Persistent and Newly Developed Chronic Bronchitis Are Associated with Worse Outcomes in Chronic Obstructive Pulmonary Disease

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Abstract

Rationale: Chronic bronchitis is, by definition, a chronic condition, but the development and remission of this condition in cigarette smokers with or without chronic obstructive pulmonary disease (COPD) are poorly understood. Also, it is unclear how the persistence or new development of chronic bronchitis affects symptoms and outcomes.

Objectives: To ascertain the relationship between smoking status and the presence or absence of chronic bronchitis and the subsequent effects on symptoms and outcomes.

Methods: We analyzed 1,775 current or ex-smokers with GOLD (Global Initiative for Chronic Obstructive Lung Disease) stage 0–IV COPD in phase 2 of the Genetic Epidemiology of COPD (COPDGene) Study, which included subjects after 5 years of follow-up from phase 1. We asked subjects at enrollment and at 5 years of follow-up about symptoms consistent with chronic bronchitis. We divided subjects into four groups: persistent chronic bronchitis– (negative at phase 1/negative at phase 2), resolved chronic bronchitis (positive/negative), new chronic bronchitis (negative/positive), and persistent chronic bronchitis+ (positive/positive). We analyzed respiratory symptoms, health-related quality of life, lung function, exacerbation frequency, and 6-minute walk distance.

Measurements and Main Results: Compared with the persistent chronic bronchitis– group, members of the persistent chronic bronchitis+ group were more likely to have continued smoking (53.4%). Subjects with new chronic bronchitis were more likely to have resumed (6.6%) or continued smoking (45.6%), whereas subjects with resolved chronic bronchitis were more likely to have quit smoking (23.5%). Compared with the persistent chronic bronchitis– group, the other groups had a shorter 6-minute walk distance, worse lung function, greater exacerbation frequency, and worse respiratory symptoms. Modified Medical Research Council dyspnea and St. George's Respiratory Questionnaire scores worsened between phase 1 and phase 2 in subjects with new chronic bronchitis but improved in the resolved chronic bronchitis group. On multinomial logistic regression, quitting smoking conferred an odds ratio (OR) of 4.289 (95% confidence interval [CI], 2.689–6.842) for resolved chronic bronchitis, whereas resuming smoking had an OR of 4.585 (95% CI, 2.008–10.471) for new chronic bronchitis. Persistent smoking had an OR of 2.621 (95% CI, 1.677–4.096) and 5.767 (95% CI, 3.702–8.983) for subjects with new chronic bronchitis and subjects with persistent chronic bronchitis, respectively.

Conclusions: Persistent and newly developed chronic bronchitis are associated with continued or resumed smoking, greater respiratory symptoms, worse health-related quality of life, worse lung function, and greater exacerbation frequency. These findings stress the importance of repeatedly assessing chronic cough and sputum production in smokers to identify those at risk for poor outcomes.

Keywords: chronic bronchitis; chronic obstructive pulmonary disease; smoking

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Chronic bronchitis is defined classically as cough and phlegm for at least 3 months/year for at least two consecutive years (1). Chronic bronchitis affects up to 22% of nonsmokers and 14–74% of patients with chronic obstructive pulmonary disease (COPD) (2). Chronic bronchitis has been associated with worse outcomes in COPD, including a greater exacerbation frequency, more respiratory hospitalizations, worse health-related quality of life, greater lung function decline, and possibly increased mortality (3–7). Chronic bronchitis is by definition a chronic condition, but it is unclear whether it is a reversible one. Long-term follow-up of patients with chronic bronchitis to determine chronicity of cough and phlegm has been limited (8); therefore, its persistence has not been scientifically established. Older literature has shown improvements in pulmonary function after smoking cessation but has not addressed its relationship to chronic bronchitis (9–11). It is possible that chronic bronchitis can resolve in some smokers and develop newly in others, but the clinical characteristics associated with a change in the presence of chronic bronchitis have not been defined.

Risk factors for chronic bronchitis include smoking, occupational exposures, and perhaps gastroesophageal reflux disease (7, 12–15). The link between cigarette smoking and chronic bronchitis is the most well established. Given the strength of this association between current smoking and chronic bronchitis, it is possible that smoking cessation could reduce cough and sputum burden. This possibility has, however, not been studied systematically in a large cohort.

In the current study we analyzed data from the first 1,775 subjects with normal baseline spirometry or GOLD (Global Initiative for Chronic Obstructive Lung Disease) stage 0–IV COPD who completed 5-year follow-up visits in phase 2 of the Genetic Epidemiology of COPD (COPDGene) Study. We hypothesized that smoking cessation would reduce chronic bronchitis prevalence, and that persistence or resumption of smoking would result in the development or persistence of chronic bronchitis. We further hypothesized that the development of chronic bronchitis would lead to worse clinical outcomes, including more COPD exacerbations, worse health-related quality of life, greater decline in lung function, and increased respiratory symptoms. Some of the data of the current study have been previously reported in the form of an abstract (16).

Methods

Study Group

The COPDGene Study is a multicenter observational study that initially recruited more than 10,000 subjects during phase 1. This study underwent institutional review board approval at all 21 clinical centers, and all study participants provided written informed consent.

Inclusion and exclusion criteria and protocols were described previously (17). Briefly, enrollees were current or ex-smoker African-Americans or non-Hispanic whites ages 45–80 years with an at least 10-pack-year smoking history. Exclusion criteria included pregnancy, history of other lung disease except asthma, prior lobectomy or lung volume reduction surgery, active cancer undergoing treatment, or known or suspected lung cancer.

During phase 1, subjects were asked detailed questions regarding respiratory symptoms, health-related quality of life, history of exacerbations in the year before enrollment, history of severe exacerbations (defined as requiring an emergency department visit or hospital admission), medical history, and smoking history. Subjects also underwent spirometry pre- and post-bronchodilator administration, and 6-minute walk test.

Five years later, phase 2 of the study re-recruited the same subjects, who were asked the same questions and underwent lung function testing. In addition, the COPD Assessment Test (CAT) and Hospital Anxiety and Depression Scale (HADS) were administered.

The current study is based on the first 2,000 Follow-Up Data Set (November 2014), excluding subjects with PRISm (preserved ratio, impaired spirometry; $FEV_1 < 80\%$ but $FEV_1/FVC > 70$). The PRISm group was excluded from the analysis because of concern that their decreased lung function, 6-minute walk distance, and respiratory symptoms would affect differences in outcomes related to changes or persistence of chronic bronchitis. Lung function data reported were the values obtained during phase 2. From these data, we ascertained whether subjects quit smoking, resumed smoking, or smoked persistently. We also determined decline in spirometry, 6-minute walk distance, and health-related quality of life by the St. George's Respiratory Questionnaire (SGRQ).

Definitions of Groups

Chronic bronchitis was diagnosed using the classic definition, as defined previously (1). Subjects were divided into four groups on the basis of the diagnosis of chronic bronchitis during phase 1 and phase 2: persistent chronic bronchitis– (no chronic bronchitis at either time point), resolved chronic bronchitis (chronic bronchitis at phase 1 but no chronic bronchitis at phase 2), new chronic bronchitis (no chronic bronchitis at phase 1 but chronic bronchitis at phase 2), and persistent chronic bronchitis+ (chronic bronchitis at both time points). Clinical and physiological differences were assessed on the basis of these groups. In terms of smoking status, the cohort was characterized as persistent ex-smokers (ex-smokers at both phase 1 and phase 2), resumed smokers (ex-smokers at phase 1 but current smokers at phase 2), quitters (current smokers at phase 1 but ex-smokers at phase 2), and persistent current smokers (current smokers at both phase 1 and

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phase 2). All values reported are those from phase 2, except for differences in clinical variables between phase 1 and phase 2. In addition, we determined new prescriptions of respiratory medications between phase 1 and phase 2 (not prescribed in phase 1 but prescribed in phase 2).

Statistical Analysis

Statistical analyses were performed with SPSS version 22.0 (IBM Corp., Armonk, NY) and SAS version 9.4 (SAS Institute Inc., Cary, NC). Distribution and probability plots were used to check normality. Differences in categorical variables were assessed by χ^2 test and in continuous variables by one-way analysis of variance or Kruskal–Wallis test ($P < 0.05$ indicates at least two groups are significantly different). Bonferroni correction for multiple comparisons was performed to discern differences between individual groups.

Multivariable linear regression was performed with the four chronic bronchitis groups (persistent chronic bronchitis– as reference, resolved chronic bronchitis, new chronic bronchitis, and persistent chronic bronchitis+ as independent variables) to determine independent effects on continuous outcomes with age, race, sex, FEV_1% predicted, and smoking status as covariates. These covariates were chosen because of their established effects on the outcomes of interest.

Multinomial logistic regression was performed to ascertain odds ratios for resolved chronic bronchitis, new chronic bronchitis, and persistent chronic bronchitis+, with persistent chronic bronchitis– as the reference group. For each regression model, diagnostic and residual plots were examined to check the assumptions of linear regression. We used smoking status as an independent variable (persistent smokers, subjects who quit smoking, subjects who resumed smoking, and persistent ex-smokers as the reference group), with FEV_1% predicted, smoking history in pack-years, gastroesophageal reflux, sex, and race as covariates. Finally, we calculated the attributable proportion of each chronic bronchitis group due to current smoking, using the formula: Attributable proportion = 100 × (rate of current smoking − rate of current nonsmoking)/(rate of current smoking).

Data are presented as means ± SD or medians (interquartile range, IQR) unless stated otherwise. P values less than 0.005 (0.05/10 outcomes) were considered statistically significant.

Results

Of the 1,775 subjects, 1,342 were in the persistent chronic bronchitis– group (75.6%), 162 had resolved chronic bronchitis (9.1%), 136 had new chronic bronchitis (7.7%), and 135 were in the persistent chronic bronchitis+ group (7.6%). The total percentage of subjects who had chronic bronchitis at any time point was 24.4%. The demographic characteristics, lung function, 6-minute walk distance, and smoking status of these subjects are summarized in Table 1. Univariate analysis revealed that, compared with the persistent chronic bronchitis– group, subjects with resolved chronic bronchitis, subjects with new chronic bronchitis, and subjects in the persistent chronic bronchitis+ group were more likely to be male, but the four groups were similar in age, race, and body mass index.

There were clear differences among the groups in the distribution of smoking status at the phase 2 visit (Figure 1), with a pronounced stepwise increase from the persistent chronic bronchitis– to persistent chronic bronchitis+ in the frequency of current smoking at phase 2 and of persistent current smoking, and a much greater number of persistent ex-smokers in the persistent chronic bronchitis– group. The frequency of quitters was greatest in the resolved chronic bronchitis group, and identical in the other groups (Figure 1).

By univariate analysis, subjects in the persistent chronic bronchitis– group were significantly less likely to be currently smoking compared with subjects in the new chronic bronchitis and persistent chronic bronchitis+ groups (Table 1). Conversely, subjects in the resolved chronic bronchitis, new chronic bronchitis, and persistent chronic bronchitis+ groups were all significantly less likely to be persistent ex-smokers than were subjects in the persistent chronic bronchitis– group. The percentage of resumed smokers was greatest in the new chronic bronchitis group, whereas the subjects with resolved chronic bronchitis were more likely to have quit smoking. Subjects in the persistent chronic bronchitis+ group were most likely to be persistently smoking, and they had the greatest smoking history. FEV_1% predicted, FVC% predicted, FEV_1/FVC, and 6-minute walk distance were all greatest in the persistent chronic bronchitis– group, and differed significantly from the other three groups.

We also performed univariate analysis of symptoms, health-related quality of life, HADS depression and anxiety scores, CAT scores, BODE indices, and exacerbation histories in the four groups (Table 1). MMRC dyspnea scores, HADS scores, BODE indices, and exacerbation frequency were the lowest in the persistent chronic bronchitis– group and differed significantly from the other three groups. SGRQ and CAT scores were greatest in the persistent chronic bronchitis+ group, followed in descending order by new chronic bronchitis, resolved chronic bronchitis, and persistent chronic bronchitis–. In multivariable linear regression, the effects of smoking status by chronic bronchitis groups on these outcomes were independent of other covariates (Table 2). GERD, nocturnal awakenings secondary to cough or dyspnea, and a history of severe exacerbations were the lowest in the persistent chronic bronchitis– group compared with the other three groups.

We also found differences between the chronic bronchitis groups in longitudinal changes in symptoms, walk distance, and lung function between phase 1 and phase 2 visits (Table 1). The greatest increase in SGRQ (worse health-related quality of life) was seen in the new chronic bronchitis group, and the resolved chronic bronchitis group had a decrease in SGRQ. MMRC dyspnea scores increased in the new chronic bronchitis group and decreased slightly in the resolved chronic bronchitis group. The decline in 6-minute walk distance between visits was most significant in the new chronic bronchitis group. By multivariable linear regression, the chronic bronchitis category was significantly and independently associated with changes in 6-minute walk distance and in SGRQ (Table 2).

To gain greater understanding of the effect of changes in smoking on chronic bronchitis, we performed univariable and multivariable multinomial logistic regression of smoking status, pack-year history, gastroesophageal reflux, lung function, sex, and race on the resolved

Table 1. Clinical and physiological characteristics of each group

	Persistent Chronic Bronchitis– (*n = 1,342*)	Resolved Chronic Bronchitis (*n = 162*)	New Chronic Bronchitis (*n = 136*)	Persistent Chronic Bronchitis+ (*n = 135*)	*P* Value
Age at current visit, yr	66.23 ± 8.93	65.37 ± 8.77	65.73 ± 9.46	65.42 ± 8.46	0.500
Race, % white	70.6*	73.5	72.8	78.5	0.235
Sex, % male	49.1*†‡	59.9	57.4	58.5	0.007
BMI, kg/m^2	28.31 ± 6.11	29.04 ± 6.04	28.85 ± 5.84	28.57 ± 6.76	0.423
Smoking status					
Current smoking (phase 2), %	31.2*‡	37.1*	45.6	53.4	<0.0001
Persistent ex-smokers, %	58.6*†‡	39.5	45.6	37.8	<0.0001
Resumed smokers, %	2.3‡	1.9‡	6.6*	1.5	<0.0001
Quitters, %	10.1†	23.5*‡	8.8	8.9	<0.0001
Persistent current smokers, %	28.9*†‡	35.2*	39.0*	51.9	<0.0001
Smoking history, pack-years	43.34 ± 22.72*‡	47.84 ± 21.48*	51.42 ± 31.25	57.17 ± 28.75	<0.0001
FEV_1% pred	79.91 ± 26.07*†‡	67.57 ± 25.72	66.16 ± 27.57	63.20 ± 25.03	<0.0001
FVC% pred	89.74 ± 18.12*†‡	83.08 ± 17.78	81.96 ± 19.43	83.18 ± 17.44	<0.0001
FEV_1/FVC	66.40 ± 15.76*†‡	60.39 ± 16.95	59.38 ± 17.37	56.45 ± 16.82	<0.0001
6-Min walk distance, ft	1,339.8 ± 421.7*†‡	1,191.4 ± 411.32	1,127.3 ± 475.35	1,164.8 ± 414.05	<0.0001
MMRC dyspnea score	0 (0–2)*†‡	2 (0–3)*	2 (0–3)	2 (1–3)	<0.0001
SGRQ score	12.5 (3.5–30.5)*†‡	30.3 (16.2–47.5)*‡	38.3 (21.2–53.2)	45.3 (29.6–61.0)	<0.0001
CAT score	8 (4–15)*†‡	16 (8–22)*‡	18 (12.5–24)	20 (14–26)	<0.0001
HADS anxiety score	4 (2–6)*†	5 (2–8)	4 (2–8)	5 (2–7)	<0.0001
HADS depression score	4 (2–6)*†‡	3 (2–6)	4 (2–7)	4 (2–8)	<0.0001
BODE Index	0 (0–2)*†‡	1 (0–3)	2 (0–3)	2 (1–4)	<0.0001
Exacerbation frequency, No./patient/yr	0 (0–0)*†‡	0 (0–1)	0 (0–0)*	0 (0–1)	<0.0001
History of severe exac, %	7.2*†‡	14.2	14.0	17.0	<0.0001
History of asthma, %	16.0*†‡	27.2	18.4	22.2	<0.0001
Gastroesophageal reflux, %	28.6*†	36.4	35.3	38.5	0.015
Noct awake cough, %	12.4*†‡	19.8*‡	43.4*	54.8	<0.0001
Noct awake SOB, %	9.8*†‡	20.4*‡	29.4	37.8	<0.0001
Longitudinal changes, phase 1 – phase 2					
Absolute change FEV_1, ml	−208.72 ± 262.38	−227.46 ± 302.32	−266.96 ± 334.22	−236.41 ± 324.02	0.090
Percent change FEV_1% pred	−2.15 ± 9.85	−3.84 ± 10.67	−4.55 ± 11.74	−3.53 ± 10.46	0.011
FEV_1 annual decline, ml/yr	−39.20 ± 49.42	−42.90 ± 57.80	−49.93 ± 64.80	−44.60 ± 61.58	0.098
Change in MMRC score	0.03 ± 1.14‡	−0.09 ± 1.35‡	0.51 ± 1.45*	0.12 ± 1.20	<0.0001
Change in SGRQ	0.17 ± 13.93†‡	−4.26 ± 17.93*‡	9.37 ± 17.77*	2.06 ± 16.28	<0.0001
Change in 6-min walk distance, ft	−100.56 ± 353.76	−126.82 ± 358.46	−183.18 ± 386.23	−115.57 ± 359.50	0.007

Definition of abbreviations: BMI = body mass index; BODE = body mass index, airflow obstruction, dyspnea, and exercise capacity; CAT = COPD Assessment Test; exac = exacerbation; FEV_1% pred = FEV_1 expressed as a percentage of the predicted value; FVC% pred = FVC expressed as a percentage of the predicted value; HADS = Hospital Anxiety and Depression Scale; MMRC = Modified Medical Research Council; Noct = nocturnal; persistent chronic bronchitis+ = subjects positive at phase 1/positive at phase 2 for chronic bronchitis; persistent chronic bronchitis– = subjects negative at phase 1/negative at phase 2 for chronic bronchitis; SGRQ = St. George's Respiratory Questionnaire; SOB = shortness of breath.
Values are expressed as means ± SD or as medians (interquartile range).
*$P < 0.05$ compared with resolved chronic bronchitis.
†$P < 0.05$ compared with new chronic bronchitis.
‡$P < 0.05$ compared with persistent chronic bronchitis+.

chronic bronchitis, new chronic bronchitis, and persistent chronic bronchitis+ groups (Table 3). Quitting smoking had an odds ratio (OR) greater than 1 for resolved chronic bronchitis, and resuming smoking had an OR greater than 1 for new chronic bronchitis. Persistent current smoking had the highest OR for persistent chronic bronchitis+ but was also greater than 1 for new chronic bronchitis and resolved chronic bronchitis. Smoking pack-year history conferred an OR greater than 1 for persistent chronic bronchitis+ only. FEV_1% predicted had ORs less than 1 for the resolved chronic bronchitis, new chronic bronchitis, and persistent chronic bronchitis+ groups in descending fashion (i.e., the worse the FEV_1% predicted the greater the OR for each group). Male sex was associated with resolved chronic bronchitis. Gastroesophageal reflux conferred an increased risk for the resolved chronic bronchitis and persistent chronic bronchitis+ groups. White race was at increased risk for persistent chronic bronchitis+.

Graphically displaying the ORs for new chronic bronchitis (Figure 2) and persistent chronic bronchitis (Figure 3) highlighted the dominant effect of changes in smoking behavior on these two categories of worsened cough and sputum production. Finally, the attributable proportions of each chronic bronchitis group due to current smoking were –16.2, 10.3, 37.0, and 53.8% in the persistent chronic bronchitis–, resolved chronic bronchitis, new chronic bronchitis, and persistent chronic bronchitis+ groups, respectively.

Table 4 shows the percentage of subjects in each group with new prescriptions of respiratory medications between phase 1 and phase 2. Overall, there were more new prescriptions of many respiratory medications in the resolved

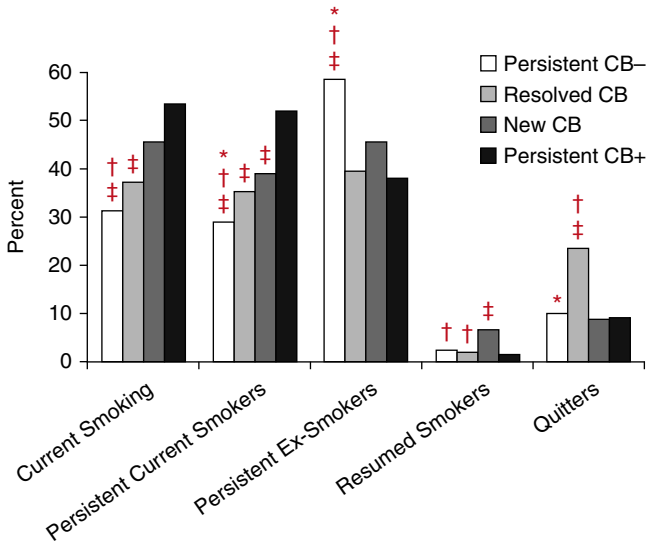

Figure 1. Chronic bronchitis (CB) groups displayed by smoking status at phase 2 visit. *Current smoking* indicates at phase 2. The numbers of persistent current smokers, persistent ex-smokers, resumed smokers, and quitters add up to 100% in each of the chronic bronchitis groups. *$P < 0.05$ compared with resolved chronic bronchitis; †$P < 0.05$ compared with new chronic bronchitis; ‡$P < 0.05$ compared with persistent chronic bronchitis+.

chronic bronchitis, new chronic bronchitis, and persistent chronic bronchitis+ groups compared with the persistent chronic bronchitis– group. In general, there were no significant differences between the resolved chronic bronchitis, new chronic bronchitis, and persistent chronic bronchitis+ groups with the exception of short-acting β-agonists, which were more likely to be newly prescribed in the new chronic bronchitis group compared with the resolved chronic bronchitis and persistent chronic bronchitis+ groups.

Discussion

We showed that chronic bronchitis was variable over time in a large cohort of current or ex-smokers with or without airflow obstruction. The main association with the waxing and waning presence of chronic bronchitis was current smoking. We also showed that those with chronic bronchitis at any time had worse lung function and 6-minute walk distance, a greater exacerbation frequency, more severe exacerbations, and greater HADS anxiety and depression scores and BODE indices than those who never had chronic bronchitis. Additional important findings include the following: MMRC dyspnea was just as bad in those with newly developed chronic bronchitis as in those with persistent chronic bronchitis; CAT scores and nocturnal symptoms were progressively worse in the new chronic bronchitis and persistent chronic bronchitis groups; health-related quality of life worsened dramatically in those who newly developed chronic bronchitis (twice the minimal clinically important difference) and conversely improved significantly in those with resolution of chronic bronchitis; and more respiratory medications were newly prescribed in the resolved chronic bronchitis, new chronic bronchitis, and persistent chronic bronchitis+ groups,

Table 2. Multivariable linear regression for continuous outcomes by chronic bronchitis group*

	Resolved Chronic Bronchitis vs. Persistent Chronic Bronchitis–		New Chronic Bronchitis vs. Persistent Chronic Bronchitis–		Persistent Chronic Bronchitis+ vs. Persistent Chronic Bronchitis–	
Outcome	**β-Coefficient (95% CI)**	***P* Value**	**β-Coefficient (95% CI)**	***P* Value**	**β-Coefficient (95% CI)**	***P* Value**
MMRC dyspnea score	0.27 (0.07 to 0.47)	**0.0044**	0.62 (0.42 to 0.82)	**<0.0001**	0.76 (0.54 to 0.98)	**<0.0001**
6-MWD, ft	−84.04 (–144.82 to –23.26)	**0.0068**	−136.10 (–201.72 to 70.48)	**<0.0001**	−87.56 (–153.96 to 21.16)	**<0.0001**
SGRQ score	8.55 (5.86 to 11.23)	**<0.0001**	14.50 (11.62 to 17.38)	**<0.0001**	20.15 (17.21 to 23.09)	**<0.0001**
CAT score	4.21 (3.05 to 5.37)	**<0.0001**	6.90 (5.65 to 8.15)	**<0.0001**	8.60 (7.32 to 9.87)	**<0.0001**
HADS-A score	0.98 (0.40 to 1.56)	**0.0009**	0.76 (0.13 to 1.38)	0.017	1.09 (0.46 to 1.72)	**0.0008**
HADS-D score	0.75 (0.26 to 1.24)	**0.003**	0.97 (0.44 to 1.50)	**0.0003**	1.5 (0.95 to 2.05)	**<0.0001**
Exacerbation frequency, no./patient/yr	0.26 (0.14 to 0.38)	**<0.0001**	0.13 (–0.01 to 0.27)	0.066	0.46 (0.32 to 0.60)	**<0.0001**
Change in MMRC	−0.19 (–0.39 to 0.01)	0.062	0.44 (0.22 to 0.66)	**<0.0001**	0.03 (–0.19 to 0.25)	0.81
Change in SGRQ	−4.67 (–7.14 to –2.20)	**0.0002**	8.78 (6.11 to 11.45)	**<0.0001**	1.46 (–1.24 to 4.16)	0.82
Change in 6-MWD, ft	−7.30 (–65.98 to 51.38)	0.8100	−66.6 (–130.42 to –3.06)	**0.0400**	−60.80 (–125.01 to 3.49)	0.064

Definition of abbreviations: 6-MWD = 6-minute walk distance; CAT = COPD Assessment Test; CI = confidence interval; HADS-A = Hospital Anxiety and Depression Scale-Anxiety score; HADS-D = Hospital Anxiety and Depression Scale-Depression score; MMRC = Modified Medical Research Council; persistent chronic bronchitis+ = subjects positive at phase 1/positive at phase 2 for chronic bronchitis; persistent chronic bronchitis– = subjects negative at phase 1/negative at phase 2 for chronic bronchitis; SGRQ = St. George's Respiratory Questionnaire.
Entries in boldface indicate a significant difference.
*Age, race, sex, FEV_1% predicted, and smoking status as covariates.

Table 3. Multinomial logistic regression

	Resolved Chronic Bronchitis*		New Chronic Bronchitis*		Persistent Chronic Bronchitis+*	
	OR	95% CI	OR	95% CI	OR	95% CI
Univariable						
Quitting smoking†	3.436	2.211–5.339	1.120	0.588–2.133	1.362	0.708–2.620
Resuming smoking†	1.190	0.364–3.999	3.369	1.679–8.087	0.996	0.232–4.277
Persistent smoking†	1.806	1.239–2.634	1.734	1.178–2.551	2.784	1.902–4.074
Smoking, pack-years	1.008	1.001–1.015	1.013	1.007–1.020	1.020	1.014–1.026
GERD	1.429	1.016–2.010	1.361	0.939–1.972	1.563	1.064–2.255
Male sex	1.547	1.110–2.155	1.394	0.976–1.990	1.462	1.021–2.093
White race	1.154	0.799–1.688	1.116	0.751–1.657	1.524	0.994–2.336
FEV_1% pred	0.983	0.977–0.989	0.981	0.975–0.988	0.977	0.971–0.984
Multivariable						
Quitting smoking†	4.289	2.689–6.842	1.328	0.682–2.585	1.859	0.936–3.691
Resuming smoking†	1.449	0.421–4.984	4.585	2.008–10.471	1.350	0.301–6.041
Persistent smoking†	2.867	1.872–4.392	2.621	1.677–4.096	5.767	3.702–8.983
Smoking, pack-years	1.001	0.993–1.008	1.007	1.000–1.015	1.013	1.006–1.020
GERD	1.572	1.099–2.249	1.430	0.970–2.109	1.697	1.145–2.515
Male sex	1.493	1.056–2.111	1.227	0.847–1.778	1.242	0.846–1.823
White race	1.651	1.089–2.503	1.327	0.843–2.090	2.287	1.415–3.697
FEV_1% pred	0.982	0.975–0.998	0.979	0.972–0.986	0.973	0.966–0.980

Definition of abbreviations: CI = confidence interval; FEV_1% pred = FEV_1 expressed as a percentage of the predicted value; GERD = gastroesophageal reflux disease; OR = odds ratio; persistent chronic bronchitis+ = subjects positive at phase 1/positive at phase 2 for chronic bronchitis.
*Versus persistent chronic bronchitis–.
†Versus persistent ex-smokers.

without many differences in these groups to account for the resolution of chronic bronchitis.

In 1974, Niewoehner and colleagues demonstrated that inflammatory changes were present in the peripheral airways of young smokers without lung disease who died suddenly (18). Since then, many studies have confirmed the relationship between smoking and chronic bronchitis, associated with or without COPD. In phase 1 of the COPDGene Study, we showed that current smoking conferred an OR of 3.53 for chronic bronchitis in those with COPD (7). In a 30-year longitudinal study, Pelkonen and colleagues determined a prevalence of chronic bronchitis in 42% of current smokers, regardless of the presence of airflow obstruction (19). A meta-analysis of 121 studies revealed that smoking conferred an overall relative risk of 3.41 for chronic bronchitis (20).

There is additional objective evidence associating smoking with chronic bronchitis. Using 24-hour cough monitoring in those with and without COPD, Sumner and colleagues found the greatest cough frequency in current smokers with COPD, followed by ex-smokers with COPD and healthy current smokers (21). In that study, reported sputum production, smoking history, and current smoking all predicted cough frequency. Two bronchoscopic studies of smokers with and without airflow obstruction have shown that current smoking was associated with increased large-airway epithelial mucin stores (22, 23).

Our findings are important because they support the concept that unlike the permanent damage due to emphysema, many of the pathophysiological changes of bronchitis are potentially reversible to some extent (24). Although chronic bronchitis has been assumed to be a chronic condition, the current data address the knowledge gap of whether smoking cessation results in resolution of chronic bronchitis.

Prior cohort studies have not addressed this phenomenon, and existing cross-sectional data are conflicting. In the aforementioned meta-analysis (20), which was not designed to answer this question, the relative risk of ex-smoking for chronic bronchitis was lower than that of current or ever-smoking but was not less than 1 (relative risk, 1.63; 95% CI, 1.50–1.78). Smoking cessation has been demonstrated to improve small-airway function in smokers without airflow obstruction and to reduce airway inflammation (25–27). A study using pathological tissue from subjects with COPD found that long-term

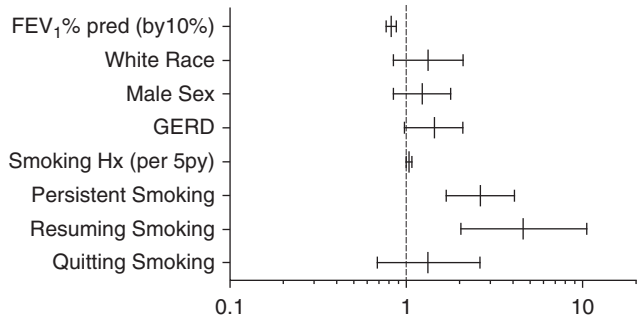

Figure 2. Odds ratios for the development of new chronic bronchitis. FEV_1% pred = FEV_1 expressed as a percentage of the predicted value; GERD = gastroesophageal reflux disease.

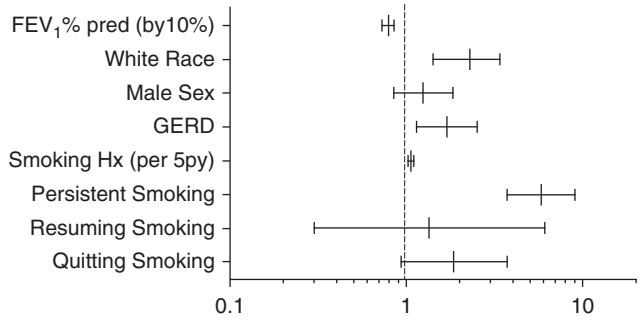

Figure 3. Odds ratios for persistent chronic bronchitis+.

quitters (≥3.5 yr) had decreased evidence of bronchial goblet cell area compared with current smokers (28). However, the lack of difference in epidermal growth factor receptor expression between groups in that study suggests that smoking cessation does not always stop the ongoing stimulus for mucus production in those with COPD.

Indeed, although we found that those with resolved chronic bronchitis included the greatest proportion of quitters (23.5%), smoking cessation could also be associated with persistent chronic bronchitis (8.9%) or new chronic bronchitis (8.8%), which is consistent with the presence of ongoing inflammation or exposure to other risk factors. Similarly, although the highest proportion of those who had resumed smoking were in the new chronic bronchitis group, this proportion was only 6.6%, suggesting that other factors such as occupational exposures may be involved.

That those with chronic bronchitis at any point had worse lung function than those in the persistent chronic bronchitis– group agrees with and extends our previous demonstration that lung function was an independent variable of chronic bronchitis in the COPDGene cohort (7). However, the finding that change in lung function did not differ among the resolved chronic bronchitis, new chronic bronchitis, and persistent chronic bronchitis groups adds a new and interesting dimension to this issue. It implies that unlike the close correlation of chronic bronchitis with adverse symptoms and health-related quality of life, development or resolution of chronic bronchitis tracks less directly with loss of lung function.

Contrary to our hypothesis, we did not find a significant difference in lung function decline in any of the three chronic bronchitis groups compared with subjects in the persistent chronic bronchitis– group. FEV_1 decrease was greater in smokers and in those with higher lung function, as established in other studies (29). Our data validate the findings in the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) Study, which showed no excess decline using the classic definition of chronic bronchitis. However, it contrasts with other literature demonstrating accelerated lung function decline with chronic bronchitis, when using variable definitions such as chronic mucus hypersecretion and chronic cough and phlegm (5, 30–32). Our negative findings may have resulted because follow-up was too short, because the classic chronic bronchitis definition is too exclusive, or because of the small number of subjects (n = 433) in our cohort who had ever had chronic bronchitis.

It is worth discussing the differences in prescription patterns between groups. More respiratory medications were prescribed for patients in the resolved chronic bronchitis, new chronic bronchitis, and persistent chronic bronchitis+ groups compared with patients in the persistent chronic bronchitis– group. Although it is possible that the new prescriptions of respiratory medications may have resulted in resolution of chronic bronchitis in some but not all subjects, the percentage of new prescriptions in the resolved chronic bronchitis group in general did not differ from those of the new chronic bronchitis or persistent chronic bronchitis+ groups, suggesting that new prescriptions of respiratory medications either did not affect chronic bronchitis or that the prescription of these respiratory medications was in reaction to the presence of chronic

Table 4. New respiratory medication prescriptions from phase 1 to phase 2

	Persistent Chronic Bronchitis– (*n = 1,260*)	Resolved Chronic Bronchitis (*n = 153*)	New Chronic Bronchitis (*n = 126*)	Persistent Chronic Bronchitis+ (*n = 126*)	Overall *P* Value
SABA	10.5*	12.9*	27.2†	12.9	<0.0001
SAMA	2.0*†‡	5.1	6.0	4.6	<0.0001
SABA/SAMA	6.5*†‡	6.4	12.1	13.6	<0.0001
LABA	1.7†‡	1.9	3.8	2.3	0.001
ICS/LABA	6.6*†‡	14.7	19.5	19.4	<0.0001
ICS	2.9†	3.8	5.3	7.6	0.029
OCS	1.4†	2.6	2.3	6.1	0.003
LAMA	5.8*†‡	16.5	14.9	14.8	<0.0001

Definition of abbreviations: ICS = inhaled corticosteroids; LABA = long-acting β-agonist; LAMA = long-acting muscarinic antagonist; OCS = oral corticosteroids; persistent chronic bronchitis+ = subjects positive at phase 1/positive at phase 2 for chronic bronchitis; persistent chronic bronchitis– = subjects negative at phase 1/negative at phase 2 for chronic bronchitis; SABA = short-acting β-agonist; SAMA = short-acting muscarinic antagonist. Values are expressed as a percentage of the group value.

*$P < 0.05$ compared with new chronic bronchitis.

†$P < 0.05$ compared with persistent chronic bronchitis+.

‡$P < 0.05$ compared with resolved chronic bronchitis.

bronchitis or the associated increases in exacerbations or dyspnea in these three groups. The data are inconclusive to suggest one reason over another. Unfortunately, we do not have data on macrolide antibiotics or roflumilast, so we are unable to draw any conclusions regarding the potential effects of these medications on chronic bronchitis status.

Limitations

Despite the significance of our findings, our study has some limitations that are worthy of mention. First, the low prevalence of chronic bronchitis in a less than optimally sized cohort might have limited our power to detect some differences between groups, especially changes in lung function. The Copenhagen City Heart Study, which analyzed 9,435 subjects with a similar prevalence of chronic bronchitis, did find significant differences in lung function decline at 5 years (5). Second, phase 1 and phase 2 of the COPDGene Study were two cross-sectional analyses 5 years apart, so we are assuming that if a subject was chronic bronchitis negative at both visits then they were not positive in between visits, and that if they were chronic bronchitis positive at both visits then they were not negative in between visits. However, if misclassification bias did not occur, it is possible that the differences found between groups would be greater. Third, data on exacerbations and some respiratory symptoms were based on patient report and not validated by medical records.

Fourth, the increases seen in SGRQ scores among the chronic bronchitis–positive groups may have been a result of the increased cough and sputum, as the SGRQ has questions directly related to these respiratory symptoms. However, we must point out that the new chronic bronchitis group had an increase in SGRQ of more than nine points, which cannot be attributed to cough and phlegm alone. Furthermore, the SGRQ asks questions regarding symptoms in the last 4 weeks, whereas the classic chronic bronchitis definition requires a time span of 2 years; thus it is possible that some individuals could be classic chronic bronchitis positive but SGRQ chronic bronchitis negative (using a definition described previously [33]). In this analysis of the phase 1 data, 12.6% of those who were classic chronic bronchitis positive were SGRQ chronic bronchitis negative. In addition, the variable time between smoking cessation and phase 2 visits may not have been sufficient to see the full effects on resolution of chronic bronchitis and outcomes, and it is unclear how long ago smoking cessation was achieved in those who quit.

Finally, we still do not understand why some subjects newly developed chronic bronchitis or had persistent chronic bronchitis despite not smoking. We have previously shown that occupational and dust exposures resulted in increased symptoms of cough, phlegm, and wheeze independently of smoking history and lung function (14). Data on these exposures, which may contribute to development of chronic bronchitis, were not available in phase 2 of the COPDGene Study.

Conclusion

We have shown that chronic bronchitis is not necessarily a chronic condition and can vary over time, with the main determinant of this variation being smoking status. Persistently or resuming smoking cigarettes increases the odds of having or developing chronic bronchitis, and quitting smoking increases the odds of the resolution of chronic bronchitis. Those with chronic bronchitis at any time had worse symptoms and outcomes than those persistently without chronic bronchitis, but the largest decline in health-related quality of life and the greatest increase in dyspnea occurred in those with newly developed chronic bronchitis.

By showing that chronic bronchitis is modifiable, our analysis highlights the significance of uncovering potential mechanisms involved in smoking-related lung disease. This has significant implications for the practicing physician to ascertain respiratory symptoms at every visit. Our data reinforce the notion of continued surveillance of smoking status and respiratory symptoms, and provide further evidence of the benefits of smoking cessation. Whether chronic bronchitis resolution eventually decreases symptoms and improves outcomes requires more long-term study and remains to be determined. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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