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The clinical impact of non-obstructive chronic bronchitis in current and former smokers☆

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Summary
Background: As the clinical significance of chronic bronchitis among smokers without airflow obstruction is unclear, we sought to determine morbidity associated with this disorder.
Methods: We examined subjects from the COPDGene study and compared those with $FEV_1/FVC \geq 0.70$, no diagnosis of asthma and chronic bronchitis as defined as a history of cough and phlegm production for ≥3 months/year for ≥2 years (NCB) to non-obstructed subjects without chronic bronchitis (CB-). Multivariate analysis was used to determine factors associated with and impact of NCB.
Results: We identified 597 NCB and 4283 CB- subjects. NCB participants were younger (55.4 vs. 57.2 years, $p < 0.001$) with greater tobacco exposure (42.9 vs. 37.8 pack-years, $p < 0.001$) and more

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often current smokers; more frequently reported occupational exposure to fumes (52.8% vs. 42.2%, $p < 0.001$), dust for ≥1 year (55.3% vs. 42.0%, $p < 0.001$) and were less likely to be currently working. NCB subjects demonstrated worse quality-of-life (SGRQ 35.6 vs. 15.1, $p < 0.001$) and exercise capacity (walk distance 415 vs. 449 m, $p < 0.001$) and more frequently reported respiratory "flare-ups" requiring treatment with antibiotics or steroids (0.30 vs. 0.10 annual events/subject, $p < 0.001$) prior to enrollment and during follow-up (0.34 vs. 0.16 annual events/subject, $p < 0.001$). In multivariate analysis, current smoking, GERD, sleep apnea and occupational exposures were significantly associated with NCB.

Conclusions: While longitudinal data will be needed to determine whether NCB progresses to COPD, NCB patients have poorer quality-of-life, exercise capacity and frequent respiratory events. Beyond smoking cessation interventions, further research is warranted to determine the benefit of other therapeutics in this population.

Clinical Trials Registration # NCT00608764 (http://clinicaltrials.gov/show/NCT00608764).

Link to study protocol: http://www.copdgene.org/sites/default/files/COPDGeneProtocol-5-0_06-19-2009.pdf.

Abbreviations

NCB	non-obstructive chronic bronchitis
CB-	chronic bronchitis symptoms absent
FEV_1	forced expiratory volume in the first second
FVC	forced vital capacity
SGRQ	Saint-George's Respiratory Questionnaire
GERD	gastro-esophageal reflux disease
COPD	chronic obstructive pulmonary disease
QOL	quality-of-life
GOLD	Global Initiative for Obstructive Lung Disease
NHANES	National Health and Nutrition Examination Survey
SF-36	Short Form Health Survey, 36-item
SF-36 PCS	physical component score of the SF-36
SF-36 MCS	mental component score of the SF-36
BMI	body mass index
MMRC	Modified Medical Research Council Dyspnea Score
6MWD	six-minute walking distance
OR	odds ratio
OSA	obstructive sleep apnea
MCID	minimal clinically important difference

Introduction

The pathways involved in the development of COPD and lung cancer after exposure to tobacco smoke involve airway inflammation, oxidative damage and impaired repair [1,2]. Chronic cough and phlegm in smokers have also been correlated with pathologic, functional, and molecular signatures of chronic inflammation [3—5]. Cross-sectional studies have validated the existence of a chronic bronchitis phenotype among smokers with established airway obstruction [6,7]. While several population based studies have reported poorer quality-of-life (QOL), more frequent infections and accelerated lung function decline [8—11] in these patients, the impact of chronic bronchitis in those without airflow obstruction is less clear. Epidemiologic studies suggest chronic bronchitis is a risk factor for incidental airflow obstruction, but mainly within subjects younger than 50 years of age [8]. Therefore is possible that in some patients, non-obstructive chronic bronchitis (NCB) is an early presentation of COPD whereas in others it may be a distinct disorder. In the absence of airflow obstruction, however, this group of patients is typically overlooked with respect to assessment and the development of treatments. Using participants from the COPDGene study who were all current or former smokers without airflow obstruction and without history of asthma, in a cross-sectional design and with additional follow-up for two years, we hypothesized that when compared to those without chronic bronchitis symptoms, subjects with non-obstructive chronic bronchitis (NCB) would have worse quality of life, poorer exercise tolerance and more frequent respiratory events at baseline and during follow-up.

Methods

Patient selection

Briefly, the COPDGene Study (http://www.copdgene.org/), described in detail previously [12] is a NHLBI-funded multicenter investigation of the genetic epidemiology of smoking-related lung disease, which recently completed inclusion of the baseline cohort of more than 10,000 participants (Clinical Trials Registration # NCT00608764). Subjects were enrolled between January 2008 and June 2011. Inclusion criteria include ability to give informed consent; age 45—80 years; cigarette smoking ≥10 pack years; and willingness to undergo study-related testing including spirometry and a chest CT scan. For our analysis, all subjects

were former or current smokers with ≥10 pack-years, not meeting GOLD criteria for COPD (absence of airflow obstruction with a post-bronchodilator FEV_1/FVC (forced vital capacity) ratio ≥0.7), with no history of physician-diagnosed asthma, selected from the full COPDGene cohort of 10,276 individuals. This research protocol was approved by the institutional review board at each participating institution (University of Michigan Health System Research Committee IRB approval HUM000014973, 07/16/2010). All participants provided written informed consent.

Data collection

Self-administered questionnaires were used to collect demographic data, smoking, occupational exposures and medical history. Coexistent diseases and chronic conditions were self-reported. Participants were presented with the question "Have you ever been told by a physician that you have…" and a list of different diseases. The MMRC scale was used to evaluate the degree of dyspnea [13]. Patients underwent spirometry using the EasyOne™ spirometry system (Zurich, Switzerland) before and after the administration of short-acting bronchodilator (albuterol). NHANES III data was used as predictive values [14], and quality control was performed for spirometry tests with both an automated system and manual review.

Health-related quality-of-life measurements

We included two QOL measures widely used in respiratory medicine research: the SGRQ total score and sub-scores (impact, symptoms, activity) [15], and the Short Form-36 Health Survey (SF-36), with its physical component (SF-36 PCS) and mental component scores (SF-36 MCS) [16]. SGRQ scores range from 0 to 100; higher scores indicate more severe impact. SF-36 scores are reported from 0 to 100, with lower scores indicating more limitations. Although SGRQ is a QOL instrument used mainly among COPD patients, there are reports of it use in "healthy smokers" and persons without airway obstruction [17,18]. Results of SGRQ were available for all participants. SF-36 was implemented after the study was initiated; henceforth the results were available for 2663 participants. Participants who responded to SF-36 were more frequently of female gender and older, and less frequently of African American race and current smokers. To account for these differences, all sociodemographic variables were maintained as covariates in models examining differences in QOL, measured by SF-36. The differences between participants with and without data on SF-36 are presented in the Supplementary Files. The clinically important difference for SF-36 is 4—6 points for analysis of groups [19,20].

Definition of chronic bronchitis and respiratory events

The definition of chronic bronchitis was based on baseline history of cough and phlegm production for ≥3 consecutive months per years for two or more years, derived from a modified form of the American Thoracic Society Diffuse Lung Disease 1978 Respiratory Epidemiology questionnaire [21]. In this manner subjects meeting these criteria were classified as NCB vs. those not meeting these criteria, CB-. Respiratory events were defined by use of antibiotic and/or steroid or hospital admission for a respiratory "flare-up". Prospective respiratory event data was captured through a longitudinal follow-up protocol conducted every six months by an automated telephonic or web based inquiry. Subjects not reached by the automated system were contacted by a research coordinator. October, 31 2012 was used as the cutoff date for available longitudinal data.

Statistical analysis

Descriptive statistics with proportions, or means and their standard deviation were used, when appropriate, to describe demographics, lung function, symptoms, individual comorbidities, and their score. The impact of demographics, socioeconomic characteristics, prior occupational exposures, and tobacco use on the presence of chronic bronchitis was evaluated with stepwise forward selection logistic regression models where gender, age, BMI, high school education (a relevant descriptor of socioeconomic status in America), smoking status, tobacco pack-years, FEV_1% and clinical center were required model elements. Zero inflated negative binomial regression was used to model respiratory events due to their skewed distribution with zero events being most frequent. The independent effect of chronic bronchitis on dyspnea, walking distance, and measures of QOL was evaluated with multivariate models adjusted for gender, age, BMI, current smoking, pack-years, FEV_1% predicted and clinical center. The selection of the covariates for the multivariate models was based on their known roles in determining impact and outcomes in COPD. All statistical analyses were conducted using SAS 9.2 statistical software (SAS Corporation, Cary, N.C.). p-Values <0.05 were considered significant.

Results

Of 4880 subjects with a post-bronchodilator FEV_1/FVC ratio ≥0.7 and no history of asthma, 597 (12.2%) met criteria for NCB and 4283 did not, CB-. Table 1 shows demographic characteristics, lung function, respiratory exposures, and comorbidities stratified by presence of chronic bronchitic symptoms. Compared with CB- group, NCB subjects were younger (55.4 vs. 57.2 years, $p < 0.001$) and had a greater proportion of men (58.5% vs. 53.6%, $p = 0.01$). NCB subjects also had a higher BMI and were more frequently current smokers with greater pack-year history. Occupational exposures also differed with NCB subjects reporting with greater frequency having been exposed at work to dust or smoke/fumes. FEV_1% predicted was slightly lower for NCB subjects, 89.6% vs. 92.6%, $p < 0.001$.

Despite the fact that NCB subjects were actually younger, fewer NCB subjects were actively working. We also examined comorbidity frequency between groups. Compared with the CB- group, more NCB participants also reported history of GERD, sleep apnea, and diabetes. The difference in cardiovascular disease bordered on statistical significance. No difference in osteoporosis was seen.

Table 1 Demographics, work history, lung function and comorbidities stratified by presence of chronic bronchitis ($n = 4880$).

	Chronic bronchitic symptoms present ($n = 597$)	Chronic bronchitic symptoms absent ($n = 4283$)	p-Value
Demographics			
Age in years (mean [s.d.])	55.4 (7.6)	57.2 (8.5)	<0.001
Female gender (%)	41.5	46.4	0.02
African American (%)	38.9	40.4	0.47
Education HS and below (%)	41.5	37.9	0.09
BMI in kg/m^2 (mean [s.d.])	30.0 (6.7)	29.1 (6.0)	0.004
Tobacco and occupational exposures			
Pack-years smoked (mean [s.d.])	42.9 (23.1)	37.8 (20.7)	<0.001
Currently smokes (%)	79.4	57.2	<0.001
Exposed to dust at job (%)	55.3	42.0	<0.001
Exposed to smoke/fumes at work (%)	52.8	42.2	<0.001
Currently works (%)	29.7	37.3	<0.001
Lung function			
FEV_1% predicted (mean [s.d.])	89.6 (16.6)	92.6 (15.2)	<0.001
FEV_1/FVC (mean [s.d.])	78.1 (5.4)	78.4 (5.2)	0.23
Comorbidities (%)			
Hypertension	41.5	37.7	0.071
Hypercholesterolemia	37.4	35.6	0.404
Gastroesophageal reflux	24.3	19.1	0.003
Sleep apnea	22.3	12.9	<0.001
Diabetes	17.3	12.4	<0.001
Cardiovascular disease[a]	13.7	11.0	0.05
Osteoporosis	5.0	5.5	0.64

[a] Cardiovascular disease includes history of myocardial infarction, coronary artery disease, angioplasty, coronary artery bypass graft, congestive heart failure, peripheral vascular disease, transient ischemic attack or stroke.

Symptoms, functional impact, and QOL differences are summarized in Table 2. NCB subjects reported more severe dyspnea. NCB subjects exhibited poorer (higher) total SGRQ scores as well as its components. NCB subjects also scored poorer (lower) for both the SF-36 PCS and SF-36 MCS. The NCB group walked a shorter distance on the 6MWD test. At baseline, more NCB subjects reported having had a respiratory event in the prior year treated with antibiotics and/or steroids than CB- subjects (0.30 vs. 0.10 events/subject, $p < 0.001$). Follow-up data for one year or longer were available in 2897 CB- subjects (67.6%) and 359 NCB subjects (60.1%), with a mean follow-up period of 2.0 years/patient. A comparison of participants with at least one year follow-up with those with less than one year is presented in the Supplementary Files. During follow-up, NCB subjects also reported higher annual rate of respiratory events requiring treatment with either antibiotics or steroids than CB- subjects (0.34 vs. 0.16 annual events/subject, $p < 0.001$). For reference, the mean annual per-person exacerbation rate in COPDGene COPD subjects during the same period was 0.25 for GOLD I and 0.47 for GOLD II subjects. NCB subjects were also more likely to be on respiratory medications across all medication classes than CB- subjects. Similar analyses but adjusted for age, gender, BMI, current smoking, pack-years, FEV_1% and clinical center are in Table 4. The strength and direction of relationships between chronic bronchitis and dyspnea, 6MWD, SGRQ and SF-36 scores and respiratory event frequency were all maintained.

Table 3 shows the association of the different hypothesized potential factors associated with the presence of chronic bronchitis among our non-obstructed cohort in a logistic regression model additionally adjusted for age, gender, smoking status, BMI, FEV_1% predicted and clinical center of recruitment. The strongest associations with chronic bronchitis were current smoking, followed by a history of sleep apnea, diabetes, and GERD. Occupational exposure to gas, smoke or chemical fumes at work was also significantly associated with NCB. Tobacco pack-years and second hand smoke exposure at work also had small but statistically significant associations with NCB. African American race was less likely to be associated with NCB. The effects of gender and FEV_1% were not significant.

Discussion

This analysis of a large cross-sectional multicenter study of current and former smokers without airflow obstruction demonstrates significant symptoms and morbidity in the subpopulation who experience chronic bronchitis. Specifically, in analyses adjusted for relevant confounders, we demonstrate that subjects with NCB (1) report more dyspnea and poorer quality of life; (2) demonstrate poorer exercise capacity; and (3) experience more frequent treated respiratory events. We also demonstrate that subjects with NCB are less likely to be actively working and more likely to be on inhaled pharmacologic therapies as opposed to CB- individuals. Multivariate analysis demonstrates that the factors with strongest associations with NCB in this population include current smoking, GERD, OSA

Table 2 Symptoms burden, and quality of life stratified by presence of chronic bronchitis ($n = 4880$).

	Chronic bronchitic symptoms present ($n = 597$)	Chronic bronchitis symptoms absent ($n = 4283$)	p-Value
Symptoms			
MMRC score			
MMRC score 0–1 (%)	50.9	78.5	<0.001
MMRC score 2–4 (%)	49.1	21.5	
MMRC dyspnea score (mean [s.d.])	1.6 (1.5)	0.7 (1.1)	<0.001
Nasal symptoms	64.8	36.6	<0.001
Ocular symptoms	54.6	33.4	<0.001
Ever previously diagnosed with pneumonia (%)	36.4	25.3	<0.001
Frequency of respiratory "flare-up" in the year prior to inclusion (mean [s.d.])	0.30 (0.8)	0.10 (0.4)	<0.001
Frequency of respiratory "flare-ups"/year during follow-up (mean [s.d.])[b]	0.3 (0.7)	0.16 (0.7)	<0.001
Functional Status			
6MWD in meters (mean [s.d.])	415 (116)	449 (110)	<0.001
Prior Diagnosis of COPD			
COPD diagnosed by Health Professional (%)	18.6	6.8	<0.001
Use of Respiratory Medications			
Short-acting beta-agonists (%)	17.6	6.5	<0.001
Inhaled corticosteroids (%)	2.9	0.8	<0.001
Long-acting beta-agonists (LABA) (%)	1.2	0.2	<0.001
Combined LABA inhaled corticosteroids (%)	8.8	2.5	<0.001
Long-acting anticholinergics (%)	5.4	2.0	<0.001
QOL Measures (All mean [s.d.])			
SGRQ			
SGRQ total	35.6 (22.2)	15.1 (16.4)	<0.001
SGRQ symptoms	49.8 (20.8)	18.4 (19.1)	<0.001
SGRQ activity	45.7 (28.9)	24.4 (25.1)	<0.001
SGRQ impact	25.9 (22.2)	8.8 (13.7)	<0.001
SF-36[a]			
SF-36 Physical Component	41.8 (10.8)	48.2 (9.7)	<0.001
SF-36 Mental Component	43.5 (13.1)	50.4 (10.6)	<0.001

[a] SF-36 was available for 2213 participants.
[b] Longitudinal follow-up for more than one year available for 359 CB+ and 2897 CB− subjects.

Table 3 Multivariate models to determine factors associated with the presence of non-obstructive chronic bronchitis.[a]

	Model 1	Model 2	Model 3
Current Smoking	2.91 (2.33, 3.63)	3.34 (2.66, 4.20)	3.31 (2.59, 4.24)
African American Race		0.53 (0.43, 0.65)	0.53 (0.43, 0.65)
Age (per year increment)		NS	NS
Exposed to dust at job		1.37 (1.11, 1.69)	1.34 (1.09, 1.65)
Exposed to smoke at work		1.26 (1.02, 1.54)	1.22 (1.00, 1.50)
Tobacco pack-years		1.00 (1.00, 1.01)	1.00 (1.00, 1.01)
BMI (kg/m^2)			
Normal or overweight (18.5–29.9)		Ref	Ref
Underweight (<18.5)		NS	NS
Obesity (≥30.0)		1.34 (1.12, 1.60)	1.20 (1.00, 1.45)
FEV_1% predicted		NS	NS
Sleep Apnea			1.53 (1.16, 2.04)
Gastroesophageal Reflux Disease			1.33 (1.07, 1.66)
Diabetes			1.38 (1.07, 1.78)

[a] Model 1 includes current smoking. Model 2 additionally adjusted for work exposures, demographics and FEV_1% predicted. Model 3 additionally adjusted for comorbidities. All models additionally adjusted for clinical center of recruitment.

Table 4 Individual adjusted models for symptom and quality of life measures for presence of non-obstructive chronic bronchitis.[a]

	Parameter estimate for presence of non-obstructive chronic bronchitis (95% CI)
	Adjusted model[a]
MMRC Dyspnea	0.75 (0.65, 0.84)
Distance walked (m)	−13.74 (−21.45, −6.03)
SGRQ Total	17.11 (15.78, 18.45)
SGRQ Impact	14.56 (13.36, 15.76)
SGRQ Activity	16.42 (14.44, 18.41)
SGRQ Symptoms	27.54 (25.99, 29.10)
[b]SF-36 PCS	−5.20 (−6.38, −4.02)
[b]SF-36 MCS	−5.10 (−6.44, −3.75)
Fold increase in treated respiratory events/year during follow-up[c]	2.47 (1.87, 3.27)

[a] Each model is adjusted for age, gender, BMI, current smoking, pack-years smoked, FEV_1% predicted, and clinical center of recruitment.
[b] SF-36 was available for 2213 participants.
[c] Zero inflated negative binomial model used for respiratory events, including only those with at least one year follow-up (n = 3256); all other models used generalized linear regression model.

and work place exposures to gas, smoke, chemicals or other fumes.

While chronic bronchitis in obstructed individuals has been previously described and associated with worse QOL and poorer outcomes [6], the prevalence and significance of NCB is less well established. Our findings of 13% NCB frequency among current or former smokers are higher than reported in other non-COPD cohorts or studies which included never smokers [22,23], and likely reflects the fact that our observational study required a 10 pack-year smoking history as requirement for participation. The higher frequency of chronic bronchitis in our cohort, compared with studies within the general population (2.6% in the European Community Respiratory Health Survey [ECRHS] [22] and 2.5% in the PLATINO [*Proyecto Latinoamericano de Investigacion en Obstruccion Pulmonar*] study conducted in South America [23]), underscores the role of tobacco in the development of CB among our participants, even prior to the development of bronchial obstruction.

We demonstrate significantly poorer symptoms and quality of life for NCB subjects. The unadjusted mean difference in SGRQ between those with and without CB was approximately 20 points which well exceeds the minimal clinically important difference (MCID) of 4 for SGRQ in COPD [24]. In fact, the mean SGRQ for NCB subjects is higher than the reported scores for smokers with no obstructive physiology [17,18], and is on par with the mean SGRQ for GOLD Stage II subjects in the COPDGene cohort (COPDGene cohort mean 33, SD 22; ECLIPSE cohort mean 42, SD 21) [25]. The impact of CB symptoms on QOL extends beyond disease-specific QOL, as demonstrated by the existent differences in QOL using generic instruments, such as SF-36, whose scores were also beyond the MCID. Our analyses also demonstrated more limited exercise capacity in NCB subjects with a difference in walk distance of approximately 34 m which is statistically significant. Although there is still debate about the MCID for 6MWD in COPD, with some authors suggesting values of 26–80 m [26,27], a value of 34 m is within the reported MCID in the most recent literature among COPD patients [28,29]. Further underscoring the clinical significance of NCB is the fact that significantly fewer NCB subjects were actively working as compared to CB- subjects.

NCB subjects also reported respiratory flare-ups treated with antibiotics or steroids in much greater frequency than those without. The mean frequency of such events during longitudinal follow-up was 0.34 events/subject/year as compared to GOLD I subjects in the COPDGene cohort (0.26 events/subject/year), and close to the reported frequency of exacerbations requiring treatment in COPD Stage II participants in the ECLIPSE project (0.37 events/patient/year) [25]. In addition, nearly 18% of NCB subjects had been given a diagnosis of COPD by a health professional despite absence of airflow obstruction on spirometry; almost 9% of such subjects had been prescribed ICS/LABA combination therapy, even in the absence of data that such agents can successfully relieve symptoms or prevent respiratory events in these individuals.

Participants with NCB had greater pack-year smoking history and were more frequently current smokers; both independent risk factors were retained in multivariate models. Smoking is the most important risk factor for presence of chronic bronchitis [8,23,30]. However, prior analysis suggests that differences in smoking habits do not completely explain the variation in frequency of chronic bronchitis [22]. While an association between occupational dust and fumes exposure and chronic bronchitis has previously been reported [23], we demonstrate that such exposure remains significant in multivariate models adjusted for smoking and other relevant confounders. A detailed description of each participant's job was not included in the analysis, but every effort was made to identify jobs with exposure to dust, fumes or smoke. Our current analysis confirms that sleep apnea and GERD are also independent and potentially modifiable risk factors for NCB among smokers. While an association between "bronchitic" symptoms and OSA have been previously reported [31,32], these studies were not clearly in subjects without airflow obstruction. Interestingly, sputum neutrophilia and IL-8 have been reported in subjects with OSA indicating a relationship between OSA and bronchial inflammation [33]. In a small series of 16 patients, radiologically assessed bronchial wall thickness was correlated with apnea-hypopnea index [34]. It has been hypothesized that mechanical trauma related to intermittent airway occlusion, nocturnal hypoxemia leading to ischemia-reperfusion injury and oxygen free radical production or low-grade systemic inflammation related to obesity may help to explain this relationship [35]. An association between GERD and both COPD and cough have been well established [36], so perhaps it is not surprising that a relationship should also exist between GERD and NCB. The mechanism for these associations is not clear; while it has previously been

suggested that micro-aspiration events might contribute to this association, recent data suggest this is less likely to be the case [37]. In any case, further elucidation of the factors and mechanisms related to NCB, probably a distinct clinical disorder, is underscored by epidemiologic evidence suggesting that bronchitic symptoms with no airflow limitation could be an early marker of susceptibility and risk for COPD [8,38]. Longer follow-up of the current cohort is required to answer the question about risk of developing COPD.

Our study has several limitations. Our population is restricted to current or former smokers; therefore the results cannot be extrapolated to the general population. We also used a very specific definition for NCB, which includes cough and sputum production which has been used by others but cough and sputum were not directly quantified. Self-report of comorbidities by participants is a potential limitation of this study. However, the design of the questions asks for physician-diagnosed conditions, to improve the certainty of the measurements, a method that in other surveys has been proved to have high sensitivity and specificity for prevalent diseases [39]. Our study has the strength of being a multicenter, large trial collecting a comprehensive array of clinical, demographic, and functional data.

Conclusions

In conclusion, we demonstrate that NCB among current and former smokers is associated with greater dyspnea, poorer health status and poorer exercise capacity. NCB subjects also report more frequent treated respiratory events and are more likely to not be currently working as opposed to current and former smokers without chronic bronchitic symptoms. Longitudinal data will be needed to determine whether and in which patients NCB progresses to COPD. However, even in the absence of airflow obstructions, these individuals have significant symptoms and respiratory events requiring treatment. Modifiable risk factors we identified include current smoking in addition to work place exposures of fumes and smoke. These data would suggest that preventive measures for NCB patients including as smoking cessation and appropriate occupational health precautions may be just as important as they are in individuals with established airflow obstruction. However, these data also highlight the need for future investigative efforts to identify and design potential therapeutic interventions for this patient population.

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Dr. C.H. Martinez: contributed to conceiving and writing the manuscript, data analysis and clinical interpretation of the data, and approving the final draft of the manuscript.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.rmed.2013.11.003.

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