…	…	…	1.7 ± 2.5	9.5 ± 10.6	< .001
% Emphysema slicer	…	…	…	1.7 ± 2.7	11.8 ± 12.5	< .001
% Emphysema UL/LL ratio	…	…	…	1.6 ± 1.3	2 ± 2.6	.25
% Emphysema upper lobes	…	…	…	2.5 ± 3.8	15.2 ± 15.6	< .001
% Emphysema upper third slicer	…	…	…	1.9	14.1	< .001

Data are presented as No. (%) or mean ± SD. COPD was defined by an absolute postbronchodilator value of FEV_1/FVC < 70%. COPD stages were taken from the GOLD standard definitions. CB was defined as the presence of at least two of the following three criteria: (1) doctor diagnosis of CB; (2) phlegm production over the previous 4 wk; and (3) phlegm production for most d for ≥ 3 consecutive mo during the y. Percent predicted values are based on the NHANES-III reference values by Hankinson et al.[17] Exclusion criterion was a history of asthma; inclusion criteria were ≥ 20 pack-y of smoking and age 40-75 y. Depression was based on any positive answer to any of the SF-36 questions 17 through 20, 9_2 through 9_4. CAO = chronic airway obstruction; CB = chronic bronchitis; CHF = congestive heart failure; COPDGene = COPD Gene Cohort; GOLD = Global Initiative for Chronic Obstructive Lung Disease; LL = lower lobe; LSC = Lovelace Smokers' Cohort; NHANES = National Health and Nutrition Examination Survey; SF-36 = 36-Item Short Form Health Survey; SGRQ = St. George's Respiratory Questionnaire; UL = upper lobe.

[a]*P* values for frequencies of categorical variables were based on χ^2 tests and for means of continuous variables were based on Student *t* test.

demonstrated greater odds for morning wheezing (OR, 1.74; 95% CI, 1.03-2.93; *P* = .038) and interrupted sleep (OR, 2.47; 95% CI, 1.48-4.14; *P* < .01). In addition, using the SF-36, CB-only subjects demonstrated worse scores on mental health, body pain, vitality, emotional health, and general health, than did CAO-only subjects. Consistent with that finding, CB-only subjects demonstrated greater odds for an SF-36-derived depressive mood score (OR, 1.61; 95% CI, 1.06-2.44; *P* = .027).

Discussion

The result provides evidence that smokers with CB only reported a worse QOL and symptoms than did those with CAO only in both the LSC primary and the COPDGene validation cohorts. For most of the comparisons, the

TABLE 2] Cross-sectional Comparison of Characteristics of Quality of Life (SGRQ and SF-36) Between CB-Only and CAO-Only Group (Univariate Analysis)

Characteristic	LSC			COPDGene		
	CB Only (n = 341)	CAO Only (n = 302)	*P* Value[a]	CB Only (n = 523)	CAO Only (n = 2,208)	*P* Value
SGRQ total score	27 ± 17	20.5 ± 16.1	< .001	33.9 ± 21.5	28.6 ± 20.9	< .001
SGRQ Symptom score	43.3 ± 19.7	26.2 ± 20.4	< .001	48.1 ± 20.5	31.2 ± 22.6	< .001
Cough	260 (76.2)	110 (44.2)	< .001	…	…	…
Phlegm	272 (79.8)	76 (30.5)	< .001	…	…	…
Shortness of breath	120 (35.2)	87 (34.9)	.95	…	…	…
Wheeze	72 (21.1)	21 (8.4)	< .001	…	…	…
Attack free	4.2 ± 1.3	4.5 ± 1.1	< .01	…	…	…
Good days	4.1 ± 1	4.3 ± 0.9	.01	…	…	…
AM wheeze	101 (29.6)	36 (13.6)	< .001	…	…	…
SGRQ Impacts score	15.2 ± 15	10.7 ± 12.2	< .001	24.3 ± 21.2	19.2 ± 18.9	< .001
SGRQ Activity score	35.8 ± 24.3	31.9 ± 24.5	.053	43.8 ± 28.7	43.6 ± 29.5	.90
SGRQ interrupted sleep	110 (32.3)	40 (15.2)	< .001	…	…	…
SF-36 Role Physical	74.9 ± 37	78.1 ± 35.7	.28	65.2 ± 30	67.6 ± 30.9	.29
SF-36 Physical Functioning	74.6 ± 24.7	75.5 ± 25.5	.66	59.9 ± 28.4	61.1 ± 28.9	.57
SF-36 General Health Perception	62.6 ± 24.9	71.3 ± 24.4	< .001	54 ± 22.5	59.8 ± 23.1	< .01
SF-36 Bodily Pain	62.6 ± 24.9	71.3 ± 24.4	< .001	56.2 ± 28.2	71.5 ± 25.6	< .001
SF-36 Vitality	49.9 ± 22.3	60.3 ± 22.1	< .001	50.7 ± 21.5	59.7 ± 21	< .001
SF-36 Mental Health	69 ± 21.2	78.1 ± 18.4	< .001	64.7 ± 22.2	76.3 ± 18.6	< .001
SF-36 Role Emotional	67.9 ± 43.3	79.1 ± 38.2	< .01	68.6 ± 30.1	79.9 ± 26.9	< .001
SF-36 Social Functioning	75.6 ± 27.3	86.7 ± 22.4	< .001	68.4 ± 30	79 ± 25.7	< .001
SF-36-derived Depression	182 (53.4)	95 (35.8)	< .001	…	…	…
Work loss	109 (32)	51 (19.3)	< .01	…	…	…
Accomplished less	117 (34.3)	62 (23.5)	< .01	…	…	…
Less careful	102 (29.9)	47 (17.8)	< .01	…	…	…
Social problems	2 (1.1)	2 (0.9)	< .001	…	…	…
Recently calm	5 (1.4)	5 (1.2)	< .001	…	…	…
Recently happy	5 (1.2)	6 (0.9)	< .001	…	…	…
Recently nervous	3 (1.3)	3 (1.2)	< .001	…	…	…

Data are presented as No. (%) or mean ± SD. COPD was defined by an absolute postbronchodilator value of $FEV_1/FVC < 70\%$. CB was defined as the presence of at least two of the following three criteria: (1) doctor diagnosis of CB; (2) phlegm production over the previous 4 wk; and (3) phlegm production for most d for ≥ 3 consecutive mo during the y. Data prefaced with "SGRQ" were obtained from the SGRQ, including its component activity, impact, and symptom subscales or from its individual items that were coded for presence or absence. Data prefaced with "SF-36" were obtained from the SF-36 questionnaire, including its component subscales or from its individual items that were coded for presence or absence. Exclusion criterion was a history of asthma; inclusion criteria were ≥ 20 pack-y of smoking and age 40-75 y. Depression was based on any positive answer to any of the SF-36 questions 17 through 20, 9_2 through 9_4. SF-36 = 36-Item Short Form Health Survey; SGRQ = St. George's Respiratory Questionnaire. See Table 1 for expansion of other abbreviations.

[a]*P* values for frequencies of categorical variables were based on χ^2 tests and for means of continuous variables were based on Student's *t* test.

differences between the two groups seen in the SGRQ total and dimension scores were well above the proposed clinically important difference of four points. When we examined the pattern of symptom scores using the SGRQ, it is clear that the difference could not simply be attributed solely to cough and phlegm, although by mere definition, these were greater in the CB-only group (Table 2). In fact, the CB-only group subjects demonstrated a greater risk of wheezing overall and morning wheezing compared with those with CAO only (Table 3), and in multivariable analyses, the other symptom scores were significantly associated with CB only. In addition, based on the SF-36 questionnaires, those with CB also had greater levels of pain and fatigue, as well as lower

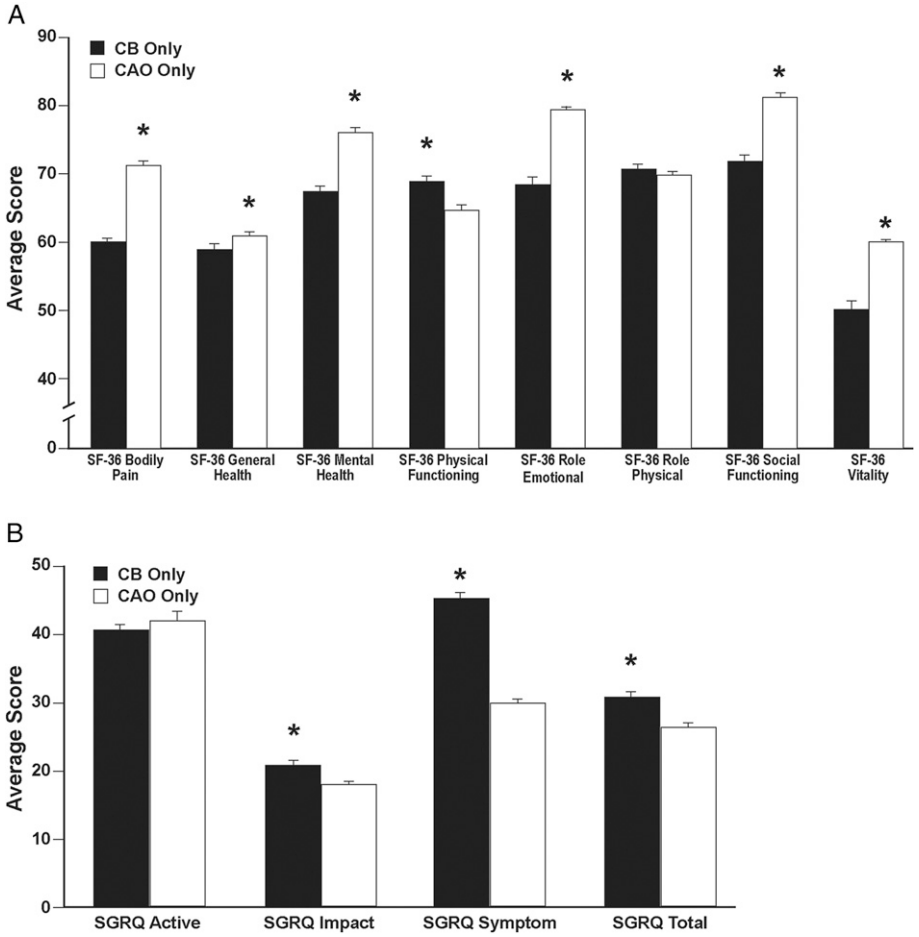

Figure 2 – *A, B, Averaged scores between the Lovelace Smokers' Cohort and the COPD Gene Cohort in quality of life as measured by the SF-36 and SGRQ. A, SF-36. B, SGRQ. Smokers with CB only are compared with those with CAO only. *P < .001. Similar results were found when the cohorts were analyzed separately. SF-36 = 36-Item Short Form Health Survey; SGRQ = St. George's Respiratory Questionnaire. See Figure 1 legend for expansion of other abbreviations.*

vitality. Overall, symptoms captured through these QOL measures were worse in those with CB only as compared with CAO-only subjects. Similar results were seen when smokers with CB were compared with smokers without CB in other population groups (e-Tables 1-3).

Although a formal sleep scale was not available, the CB-only group had a twofold increased risk of sleep interruption. Sleep disturbance in individuals with CB has been reported previously,[18] and many investigations have focused on the overlap between OSA and chronic airflow limitation.[19] The greater BMI in the CB-only group raises concern that sleep apnea may be an explanatory mechanism. However, adjustment for BMI in the multivariable analysis (Table 3) did not explain away these findings, suggesting that alternative mechanisms such as nocturnal worsening of cough, gastroesophageal reflux, or congestive heart failure may explain the sleep interruption. Nocturnal awakenings secondary to cough and dyspnea and gastroesophageal reflux were significantly associated with CB in previous studies.[3,6] Our findings suggest that greater clarification of the phenotypes of CAO and CB would potentially add clarity to the nature of the sleep disturbances seen in COPD.

In addition, individuals with CB are at greater risk of poor mental health, social functioning, and emotional base, and role functioning, with decreased vitality compared with those with CAO. These findings may be consequent to the increase in respiratory symptoms and sleep disruption. However, it is clear that physical activity is not impacted by these symptom differences given the lack of significant differences in the SGRQ activity and SF-36 Role Physical dimensions and even better reports of SF-36 Physical Functioning in the CB only group (Table 2). In our analysis, mental health, social functioning, and well-being were important contributors to differences in QOL between groups because these variables were associated with relatively larger parameter estimates in the multivariate analysis (Table 3) in both cohorts. It is unlikely that these differences can be explained by differences in current smoking status or FEV_1 % predicted values between the two groups, because inclusion in the multivariable model

TABLE 3] Multivariable Analysis of the Cross-sectional Associations of Individual QOL Outcomes on CB-Only Status as Predictor (Referent: CAO Only)

Indexes	LSC (n = 643)	*P* Value	COPDGene (n = 2,731)	*P* Value
SGRQ				
Total score	0.26 ± 0.02	< .001	0.67 ± 0.01	< .001
Impacts score	0.45 ± 0.03	< .001	0.81 ± 0.01	< .001
Activity score	0.24 ± 0.02	< .001	0.54 ± 0.01	< .001
Symptom score	0.43 ± 0.02	< .001	0.71 ± 0.01	< .001
Cough	3.42 (2.16-5.40)	< .001	…	…
Phlegm	6.80 (4.25-10.86)	< .001	…	…
Wheeze	3.49 (1.81-6.72)	< .001	…	…
Attack-free days	-0.08 ± 0.05	.13	…	…
Good days	-0.05 ± 0.05	.31	…	…
AM wheeze	1.74 (1.03-2.93)	.04	…	…
Item interrupted sleep	2.47 (1.48-4.14)	< .001	…	…
SF-36				
General Health Perception	−0.11 ± 0.01	< .001	−0.25 ± 0.01	< .001
Bodily Pain	−0.11 ± 0.01	< .001	−0.22 ± 0.01	< .001
Vitality	−0.14 ± 0.01	< .001	−0.24 ± 0.01	< .001
Mental Health	−0.06 ± 0.01	< .001	−0.13 ± 0.01	< .001
Role Emotional	−0.07 ± 0.01	< .001	−0.19 ± 0.01	< .001
Social Functioning	−0.09 ± 0.01	< .001	−0.19 ± 0.01	< .001
Derived Depressive Mood	1.61 (1.06-2.44)	.03	…	…

Data are presented as PE ± SE or OR (95% CI). CAO was defined by an absolute postbronchodilator value of $FEV_1/FVC < 70\%$. CB was defined as the presence of at least two of the following three criteria: (1) doctor diagnosis of CB; (2) phlegm production over the previous 4 wk; and (3) phlegm production for most days for ≥ 3 consecutive months during the year. After 18 comparisons, the Bonferroni correction is estimated to be 0.003. Data prefaced with "SGRQ" were obtained from the SGRQ, including its component activity, impact, and symptom dimension, or from its individual items that were coded for presence or absence and significant in the univariate analysis. A positive parameter estimate suggests a worse QOL for the CB group. Data prefaced with "SF-36" were obtained from the SF-36 questionnaire, including its component dimensions, or from its individual items that were coded for presence or absence. A negative parameter estimate suggests a worse QOL for the CB group. Exclusion criterion was a history of asthma; inclusion criteria were ≥ 20 pack-y of smoking and age 40-75 y. A priori covariates included self-reported age, sex, Hispanic ethnicity, pack-years of smoking, current smoking status, and baseline FEV_1 % predicted. *P* values for categorical variables were based on logistic regression (OR = OR as estimate of strength of association) and for continuous variables were based on linear regression methods (PE = PE as estimate of strength of association). PE = parameter estimate; QOL = quality of life. See Table 1 for expansion of other abbreviations.

did not explain away the results. The literature indicates that women generally report greater symptoms and lower QOL levels do than men. However, in relation to the SGRQ, symptoms were not found to be different by sex when controlled for FEV_1 % predicted values.[20] These findings are also consistent with those of previous reports of the SGRQ symptoms domain score when those with CB were compared with those without CB.[3]

This analysis is one of the first, to our knowledge, to suggest that subjects with CB can have significantly more disruption in mental well-being than do subjects with CAO. Spirometry for the classification of disease severity and the need for treatment have been based primarily on the GOLD criteria.[21] The new GOLD guidelines assess not only the degree of airflow limitation, but also the number of exacerbations per year and the modified Medical Research Council dyspnea scale and COPD Assessment Test (CAT) score, which take symptoms, activity limitations, and impact into account.[22] Although our data support the use of the CAT score, the new guidelines exclude patients with CB only with GOLD stage 0 disease, who, according to our findings, have even more symptoms than do those with CAO only. In addition, the CAT score does not take into account emotional and mental health, particularly depressive mood.

A limitation of this investigation is that some effect sizes, while statistically significant, may be small and possibly not clinically significant, especially given the lack of a documented clinically important difference in the SF-36. However, the SGRQ does demonstrate not only statistically significant effect sizes in the Total, Symptom, and

Impact scores, but also a four-point or more clinically significant difference in each score. Another important limitation is the lack of formal sleep, anxiety, and depression measures, which restricted our ability to make more robust statements concerning impaired sleep, anxiety, or depressive mood. However, the pattern of response to the SF-36 emotional and social dimensions seen in the LSC and validated in the COPDGene deserves further investigation of potential sleep disturbances, increased anxiety, and depressive mood.

Further, smoking behavior (ie, type of cigarettes, depth of inhalation, or number of puffs per cigarette) is a complex variable that may not be captured completely by measures such as pack-years and current smoking status. We also did not adjust for differences in occupational and environmental exposures or in dietary habits among the various baseline weight categories. Finally, because our cohort participants were recruited from the community using newspaper and radio advertisements, our study cohort may not be representative of all smokers in New Mexico. However, the smoking behaviors in our study were consistent with those observed in representative state surveys of smokers[23] and, because the findings in the LSC were replicated in the multicenter COPDGene, we believe that these findings are representative of other parts of the United States.

Despite these limitations, our study has several strengths. The predominance in the LSC of women is a clear strength, because many large cohorts are predominately male. In addition, the use of postbronchodilator spirometric values and strict adherence to the American Thoracic Society guidelines in the performance of spirometry provides strong support that the classification of groups in these samples was correct. Further, the differences in well-being between those with CB and those with CAO identified in this investigation, and validated in a separate well-described cohort, have the potential for a tremendous public health impact.

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References

1. Centers for Disease Control and Prevention (CDC). Chronic obstructive pulmonary disease among adults—United States, 2011. *MMWR Morb Mortal Wkly Rep*. 2012;61(46):938-943.
2. Mannino DM. Chronic obstructive pulmonary disease: definition and epidemiology. *Respir Care*. 2003; 48(12): 1185-1191.
3. Kim V, Han MK, Vance GB, et al; COPDGene Investigators. The chronic bronchitic phenotype of COPD: an analysis of the COPDGene Study. *Chest*. 2011;140(3):626-633.
4. Allen-Ramey FC, Gupta S, DiBonaventura MD. Patient characteristics, treatment patterns, and health outcomes among COPD phenotypes. *Int J Chron Obstruct Pulmon Dis*. 2012;7: 779-787.
5. Kim V, Davey A, Comellas AP, et al; COPDGene® Investigators. Clinical and computed tomographic predictors of chronic bronchitis in COPD: a cross sectional analysis of the COPDGene study. *Respir Res*. 2014;15:52.1-52.9.
6. Martinez CH, Kim V, Chen Y, et al; COPDGene Investigators. The clinical impact of non-obstructive chronic bronchitis in current and former smokers. *Respir Med*. 2014;108(3):491-499.
7. Murray JF, Mason RJ. *Murray and Nadel's Textbook of Respiratory Medicine*. 5th ed. Philadelphia, PA: Saunders/Elsevier; 2010.
8. Sood A, Stidley CA, Picchi MA, et al. Difference in airflow obstruction between Hispanic and non-Hispanic White female smokers. *COPD*. 2008;5(5): 274-281.
9. Bruse S, Sood A, Petersen H, et al. New Mexican Hispanic smokers have lower odds of chronic obstructive pulmonary disease and less decline in lung function than non-Hispanic whites. *Am J Respir Crit Care Med*. 2011;184(11): 1254-1260.
10. Taylor DR, Bateman ED, Boulet LP, et al. A new perspective on concepts of asthma severity and control. *Eur Respir J*. 2008; 32(3):545-554.
11. Mosen DM, Schatz M, Magid DJ, Camargo CA Jr. The relationship between obesity and asthma severity and control in adults. *J Allergy Clin Immunol*. 2008;122(3): 507-511.
12. Tantisira KG, Litonjua AA, Weiss ST, Fuhlbrigge AL; Childhood Asthma Management Program Research Group. Association of body mass with pulmonary function in the Childhood Asthma Management Program (CAMP). *Thorax*. 2003;58(12):1036-1041.
13. Sutherland ER, Ellison MC, Kraft M, Martin RJ. Altered pituitary-adrenal interaction in nocturnal asthma. *J Allergy Clin Immunol*. 2003;112(1):52-57.
14. Wenzel SE, Busse WW; National Heart, Lung, and Blood Institute's Severe Asthma Research Program. Severe asthma: lessons from the Severe Asthma Research Program. *J Allergy Clin Immunol*. 2007;119(1):14-21.
15. Ferris BG. Epidemiology Standardization Project (American Thoracic Society). *Am Rev Respir Dis*. 1978;118(6 pt 2):1-120.
16. Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow

limitation. The St. George's Respiratory Questionnaire. *Am Rev Respir Dis*. 1992;145(6):1321-1327.

17. Hankinson JL, Oderantz JR, Fedman KB. Spirometric reference values from a sample of the general US population. *Am J Respir Crit Care Med*. 1999;159(1): 179-187.
18. Magnússon S, Gislason T. Chronic bronchitis in Icelandic males: prevalence, sleep disturbances and quality of life. *Scand J Prim Health Care*. 1999;17(2):100-104.
19. Ioachimescu OC, Teodorescu M. Integrating the overlap of obstructive lung disease and obstructive sleep apnoea: OLDOSA syndrome. *Respirology*. 2013; 18(3):421-431.
20. Jones PW, Anderson JA, Calverley PM, et al; TORCH investigators. Health status in the TORCH study of COPD: treatment efficacy and other determinants of change. *Respir Res*. 2011;12:71.1-71.8.
21. GOLD. Global initiative for chronic obstructive lung disease (GOLD): global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. http://www.goldcopd.org/Guidelines/guidelines-resources.html. Published 2014. Accessed September 5, 2014.
22. Vestbo J, Hurd SS, Agustí AG, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med*. 2013;187(4):347-365.
23. Centers for Disease Control and Prevention (CDC). *Behavioral Risk Factor Surveillance System Survey Data*. Atlanta, Georgia: US Department of Health and Human Services, Centers for Disease Control and Prevention; 2006.