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Association of Nonobstructive Chronic Bronchitis With Respiratory Health Outcomes in Adults

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IMPORTANCE Chronic bronchitis has been associated with cigarette smoking as well as with e-cigarette use among young adults, but the association of chronic bronchitis in persons without airflow obstruction or clinical asthma, described as nonobstructive chronic bronchitis, with respiratory health outcomes remains uncertain.

OBJECTIVE To assess whether nonobstructive chronic bronchitis is associated with adverse respiratory health outcomes in adult ever smokers and never smokers.

DESIGN, SETTING, AND PARTICIPANTS This prospective cohort study included 22 325 adults without initial airflow obstruction (defined as the ratio of forced expiratory volume in the first second [FEV_1] to forced vital capacity [FVC] of <0.70) or clinical asthma at baseline. The National Heart, Lung, and Blood Institute (NHLBI) Pooled Cohorts Study harmonized and pooled data from 9 US general population–based cohorts. Thus present study is based on data from 5 of these cohorts. Participants were enrolled from August 1971 through May 2007 and were followed up through December 2018.

EXPOSURES Nonobstructive chronic bronchitis was defined by questionnaire at baseline as both cough and phlegm for at least 3 months for at least 2 consecutive years.

MAIN OUTCOMES AND MEASURES Lung function was measured by prebronchodilator spirometry. Hospitalizations and deaths due to chronic lower respiratory disease and respiratory disease–related mortality were defined by events adjudication and administrative criteria. Models were stratified by smoking status and adjusted for anthropometric, sociodemographic, and smoking-related factors. The comparison group was participants without nonobstructive chronic bronchitis.

RESULTS Among 22 325 adults included in the analysis, mean (SD) age was 53.0 (16.3) years (range, 18.0-95.0 years), 58.2% were female, 65.9% were non-Hispanic white, and 49.6% were ever smokers. Among 11 082 ever smokers with 99 869 person-years of follow-up, participants with nonobstructive chronic bronchitis (300 [2.7%]) had accelerated decreases in FEV_1 (4.1 mL/y; 95% CI, 2.1-6.1 mL/y) and FVC (4.7 mL/y; 95% CI, 2.2-7.2 mL/y), increased risks of chronic lower respiratory disease–related hospitalization or mortality (hazard ratio [HR], 2.2; 95% CI, 1.7-2.7), and greater respiratory disease–related (HR, 2.0; 95% CI, 1.1-3.8) and all-cause mortality (HR, 1.5; 95% CI, 1.3-1.8) compared with ever smokers without nonobstructive chronic bronchitis. Among 11 243 never smokers with 120 004 person-years of follow-up, participants with nonobstructive chronic bronchitis (151 [1.3%]) had greater rates of chronic lower respiratory disease–related hospitalization or mortality (HR, 3.1; 95% CI, 2.1-4.5) compared with never smokers without nonobstructive chronic bronchitis. Nonobstructive chronic bronchitis was not associated with FEV_1:FVC decline or incident airflow obstruction. The presence of at least 1 of the component symptoms of nonobstructive chronic bronchitis (ie, chronic cough or phlegm), which was common in both ever smokers (11.0%) and never smokers (6.7%), was associated with adverse respiratory health outcomes.

CONCLUSIONS AND RELEVANCE The findings suggest that nonobstructive chronic bronchitis is associated with adverse respiratory health outcomes, particularly in ever smokers, and may be a high-risk phenotype suitable for risk stratification and targeted therapies.

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Supplemental content

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Chronic bronchitis, defined by chronic cough and sputum, affected 5% of US adults aged 45 years or older in 2018.[1] Presence of chronic bronchitis is an indication for pulmonary function testing[2,3]; however, chronic bronchitis is not included in the diagnostic criteria for chronic obstructive pulmonary disease (COPD)[3] and frequently occurs without comorbid COPD.[4-6] The prognostic significance of chronic bronchitis in the context of normal pulmonary function test results, or nonobstructive chronic bronchitis, remains a subject of debate.

Chronic bronchitis was considered an important step in COPD development[7,8]; however, associations between nonobstructive chronic bronchitis and incident airflow obstruction have not been consistently observed in previous studies,[9-14] possibly because of inconsistent definitions of chronic bronchitis,[9-14] inclusion of persons with COPD and/or predominance of heavy smokers,[10-12,14] use of occupational cohorts,[14-16] and reliance on subgroup analyses.[5,6] In this context, establishment of whether associations between nonobstructive chronic bronchitis and COPD could be explained by shared associations with smoking has been difficult.[14,17,18] Regardless of whether nonobstructive chronic bronchitis is a precursor to COPD in some individuals, evidence for adverse clinical outcomes in symptomatic smokers without COPD has prompted renewed debates and clinical trials[19-21] about whether to expand indications for current COPD therapies to patients with nonobstructive chronic bronchitis. Furthermore, recent studies[22,23] showing mucin abnormalities in smokers and e-cigarette users have raised the possibility of novel targeted therapies for chronic bronchitis with or without concomitant COPD.

To inform clinical risk stratification for adults with chronic cough and phlegm but without COPD, we assessed whether nonobstructive chronic bronchitis was associated with accelerated lung function decline and increased respiratory disease–related hospitalization and mortality in the largest US general population–based study to our knowledge. Because smoking is a major risk factor for both nonobstructive chronic bronchitis and adverse respiratory health outcomes, these hypotheses were tested separately in never smokers and ever smokers.

Key Points

Question Is there an association of chronic bronchitis in the absence of asthma or airflow obstruction with adverse respiratory health outcomes in adults who have ever smoked and in those who have never smoked?

Findings In this cohort study of 22 325 US adults without asthma or airflow obstruction at baseline, ever smokers with nonobstructive chronic bronchitis had faster decreases in the forced expiratory volume in the first second and the forced vital capacity, a greater incidence of hospitalization or mortality due to respiratory causes, and increased all-cause mortality compared with ever smokers without nonobstructive chronic bronchitis. Never smokers with nonobstructive chronic bronchitis had greater rates of hospitalization and mortality due to incident respiratory causes but no significant difference in the rate of lung function decline or all-cause mortality compared with never smokers without nonobstructive chronic bronchitis.

Meaning The findings suggest that nonobstructive chronic bronchitis is associated with adverse respiratory health outcomes, particularly among ever smokers.

Methods

Study Population

The NHLBI (National Health, Lung, and Blood Institute) Pooled Cohorts Study[24] harmonized and pooled data from 9 US cohorts with spirometry assessment. The present cohort study included data from 5 cohorts for which information on respiratory symptoms was collected and at least 2 spirometry examinations were performed: Atherosclerosis Risk in Communities (ARIC) study, Coronary Artery Risk Development in Young Adults (CARDIA) study, Cardiovascular Health Study (CHS), Framingham Offspring Cohort (FOC), and the Multi-Ethnic Study of Atherosclerosis (MESA)–Lung Study (**Figure 1** and eFigure 1 and eTable 1 in the Supplement).[25-29] Participants were enrolled from August 1971 through May 2007 and were followed up through December 2018. All studies were approved by institutional review boards at participating institutions. Secondary analysis for this work was approved by the Columbia University institutional review board. Participants who did not consent to having their data analyzed for noncardiovascular research were excluded from the present work.

Participants with initial airflow obstruction, defined as a ratio of forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC) of less than 0.70[30] and/or baseline self-reported physician-diagnosed asthma, were excluded. In sensitivity analyses, we applied an alternative definition of airflow obstruction (FEV_1:FVC less than the lower limit of normal),[31] included persons with clinical asthma, and excluded participants who developed incident airflow obstruction at follow-up spirometry.

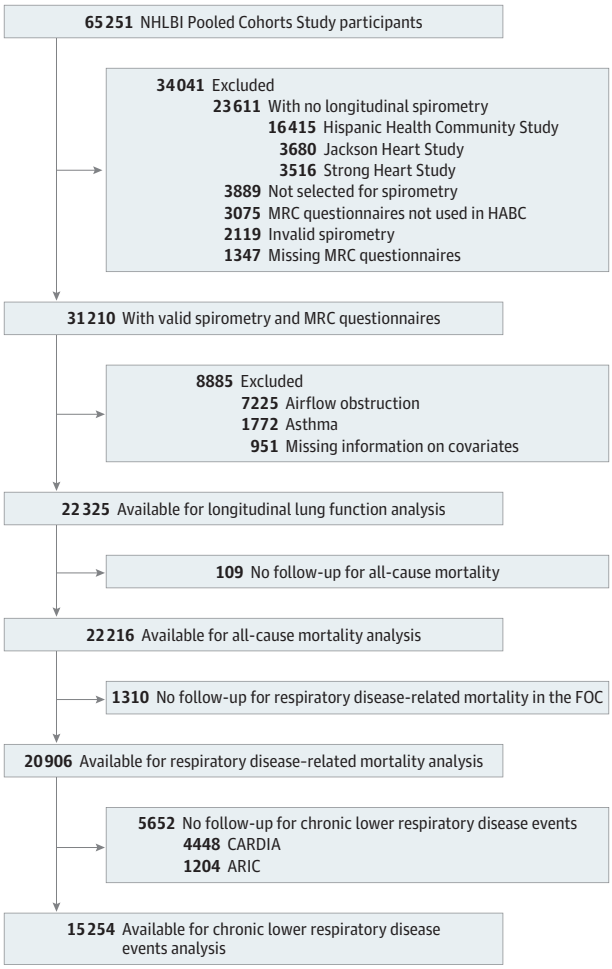
Nonobstructive Chronic Bronchitis

Nonobstructive chronic bronchitis was defined at baseline using modified Medical Research Council questions as both cough and phlegm for at least 3 months for 2 or more consecutive years (eTable 2 in the Supplement).[32] In secondary analyses, associations were tested separately for chronic cough and chronic phlegm.[5,10,12,33]

Spirometry Measurements

Prebronchodilator lung function was measured using water-seal, dry-rolling seal, or flow-sensing spirometers. The included 5 cohorts used different spirometers at various time points during the study: WS (Collins), DRS (SM/OMI), FS (ndd) and DRS (Mijnhardt).[24] To harmonize spirometry data, we applied a standardized grading system for quality based on the 2005 American Thoracic Society and European Respiratory Society guidelines.[24,34] Incident airflow limitation was defined as FEV_1:FVC less than 0.70 at the final spirometry examination during follow-up.

Figure 1. Flowchart of the 5 Study Cohorts With Data on Respiratory Symptoms and Repeated Spirometric Examination That Were Included in the Present Analysis



The 5 cohorts included the Atherosclerosis Risk In Communities (ARIC) Study, Coronary Artery Risk Development in Young Adults (CARDIA) Study, Cardiovascular Health Study (CHS), Framingham Offspring Cohort (FOC), and Multi-Ethnic Study of Atherosclerosis (MESA)–Lung Study. Of the remaining 4 cohorts included in the National Heart, Lung, and Blood Institute (NHLBI) Pooled Cohorts Study, the Health, Aging, and Body Composition (HABC) Study did not assess chronic bronchitis at baseline or at any follow-up examinations; the Hispanic Health Community Study, Jackson Heart Study, and Strong Heart Study performed only 1 spirometric examination to date. MRC indicates Medical Research Council.

Events

Follow-up for chronic lower respiratory disease–related hospitalizations and mortality varied by cohort (Figure 1 and eFigure 1 in the Supplement). Events were classified by adjudication or administrative criteria following a previously validated protocol using *International Classification of Diseases, Ninth Revision (ICD-9)* and *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)* diagnosis codes for chronic lower respiratory disease (asthma [*ICD-9*: 493; *ICD-10*: J45-6], COPD [*ICD-9*: 496; *ICD-10*: J44], chronic bronchitis [*ICD-9*: 490-1; *ICD-10*; J40-2], and emphysema [*ICD-9*: 492; *ICD-10*: J43]).[30,35-37] Chronic lower respiratory disease–related events were defined as hospitalizations or deaths for which chronic lower respiratory disease was classified as a primary, underlying, or contributing cause. In previous work in MESA and another cohort,[35] 82% of events meeting this definition were confirmed by 2-physician review of medical records as evidence of clinical chronic lower respiratory disease. Chronic lower respiratory disease–related events were substratified into events attributed to asthma vs COPD, the latter of which was defined to include COPD, emphysema, and chronic bronchitis. In sensitivity analyses, severe chronic lower respiratory disease events were defined as the subset of chronic lower respiratory disease–related events for which chronic lower respiratory disease was a primary or underlying cause, which has a positive predictive value of 97% for physician-adjudicated chronic lower respiratory disease exacerbations.[35]

For secondary analyses, heart failure events were classified by physician adjudication of medical records from hospitalizations and deaths.[38-42] All-cause mortality was ascertained via follow-up calls and supplemented by the National Death Index.[43] Respiratory disease–related deaths were defined by adjudication or administrative criteria (*ICD-10*: J1-J99).

Covariates

Covariate measurement was harmonized systematically.[24] Smoking status was self-reported, with confirmation by cotinine in a subset (eTable 3 in the Supplement).[44,45] Ever smokers were mainly defined as participants reporting smoking at least 100 lifetime cigarettes and current smokers as those self-reporting smoking within the past 30 days. For secondary analyses, participants reporting the same smoking status at all spirometry examinations were classified as sustained never, former, and current smokers.[46] Pack-years were calculated as follows: ([cigarettes per day × years smoked]/20). Race/ethnicity, sex, and educational attainment were self-reported. Anthropometric measurements were performed using standard methods.

Statistical Analyses

Linear mixed models were used to test associations between nonobstructive chronic bronchitis and longitudinal lung function, treating age (age at examination) as the time scale. Cohort-specific unstructured covariance matrixes were used to model between- and within-participant variability, allowing for differences between cohorts, autocorrelation in repeated measures, and nonlinear effects of time.[47] The model-based mean change in lung function in never and ever smokers was calculated using a model including only age and age^2.

The coefficient for the multiplicative interaction term (nonobstructive chronic bronchitis × age) was interpreted as the association with lung function decline. The comparison group comprised individuals without nonobstructive chronic bronchitis, which in the primary analyses included those who reported only chronic cough or chronic phlegm. Models were adjusted for the following a priori confounders and precision variables: age, age^2, height^2, weight, baseline age, birth year, sex, race/ethnicity, educational attainment, clinical site, and

among ever smokers, current smoking status and pack-years. Multiplicative interaction terms with age were included for all time-invariant covariates.[47]

Associations with incident airflow obstruction, chronic lower respiratory disease events, and mortality were tested using proportional hazards regression. The proportional hazards assumption was confirmed by residual plots. Time to event was treated as age at event, with left truncation at age when nonobstructive chronic bronchitis was defined. Study was treated as a stratum term, allowing cohort-specific differences in the underlying survival function. In addition to covariates included in mixed models, proportional hazards models were adjusted for baseline FEV_1:FVC.

A priori, all analyses were performed separately for never and ever smokers.[13,14,17,18,48] Analyses using multiplicative interaction terms confirmed that ever smoking status modified associations between nonobstructive chronic bronchitis and lung function decline and all-cause mortality (eTable 4 in the Supplement). Effect modification for current vs former smoking and other sociodemographic characteristics was similarly assessed.

Analyses were completed using SAS, version 9.4 (SAS Institute Inc). Tests were 2-sided, and $P < .05$ was considered to be statistically significant. There were only 4% missing data on the covariates included in the analyses[24]; therefore, complete case analyses are reported.

Results

Baseline Characteristics

Among 22 325 adults (Figure 1), mean (SD) age was 53.0 (16.3) years (range: 18.0-95.0 years), 58.2% were female, 65.9% were non-Hispanic white, and 28.2% were African American. Of 11 082 (49.6%) ever smokers, 31.9% were former and 17.8% were current smokers. Among ever smokers, the median pack-years was 13.5 (range, 4.0-30.0) (**Table 1**). Nonobstructive chronic bronchitis was present in 2.7% of ever smokers, including 1.4% of former and 5.0% of current smokers and 1.3% of never smokers (eFigure 2 in the Supplement).

Lung Function

Ever smokers had a median of 2 (interquartile range [IQR], 1-5) valid spirometry examinations over 9 years, yielding 99 869 person-years. Among ever smokers, the mean (SD) baseline FEV_1 percent-predicted was 97.0% (14.5%), baseline FEV_1:FVC was 0.78 (0.05), and FEV_1 declined by 34.0 mL per year (95% CI, 33.6-34.5 mL per year). Unadjusted FEV_1 decline was 37.3 mL per year (95% CI, 35.4-39.1 mL per year) in ever smokers with nonobstructive chronic bronchitis and 32.9 mL per year (95% CI, 32.5-33.3 mL per year) in ever smokers without nonobstructive chronic bronchitis. In adjusted models, nonobstructive chronic bronchitis was associated with accelerated decline in FEV_1 (mean, 4.1 mL per year; 95% CI, 2.1-6.1 mL per year) and FVC (mean, 4.7 mL per year; 95% CI, 2.2-7.2 mL per year) (**Table 2** and eFigure 3 in the Supplement). The rates of FEV_1 and FVC decline were equivalent to 12.5% and 13.6% of the mean rates of decline in ever smokers without nonobstructive chronic bronchitis, respectively. Consistent with similar accelerations in FEV_1 and FVC declines, nonobstructive chronic bronchitis was not associated with accelerated FEV_1:FVC decline (mean 0.002; 95% CI, 0.030 to -0.030; $P = .92$) (Table 2) or with greater incidence of airflow limitation (hazard ratio [HR], 1.2; 95% CI, 0.9-1.7). Similar associations were found after restricting the sample to individuals with at least 3 spirometric assessments (eTable 5 in the Supplement).

Compared with ever smokers, spirometry follow-up was longer (120 002 person-years) and baseline lung function was less impaired for never smokers (Table 1). No significant associations were observed between nonobstructive chronic bronchitis and any spirometry end points in never smokers (Table 2).

Chronic Lower Respiratory Disease Events

Among ever smokers, 7768 participants were assessed for incident chronic lower respiratory disease–related hospitalizations or mortality, with a median follow-up of 16.6 years (IQR, 9.7-24.2 years) yielding 134 850 person-years of events follow-up. There were 1399 chronic lower respiratory disease–related events (incidence density rate [IDR] per 1000 person-years, 10.4), of which 1131 were incident COPD-related events (IDR, 8.4) and 277 were incident asthma-related events (IDR, 2.1). The IDRs for chronic lower respiratory disease–related events were 28.4 in ever smokers with nonobstructive chronic bronchitis and 10.5 in ever smokers without nonobstructive chronic bronchitis. In adjusted models, nonobstructive chronic bronchitis was associated with a higher rate of incident chronic lower respiratory disease–related events (HR, 2.2; 95% CI, 1.7-2.7) and COPD-related events (HR, 2.0; 95% CI, 1.6-2.6) (**Table 3**, **Figure 2**). Among ever smokers, associations with COPD-related events were stronger among former smokers (HR, 2.9; 95% CI, 1.7-4.9) compared with current smokers (HR, 1.9; 95% CI, 1.4-2.6) (eTable 6 in the Supplement).

In never smokers, incident chronic lower respiratory disease–related events were less frequent but nonobstructive chronic bronchitis remained strongly associated (Table 3, Figure 2, and eFigure 4 in the Supplement). There were 683 chronic lower respiratory disease–related events (IDR, 5.2), of which 380 were incident COPD-related events (IDR, 2.9) and 306 were incident asthma-related events (IDR, 2.3). The IDRs for chronic lower respiratory disease–related events were 18.5 in never smokers with nonobstructive chronic bronchitis and 5.1 in never smokers without nonobstructive chronic bronchitis. After adjustment, in never smokers, nonobstructive chronic bronchitis was associated with incident chronic lower respiratory disease–related events (HR, 3.1; 95% CI, 2.1-4.5).

In secondary analyses, nonobstructive chronic bronchitis demonstrated similar associations with incident severe chronic lower respiratory disease events. Of note, nonobstructive chronic bronchitis was associated with incident severe asthma events in never smokers but not ever smokers (eTable 7 in the Supplement). Nonobstructive chronic bronchitis was not associated with incident heart failure events in ever smokers (HR, 0.8; 95% CI, 0.5-1.4) or never smokers (HR, 1.2; 95% CI, 0.9-1.7).

Table 1. Baseline Characteristics Stratified by Nonobstructive Chronic Bronchitis and Smoking Status[a]

Characteristic	Never Smokers (n = 11 243)		Ever Smokers (n = 11 082)		Total (N = 22 325)
	Without Nonobstructive Chronic Bronchitis (n = 11 092)	With Nonobstructive Chronic Bronchitis (n = 151)	Without Nonobstructive Chronic Bronchitis (n = 10 782)	With Nonobstructive Chronic Bronchitis (n = 300)	
Total spirometric follow-up, person-years	118 760	1244	97 270	2599	219 873
Age, mean (SD), y	52.4 (17.1)	59.7 (15.7)	53.6 (15.4)	51.8 (16.4)	53.0 (16.3)
Sex					
Men	3705 (33.4)	45 (29.8)	5451 (50.6)	136 (45.3)	9337 (41.8)
Women	7387 (66.6)	106 (70.2)	5331 (49.4)	164 (54.7)	12 988 (58.2)
Body mass index, mean (SD)[b]	27.4 (5.6)	29.1 (6.4)	27.5 (5.4)	27.2 (5.4)	27.4 (5.5)
Race/ethnicity[c]					
Non-Hispanic white	7061 (63.7)	101 (66.9)	7323 (67.9)	225 (75.0)	14 710 (65.9)
African American	3257 (29.4)	36 (23.8)	2935 (27.2)	62 (20.7)	6290 (28.2)
Asian American	381 (3.4)	3 (2.0)	139 (1.3)	1 (0.3)	524 (2.4)
Hispanic or Latino	383 (3.5)	11 (7.3)	373 (3.5)	12 (4.0)	779 (3.5)
Other	10 (0.1)	NA	12 (0.1)	NA	22 (0.1)
Educational attainment					
Less than high school	997 (9.0)	15 (9.9)	1308 (12.1)	50 (16.7)	2370 (10.6)
High school	3126 (28.2)	41 (27.2)	3079 (28.6)	85 (28.3)	6331 (28.4)
More than high school	6969 (62.8)	95 (62.9)	6395 (59.3)	165 (55.0)	13 624 (61.0)
Smoking status					
Never	11 092 (100)	151 (100)	NA	NA	11 243 (50.4)
Former	NA	NA	7013 (65.0)	103 (34.3)	7116 (31.9)
Current	NA	NA	3769 (35.0)	197 (65.7)	3966 (17.8)
Pack-years, median (IQR)	NA	NA	13.0 (4.0-29.5)	25.3 (10.0-41.1)	13.5 (4.0-30.0)
Lung function at baseline, mean (SD)	NA	NA	NA	NA	NA
Predicted FEV_1, %	100 (14.1)	97.8 (14.8)	97.6 (14.4)	92.8 (15.9)	98.7 (14.3)
FEV_1, mL	2843.2 (849.1)	2562.8 (816.8)	2947.2 (808.5)	2821.3 (933.0)	2891.2 (832.7)
FVC, mL	3781.3 (1020.5)	3277.6 (1038.6)	3581.2 (1045.0)	3630.1 (1157.3)	3676.4 (1040.0)
FEV_1:FVC	0.79 (0.05)	0.78 (0.05)	0.78 (0.05)	0.78 (0.05)	0.79 (0.05)
Restrictive ventilatory pattern	618 (5.6)	13 (8.6)	865 (8.0)	42 (14.0)	1538 (6.9)
Spirometric examinations, median (IQR), No.	2.0 (1.0-5.0)	2.0 (2.0-5.0)	2.0 (1.0-5.0)	2.0 (1.0-5.0)	2.0 (1.0-5.0)
Spirometric follow-up, mean (SD), y	10.7 (10.7)	8.2 (9.3)	9.0 (10.0)	8.2 (9.3)	9.8 (10.4)
Cohort					
ARIC	5118 (46.1)	54 (35.8)	5476 (50.8)	150 (50.0)	10 798 (48.4)
CARDIA	2474 (22.3)	18 (11.9)	1899 (17.6)	67 (22.3)	4458 (20.0)
CHS	1293 (11.7)	26 (17.2)	1039 (9.6)	34 (11.3)	2392 (10.7)
FOC	559 (5.0)	7 (4.6)	746 (6.9)	7 (2.3)	1319 (5.9)
MESA	1648 (14.9)	46 (30.5)	1622 (15.0)	42 (14.0)	3358 (15.0)

Abbreviations: ARIC, Atherosclerosis Risk in Communities; CARDIA, Coronary Artery Risk Development in Young Adults; CHS, Cardiovascular Health Study; FEV_1, forced expiratory volume in 1 second; FOC, Framingham Offspring Cohort; FVC, forced vital capacity; IQR, interquartile range; MESA, Multi-Ethnic Study of Atherosclerosis–Lung Study; NA, not applicable.

[a] Data are presented as number (percentage) of individuals unless otherwise indicated.

[b] Calculated as weight in kilograms divided by height in meters squared.

[c] Race/ethnicity was self-reported according to fixed, mutually exclusive categories that differed by cohort: in ARIC, white, black, Asian-Pacific Islander, or American Indian; in CARDIA, white, black, Hispanic, American Indian or Alaskan Native, or Asian or Pacific Islander; in CHS, white, black, Asian or Pacific Islander, American Indian, or other; and in MESA, white, black, Hispanic, or Asian. The FOC study was conducted in offspring of the original Framingham Heart Study cohort, which was exclusively Non-Hispanic white race. No separate question regarding ethnicity was administered at enrollment for any of the cohorts.

Mortality

In ever smokers, nonobstructive chronic bronchitis was associated with increased respiratory disease–related mortality (HR, 2.0; 95% CI, 1.1-3.8) and all-cause mortality (HR, 1.5; 95% CI, 1.3-1.8) (Table 3, Figure 2). In never smokers, nonobstructive chronic bronchitis was not associated with mortality.

Alternative Definitions for Nonobstructive Chronic Bronchitis

Results were similar for the component symptoms of nonobstructive chronic bronchitis (eFigure 2 and eTables 8-10 in the Supplement). Among ever smokers with at least 1 symptom, chronic cough or phlegm (11.0%), there were accelerated de-

Table 2. Associations Between Nonobstructive Chronic Bronchitis and Change in Lung Function[a]

	Never Smokers (n = 11 243)			Ever Smokers (n = 11 082)		
	Nonobstructive Chronic Bronchitis, Estimate (95% CI)			Nonobstructive Chronic Bronchitis, Estimate (95% CI)		
Spirometry	Without (n = 11 092)	With (n = 151)	*P* Value	Without (n = 10 782)	With (n = 300)	*P* Value
FEV_1, mL/y	[Reference]	0.2 (−2.6 to 3.0)	.87	[Reference]	−4.1 (−6.1 to −2.1)	<.001
FVC, mL/y	[Reference]	0.6 (−2.9 to 4.2)	.73	[Reference]	−4.7 (−7.2 to −2.2)	<.001
FEV_1:FVC, %/y	[Reference]	−0.02 (−0.06 to 0.02)	.37	[Reference]	−0.002 (−0.030 to 0.030)	.92

Abbreviations: FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.

[a] For analysis of lung function, linear mixed models with cohort-specific unstructured covariance matrix were used. The coefficient for the multiplicative interaction term (nonobstructive chronic bronchitis × age) was interpreted as the longitudinal association with rate of change in lung function. Models were adjusted for age, age^2, height^2, weight, sex, race/ethnicity, educational attainment, baseline age (centered), birth year (centered), clinical site, and, among ever smokers, smoking status and pack-years. Multiplicative interaction terms with age were included for all time-invariant covariates.

Table 3. Associations Between Nonobstructive Chronic Bronchitis and Chronic Lower Respiratory Disease–Related Hospitalizations and Mortality, Respiratory Mortality, and All-Cause Mortality[a]

	Never Smokers (n = 7486)			Ever Smokers (n = 7768)		
Outcome	Events, No. (Cumulative Incidence, %)	Hazard Ratio (95% CI)	*P* Value	Events, No. (Cumulative Incidence, %)	Hazard Ratio (95% CI)	*P* Value
Chronic lower respiratory disease–related events	683 (9.1)	3.1 (2.1-4.5)	<.001	1399 (18.0)	2.2 (1.7-2.7)	<.001
COPD-related events	380 (5.1)	2.3 (1.3-4.1)	.003	1131 (14.6)	2.0 (1.6-2.6)	<.001
Asthma-related events	306 (4.1)	3.6 (2.2-6.1)	<.001	277 (3.6)	3.3 (2.1-5.4)	<.001
Mortality						
All-cause[b]	3215 (28.7)	1.2 (0.9-1.6)	.14	3901 (35.4)	1.5 (1.3-1.8)	<.001
Respiratory disease related[c]	105 (1.0)	1.1 (0.3-4.5)	.89	187 (1.8)	2.0 (1.1-3.8)	.03

Abbreviation: COPD, chronic obstructive pulmonary disease.

[a] For analysis of chronic lower respiratory disease–related hospitalization and mortality, associations were tested using proportional hazards regression. Time to event was treated as age at event, with left truncation at age when nonobstructive chronic bronchitis was defined. Study was treated as a stratum term, allowing for cohort-specific differences in the underlying survival function. Models adjusted for baseline age, birth year, site, height, weight, sex, race/ethnicity, educational attainment, smoking status, pack-years of smoking, and baseline ratio of forced expiratory volume in 1 second to forced vital capacity. The comparison group consisted of individuals without nonobstructive chronic bronchitis.

[b] All-cause mortality follow-up was available for all 5 cohorts; the number of never smokers at risk was 11 191, and the number of ever smokers at risk was 11 025.

[c] Because respiratory disease–related mortality follow-up was not available for the Framingham Offspring Cohort, the number of never smokers at risk was 10 630, and the number of ever smokers at risk was 10 276.

clines in FEV_1 (1.8 mL/y; 95% CI, 0.8-2.9 mL/y) and FVC (1.9 mL/y; 95% CI, 0.6-3.2 mL/y), increased incident chronic lower respiratory disease–related events (HR, 1.7; 95% CI, 1.5-2.0), and increased respiratory disease–related mortality (HR, 1.8; 95% CI, 1.2-2.6) and all-cause mortality (HR, 1.2; 95% CI, 1.1-1.3). Among never smokers, presence of either chronic cough or phlegm (6.7%) was associated with increased incident chronic lower respiratory disease–related events only (HR, 1.9; 95% CI, 1.5-2.4) (eTables 8-10 in the Supplement).

Findings were similar when using a lower-limit-of-normal definition for airflow obstruction (eTable 11 in the Supplement), including participants with baseline asthma (eTable 12 in the Supplement) and excluding participants who developed incident airflow obstruction during follow-up (eTable 13 in the Supplement).

Additional Sensitivity Analyses

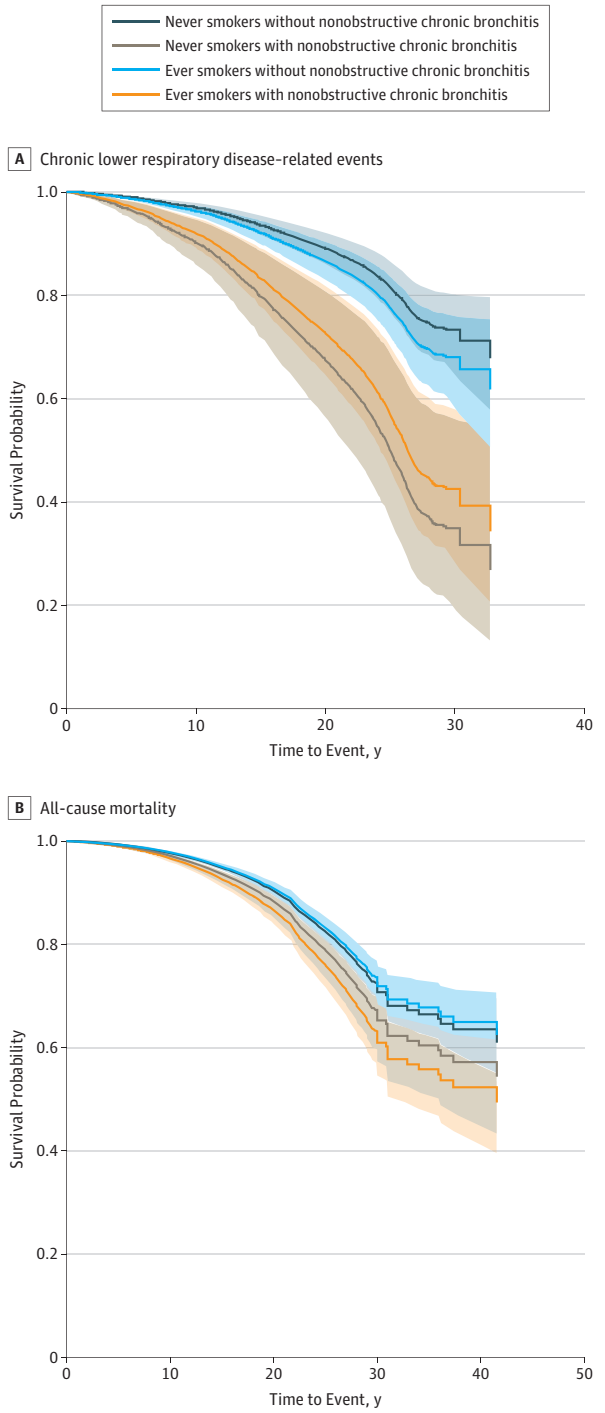
Results were similar using baseline and longitudinal smoking status (eFigures 5-7 and eTable 14 in the Supplement). Associations were strongest in middle-aged individuals but consistent across age ranges and study cohorts. There was no evidence of effect modification by sex or race/ethnicity (eFigures 5-7 in the Supplement).

Discussion

Among adults without clinical asthma or spirometry-defined COPD, chronic cough and phlegm were associated with adverse respiratory health outcomes in a large, multiethnic, US general population–based study. Nonobstructive chronic bronchitis was associated with accelerated lung function decline in ever smokers and increased risks of chronic lower respiratory disease–related hospitalization or mortality in both ever smokers and never smokers. These findings support consideration of chronic bronchitis as a clinically important condition independent of COPD.

We did not find evidence that nonobstructive chronic bronchitis was associated with spirometry-defined COPD in the general population of adults regardless of age group. These results are contrary to 2 relatively recent studies[5,6] that suggested associations between nonobstructive chronic bronchi-

Figure 2. Associations Between Nonobstructive Chronic Bronchitis, Chronic Lower Respiratory Disease–Related Events, and All-Cause Mortality Stratified by Smoking Status



tis and incident airflow obstruction among participants younger than 50 years.[5,6] Nonetheless, our findings among ever smokers corroborated previous research showing associations between chronic bronchitis and proportionally accelerated declines in FEV_1 and FVC,[12-17,48-52] consistent with progressive physiologic impairment associated with accelerated aging.[53]

Both respiratory disease-related and all-cause mortality rates were higher in ever smokers with nonobstructive chronic bronchitis compared with those without; these results were similar to some but not all previous studies.[10,12,14] These findings were independent of baseline lung function and remained consistent after excluding participants who developed incident airflow obstruction during follow-up. This result underscores the importance of evidence-based risk factor optimization in patients with nonobstructive chronic bronchitis, including smoking avoidance and cessation.[46]

Our study showed that smoking history modified association of nonobstructive chronic bronchitis with adverse respiratory health outcomes, with greater lung function decline and mortality among ever smokers but not among never smokers. Among never smokers, nonobstructive chronic bronchitis was associated only with chronic lower respiratory disease events; in contrast to the results for ever smokers, there were significant associations with severe asthma events. This finding raises several considerations. First, our analysis among never smokers may have been relatively underpowered. In a Danish population-based cohort study[9] of adults without airflow obstruction, chronic respiratory symptoms, which did not correspond directly with the standard diagnostic criteria for chronic bronchitis used in this report, were present in 30.6% of never smokers and were associated with increased all-cause mortality in this group.[9] Second, although participants with self-reported asthma were excluded, it is possible that some never smokers had undiagnosed asthma. Third, contrary to epidemiologic evidence that up to 20% of COPD cases occur in never smokers, their respiratory symptoms may be more likely to be attributed to asthma.[54,55]

Although confounding by smoking could contribute to our findings,[10,12] differences in the association of nonobstructive chronic bronchitis with respiratory health outcomes in never smokers vs ever smokers could be consistent with mechanistic differences between these 2 groups. Mechanisms for smoking-related obstructive chronic bronchitis include airway wall thickening, chronic inflammation, bacterial infection,[20,56-58] and alterations in airway mucin concentrations (particularly increases in mucin polymer *MUC5AC*[22]), the last of which has also been observed in e-cigarette users.[23] Of importance, nonobstructive chronic bronchitis was present in a small number of smokers, and associations were observed after adjustment for smoking status and pack-years, suggesting a specific, clinically relevant pathophysiologic response to smoking that occurs in some but not all ever smokers and that may persist after cessation. Our findings in ever smokers are consistent with a cross-sectional study[19] of symptomatic smokers (defined using the COPD Assessment Test) with at least 10 pack-years but without airflow obstruction who were shown to have lower lung function, more self-reported respiratory disease exacerbations, and greater airway wall thickening on imaging. Our results extend these findings to a general population sample, including a large number of ever smokers with less than 10 pack-years. Meanwhile, additional investigations are needed with respect to risk factors for nonobstructive chronic bronchitis in never smokers, which may include environmental pollution, occu-

pational exposures, and genetic risk factors (eg, α-1-antitrypsin deficiency).[59,60]

Strengths and Limitations

Strengths of the current work include the large, multiethnic population-based study; nonobstructive chronic bronchitis classification using the diagnostic standard; extensive follow-up; and examination of physiologic and clinical end points, which were quality controlled using rigorous and validated criteria.

This study has limitations. Although some misclassification of respiratory health events was anticipated, we used a previously validated protocol, and results were similar using more sensitive and more specific definitions. We found no association of nonobstructive chronic bronchitis with either incident heart failure or interstitial lung diseases, which are also characterized by chronic cough and/or chronic phlegm.[61-64] Postbronchodilator measures, which are required to diagnose COPD, were unavailable. Nevertheless, prebronchodilator measures are highly correlated with postbronchodilator measures in the general population.[65-67] Furthermore, participants with reversible airflow obstruction who were excluded by using prebronchodilator measures were likely to have more respiratory impairment at baseline; thus, this would be expected to bias our results toward the null. We were not able to rule out bronchiectasis, which may confound the observed associations, but this condition is rare in the general population.[68] To minimize heterogeneity in measurement and classification across cohorts, our data were rigorously harmonized and quality controlled. Analyses were adjusted for period and cohort variables, and results were consistent in cohort-stratified analyses. Only 2 spirometric examinations were available for many participants, limiting estimation of lung function trajectories,[69] but our results were similar when restricted to participants with at least 3 measures. Excess declines in FEV_1 and FVC among ever smokers with nonobstructive chronic bronchitis were modest in absolute terms, but they were equivalent to 13% of the mean decline in ever smokers without nonobstructive chronic bronchitis.[70] We cannot rule out the possibility of selection bias introduced because of exclusion of 3 cohorts with only 1 spirometric examination. Because this was a design feature of these cohorts, any potential selection bias would operate on the cohort level. A consequence of these exclusions was a reduction in racial/ethnic diversity, particularly with respect to Hispanic or Latino participants. In addition, nonobstructive chronic bronchitis was present in a relatively small proportion of individuals (2.0%) compared with other cohort studies (5%-32%).[5,6,9,10,12,13,33] This may be attributed to our exclusion of participants with prebronchodilator airflow obstruction and clinical asthma and our application of the specific but relatively insensitive diagnostic standard.[9,10,12,13,33,71] Nonetheless, more than 1 in 10 ever smokers in our study had either chronic cough or chronic phlegm, and presence of at least 1 of these symptoms was associated with a similar prognosis compared with nonobstructive chronic bronchitis.

Conclusions

In this study, nonobstructive chronic bronchitis was associated with adverse respiratory health outcomes, particularly in ever smokers. This finding supports consideration of nonobstructive chronic bronchitis as clinically important independent of COPD. Assessment for chronic bronchitis may be suitable for risk stratification and targeting of aggressive risk factor modification and evidence-based preventive measures. Our results support the importance of evidence-based approaches to smoking cessation as well as suggest precaution with respect to any exposure associated with development of chronic bronchitis symptoms.

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Invited Commentary

Long-term Sequelae of Nonobstructive Chronic Bronchitis—Is Airflow Obstruction Important?

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Chronic bronchitis is generally considered to be a phenotype of chronic obstructive pulmonary disease (COPD). However, at a Ciba Foundation Symposium in 1958,[1] British investigators asserted that, "chronic bronchitis may be present without impairment of lung function." The significance of nonobstructive chronic bronchitis remains poorly understood. In this issue of *JAMA Internal Medicine*, Balte et al[2] describe lung function and respiratory tract morbidity and mortality longitudinally in a large study that involved data pooled from 5 US general population–based cohorts. The National Heart, Lung, and Blood Institute (NHLBI) Pooled Cohorts Study[3] harmonized and pooled data from 9 US epidemiologic cohorts that included spirometric measurements. In 5 of these studies, data on repeated spirometric measurements and respiratory symptoms were collected; these 5 studies form the basis of the study by Balte et al.[2] The authors studied 22 325 adults whose spirometric results did not demonstrate airflow obstruction using the usual definition of the ratio of forced expiratory volume in the first second of expiration (FEV_1) to forced vital capacity (FVC) of less than 0.70. Among 11 082 ever smokers with 99 869 person-years of follow-up, 2.7% had nonobstructive chronic bronchitis and demonstrated an accelerated decline in FEV_1 and FVC, increased risk of chronic lower respiratory tract disease–related hospitalization or mortality, and greater respiratory tract disease–related mortality and all-cause mortality. Among 11 243 never smokers with 120 004 person-years of follow-up, the prevalence of nonobstructive chronic bronchitis was 1.3%, and nonobstructive chronic bronchitis was associated with chronic lower respiratory tract disease–related hospitalization and mortality but not with decline in FEV_1:FVC or incident airflow obstruction.

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This large, multiethnic, general population–based study[2] was well done and used well-validated definitions of disease and standardized assessment of lung function. An additional strength of the study was the large study population and the effect sizes. Although shedding light on what appears to be an important lung disease phenotype, these observations also raise several important questions: Is nonobstructive chronic bronchitis a unique clinical entity or is it precursor to COPD? Are standard criteria for COPD too insensitive to detect early obstructive lung disease? Is it time to abandon spirometric results as a defining characteristic for COPD? Does the pattern of airway inflammation or the pattern of response to airway inflammation differ between ever smokers and never smokers?

Both the British Medical Research Council and the American Thoracic Society have defined chronic bronchitis, as "cough and sputum for at least 3 months a year during a period of 2 consecutive years."[4] Using this definition, chronic bronchitis has been considered a major phenotype of COPD at one end of a spectrum with emphysema at the other, with most patients falling between the 2 extremes. Cigarette smoking is the most important risk factor for chronic bronchitis, but a substantial proportion of cases are associated with occupational exposure, livestock farming, agricultural pesticides, air pollution, and biomass fuel. Given the diversity of these exposures, it is not difficult to imagine that different stimuli might result in chronic bronchitis via different inflammatory pathways, leading to different clinical manifestations. In addition, various exposures or interventions may simultaneously act to drive clinical end points in different directions. For example, chronic bronchitis is associated with mucus hypersecretion and overexpression of the gel-forming mucin 5AC (MUC5AC); azithromycin downregulates MUC5AC and decreases acute exacerbations of COPD; however, azithromycin does not reduce exacerbations in active smokers, perhaps because smoking is associated with goblet cell hypersecretion and upregulation of MUC5AC.[5]

Although the clinical literature has focused primarily on chronic bronchitis with COPD, publications following the summary of the Ciba Foundation Symposium consensus[1] have continued to show that chronic bronchitis can exist without evidence of airflow obstruction, and the current study[2] showed that this nonobstructive chronic bronchitis may be associated with significant respiratory tract disease–related morbidity and mortality over time. The NHLBI's Subpopulations and Intermediate Outcomes Measures in COPD Study (SPIROMICS) described a group of current or former smokers who had respiratory symptoms similar to COPD despite an FEV_1:FVC of at least 0.70.[6] Patients in this SPIROMICS cohort were not identical to those with nonobstructive chronic bronchitis in the current study[2] in that their