Supplementary Online Content

Balte PP, Chaves PHM, Couper DJ, et al. Association of nonobstructive chronic bronchitis with respiratory health outcomes in adults. *JAMA Intern Med*. Published online March 2, 2020. doi:10.1001/jamainternmed.2020.0104.

eTable 1. Design Features of Cohorts Included in the Current Study: the NHLBI Pooled Cohorts Study

eTable 2. Assessment of Chronic Bronchitis, by Cohort: the NHLBI Pooled Cohorts Study

eTable 3. Assessment of Smoking Status, by Cohort: the NHLBI Pooled Cohorts Study

eTable 4. Effect Modification by Smoking Status of Association on Nonobstructive Chronic Bronchitis, (A) Lung Function Decline, (B) Chronic Lower Respiratory Disease-related Hospitalizations and Mortality, and (C) Respiratory and All-cause Mortality

eTable 5. Associations Between Nonobstructive Chronic Bronchitis and Lung Function Decline, in Sample Restricted to 3 or More Spirometry Assessments

eTable 6. Associations Between Nonobstructive Chronic Bronchitis, (A) Lung Function Decline, (B) Chronic Lower Respiratory Disease-related Hospitalizations and Mortality, and (C) Respiratory and All-cause Mortality, Stratified by Former and Current Smokers

eTable 7. Associations Between Nonobstructive Chronic Bronchitis and Severe Chronic Lower Respiratory Disease Events for Which Chronic Lower Respiratory Disease was the Principal Cause of Admission/Mortality

eTable 8. Associations Between Nonobstructive Chronic Bronchitis, Defined as Chronic Cough With or Without Chronic Phlegm, (A) Lung Function Decline, (B) Chronic Lower Respiratory Disease-related Hospitalizations and Mortality, and (C) Respiratory and All-cause Mortality

eTable 9. Associations Between Nonobstructive Chronic Bronchitis, Defined as Chronic Phlegm With or Without Chronic Cough, (A) Lung Function Decline, (B) Chronic Lower Respiratory Disease-related Hospitalizations and Mortality, and (C) Respiratory and All-cause Mortality

eTable 10. Associations Between Nonobstructive Chronic Bronchitis, Defined as Chronic Cough or Chronic Phlegm, (A) Lung Function Decline, (B) Chronic Lower Respiratory Disease-related Hospitalizations and Mortality, and (C) Respiratory and All-cause Mortality

eTable 11. Associations Between Nonobstructive Chronic Bronchitis as Defined by FEV_1/FVC < Lower-limit-normal, (A) Lung Function Decline, (B) Chronic Lower Respiratory Disease-related Hospitalizations and Mortality, and (C) Respiratory and All-cause Mortality

© 2020 American Medical Association. All rights reserved.

eTable 12. Associations Between Nonobstructive Chronic Bronchitis, (A) Lung Function Decline, (B) Chronic Lower Respiratory Disease-related Hospitalizations and Mortality, and (C) Respiratory and All-cause Mortality, in Sample Including Baseline Self-reported Physician-diagnosed Asthma

eTable 13. Associations Between Nonobstructive Chronic Bronchitis, (A) Lung Function Decline, (B) Chronic Lower Respiratory Disease-related Hospitalizations and Mortality, and (C) Respiratory and All-cause Mortality, in a Sample Excluding Incident Airflow Obstruction

eTable 14. Associations between Nonobstructive Chronic Bronchitis, (A) Lung Function Decline, (B) Chronic Lower Respiratory Disease-related Hospitalizations and Mortality, and (C) Respiratory and All-cause Mortality, Stratified by Sustained Smoking Status

eFigure 1. Follow-up for Chronic Bronchitis and Respiratory Outcomes in the NHLBI Pooled Cohorts Study

eFigure 2. Alternative Definitions of Nonobstructive Chronic Bronchitis

eFigure 3. Associations Between Nonobstructive Chronic Bronchitis and Lung Function Decline in (A) Never-smokers and (B) Ever-smokers

eFigure 4. Unadjusted Kaplan Meier Curve to Illustrate the Differences in Observed (A) Chronic Lower Respiratory Disease Events and (B) All-cause Mortality, According to Nonobstructive Chronic Bronchitis and Smoking Status

eFigure 5. Associations between Nonobstructive Chronic Bronchitis and Decline in the FEV_1, FVC, and FEV_1/FVC, Stratified by Sociodemographic Factors Among Ever-smokers

eFigure 6. Associations Between Nonobstructive Chronic Bronchitis and Incident Chronic Lower Respiratory Diseases-related Events, Stratified by Sociodemographic Factors Among Never-smokers and Ever-smokers.

eFigure 7. Associations Between Nonobstructive Chronic Bronchitis and All-cause Mortality Among Ever-smokers, Stratified by Sociodemographic Factors

This supplementary material has been provided by the authors to give readers additional information about their work.

© 2020 American Medical Association. All rights reserved.

eTable 1. Design Features of Cohorts Included in the Current Study: the NHLBI Pooled Cohorts Study

Cohort	Sites	Enrollment year	Major eligibility criteria
Atherosclerosis Risk in Communities Study (ARIC) [a]	Winston-Salem, NC	1987-89	Age 45 -64 years
	Jackson, MS		
	Minneapolis, MN		
	Washington County, MD		
Coronary Artery Risk Development in Young Adults Study (CARDIA)	Chicago, IL	1985-1986	Age 18 – 30 years
	Oakland, CA		
	Birmingham, AL		
	Minneapolis, MN		
Cardiovascular Health Study (CHS)	Pittsburgh, PA	1989-90	Age 65 + years
	Winston-Salem, NC		
	Sacramento, CA		
	Baltimore, MD		
	Memphis, TN		
	San Francisco, CA		
Framingham Offspring Cohort (FOC)	Framingham, MA	1971–1975	Offspring of the Framingham heart Study- Original Cohort and their spouses
Multi-Ethnic Study of Atherosclerosis (MESA)	Winston-Salem, NC	2000-02	Age 45-84 years Participants required to be free of clinical cardiovascular disease.
	Upper Manhattan/Bronx, NY		
	Los Angeles, CA		
	Baltimore, MD		
	Chicago, IL		
	Minneapolis, MN		

© 2020 American Medical Association. All rights reserved.

[a] A subset of ARIC participants was co-recruited into the Jackson Heart Study, which completed one spirometry exam at its study baseline in 2000-2004, which occurred between ARIC spirometry exams 2 and 3. Hence, spirometry exams completed by the Jackson Heart Study were included in the spirometry follow-up for ARIC participants.

© 2020 American Medical Association. All rights reserved.

eTable 2. Assessment of Chronic Bronchitis, by Cohort: the NHLBI Pooled Cohorts Study

Cohort	Questions for cough and phlegm
ARIC	1. Do you usually have cough? 2. Do you usually cough like this on most days for 3 consecutive months or more during the year? 3. For how many years have you had this cough? 4. Do you usually bring up phlegm from your chest? 5. Do you usually bring up phlegm like this on most days for 3 consecutive months or more during the year? 6. For how many years have you had trouble with phlegm?
CARDIA	1. Do you usually have cough? 2. Do you usually cough like this on most days for 3 consecutive months or more during the year? 3. For how many years have you had this cough? 4. Do you usually bring up phlegm from your chest? 5. Do you usually bring up phlegm like this on most days for 3 consecutive months or more during the year? 6. For how many years have you had trouble with phlegm?
CHS	1. Do you usually have cough? 2. Do you usually cough like this on most days for 3 consecutive months or more during the year? 3. For how many years have you had this cough? 4. Do you usually bring up phlegm from your chest? 5. Do you usually bring up phlegm like this on most days for 3 consecutive months or more during the year? 6. For how many years have you had trouble with phlegm?
FOC	1. Do you usually have cough? 2. Do you usually cough like this on most days for 3 consecutive months or more during the year? 3. How many years have you had this cough? 4. Do you usually bring up phlegm from your chest? 5. Do you bring up phlegm from your chest on most days (4 or more days/week) for 3 consecutive months or more during the year? 6. How many years have you had trouble with phlegm?
MESA	1. Do you usually have a cough on most days for 3 or more months during the year? 2. For how many years have you had this cough? 3. Do you usually bring up phlegm from your chest on most days for 3 or more months during the year? 4. For how many years have you brought up phlegm from your chest like this?

ARIC = Atherosclerosis Risk in Communities Study; CARDIA = Coronary Artery Risk Development in Young Adults; CHS = Cardiovascular Health Study; FOC = Framingham Offspring Cohort; MESA = Multi-Ethnic Study of Atherosclerosis.

© 2020 American Medical Association. All rights reserved.

eTable 3. Assessment of Smoking Status, by Cohort: the NHLBI Pooled Cohorts Study

Cohort	Ever smoking	Current smoking	Cigarettes per day	Smoking initiation	Smoking cessation
ARIC	Have you ever smoked cigarettes?	Do you now smoke cigarettes?	On the average of the entire time you smoked, how many cigarettes did you smoke per day?	How old were you when you first started regular cigarette smoking?	How old were you when you stopped?
CARDIA	Have you ever smoked cigarettes regularly for at least three months? By "regularly", we mean at least 5 cigarettes per week, almost every week.	Do you still smoke cigarettes regularly?	How many cigarettes do you smoke per day?	How old were you when you started smoking cigarettes regularly?	Altogether, how many years have you smoked cigarettes regularly?
CHS	Have you smoked more than 100 cigarettes or 5 packs in your lifetime?	Have smoked cigarettes in last 30 days?	On the average of the entire time you smoked, how many cigarettes did you smoke per day?	How old were you when you first started to smoke cigarettes?	If you have stopped smoking cigarettes completely, how old were you when you stopped?
FOC	Smoked cigarettes at least for one year?	Smoking: Yes – now?	Usual number of cigarettes smoked (now or formerly)	Age started smoking regularly	If stopped, age stopped
MESA	Have you smoked at least 100 cigarettes in your lifetime?	Have smoked cigarettes in last 30 days?	On average, about how many cigarettes a day do/did you smoke?	How old were you when you first started smoking cigarettes?	How old were you when you quit smoking cigarettes?

ARIC = Atherosclerosis Risk in Communities Study; CARDIA = Coronary Artery Risk Development in Young Adults; CHS = Cardiovascular Health Study; FOC = Framingham Offspring Cohort; MESA = Multi-Ethnic Study of Atherosclerosis.

© 2020 American Medical Association. All rights reserved.

eTable 4. Effect Modification by Smoking Status of Association of Nonobstructive Chronic Bronchitis With, (A) Lung Function Decline, (B) Chronic Lower Respiratory Disease-related Hospitalizations and Mortality, and (C) Respiratory and All-cause Mortality

	β estimate for the interaction term[a]	P-value [b]
A. Lung function decline		
FEV1, mL/year	-2.98	<.0001
FVC, mL/year	-3.38	<.0001
FEV1/FVC, %/year	-0.01	0.0528
B. Clinical events		
Chronic lower respiratory disease -related events	-0.22	0.3309
COPD-related events	0.08	0.8039
Asthma-related events	-0.17	0.6270
C. Mortality		
All-cause	0.32	0.0461
Respiratory	0.92	0.2380

COPD = Chronic obstructive pulmonary disease; FEV1 = Forced expiratory volume in one second; FVC = Forced vital capacity

[a] Estimates for ever-smokers with non-obstructive chronic bronchitis compared to never-smokers without non-obstructive chronic bronchitis.

[b] P-value for the interaction terms, "non-obstructive chronic bronchitis*age*smoking status" in analysis of lung function decline and "non-obstructive chronic bronchitis*smoking status" in analysis of clinical events.

For analysis of lung function (A), linear mixed models with cohort-specific unstructured covariance matrix were used. The coefficient for the three-way multiplicative interaction term (non-obstructive chronic bronchitis*age*smoking status) was interpreted as the longitudinal association with rate of change in lung function ever-smokers compared to never-smokers. Models were adjusted for age, age-squared, height-squared, weight, sex, race/ethnicity, educational attainment, baseline age (centered), birth-year (centered), clinical site, and, among

© 2020 American Medical Association. All rights reserved.

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

For analysis of chronic lower respiratory diseases-related hospitalization and mortality (B and C), associations were tested via proportional-hazards regression. Time-to-event was treated as age-at-event, with left truncation at age when non-obstructive chronic bronchitis was defined. Study was treated as a stratum term, allowing for cohort-specific differences in the underlying survival function. The coefficient for the multiplicative interaction term (non-obstructive chronic bronchitis*smoking status) was interpreted as the log-hazards of non-obstructive chronic bronchitis in ever-smokers compared to never-smokers. Models adjusted for baseline age, birth-year, site, height, weight, sex, race/ethnicity, educational attainment, smoking status, pack-years of smoking, and baseline FEV1/FVC.

© 2020 American Medical Association. All rights reserved.

eTable 5: Associations Between Nonobstructive Chronic Bronchitis and Lung Function Decline, in Sample Restricted to 3 or More Spirometry Assessments

	Never-smokers (n=4,549)			**Ever-smokers (n=3,700)**		
	Without non-obstructive chronic bronchitis n=4,500	**With non-obstructive chronic bronchitis n=49**		**Without non-obstructive chronic bronchitis n=3,594**	**With non-obstructive chronic bronchitis n=106**	
		Estimate (95% CI)	**P-value**		**Estimate (95% CI)**	**P-value**
FEV1, mL/year	Ref.	2.0 (-1.2, 5.3)	0.22	Ref.	-4.2 (-6.6, -1.8)	<.001
FVC, mL/year	Ref.	1.3 (-2.6, 5.2)	0.52	Ref.	-4.7 (-7.6, -1.8)	0.001
FEV1/FVC, %/year	Ref.	0.05 (-0.05, 0.06)	0.86	Ref.	-0.004 (-0.04, 0.03)	0.83

CI = Confidence interval; FEV1 = Forced expiratory volume in one second; FVC = Forced vital capacity

For analysis of lung function, linear mixed models with cohort-specific unstructured covariance matrix were used. The coefficient for the multiplicative interaction term (non-obstructive chronic bronchitis*age) was interpreted as the longitudinal association with rate of change in lung function. Models were adjusted for age, age-squared, height-squared, 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.

© 2020 American Medical Association. All rights reserved.

eTable 6. Associations Between Nonobstructive Chronic Bronchitis, (A) Lung Function Decline, (B) Chronic Lower Respiratory Disease-related Hospitalizations and Mortality, and (C) Respiratory and All-cause Mortality, Stratified by Former and Current Smokers

A. Lung function decline							
	Former smokers (n=7,116)			**Current smokers (n=3,966)**			**Interaction term P-value#**
	Without non-obstructive chronic bronchitis	**With non-obstructive chronic bronchitis**		**Without non-obstructive chronic bronchitis**	**With non-obstructive chronic bronchitis**		
		Estimate (95% CI)	**P-value**		**Estimate (95% CI)**	**P-value**	
FEV1, mL/year	Ref.	-1.9 (-5.8, 1.9)	0.33	Ref.	-4.8 (-7.2, -2.3)	0.0002	0.30
FVC, mL/year	Ref.	-2.0 (-6.8, 2.8)	0.41	Ref.	-6.4 (-9.5, -3.2)	<.0001	0.45
FEV1/FVC, %/year	Ref.	0.003 (-0.05, 0.1)	0.90	Ref.	-0.01 (-0.02, 0.05)	0.53	0.28
B. Chronic lower respiratory disease-related hospitalization and mortality							
	Former smokers (n=5,372)			**Current smokers (n=2,396)**			**Interaction term P-value#**
	Events (Cum. Inc.)	**HR (95% CI)**	**P-value**	**Events (Cum. Inc.)**	**HR (95% CI)**	**P-value**	
Chronic lower respiratory disease-related events	705 (13.1)	4.0 (2.7, 5.9)	<.0001	694 (29.0)	1.8 (1.4, 2.4)	<.0001	0.044
COPD-related events	520 (9.7)	2.9 (1.7, 4.9)	<.0001	611 (25.5)	1.9 (1.4, 2.6)	<.0001	0.43
Asthma-related events	189 (3.5)	6.2 (3.4, 11.4)	<.0001	88 (3.7)	1.9 (0.8, 4.5)	0.12	0.08
C. Mortality							
	Former smokers (n=7,070)			**Current smokers (n=3,955)**			**Interaction term P-value** [b]
	Events (Cum. Inc.)	**HR (95% CI)**	**P-value**	**Events (Cum. Inc.)**	**HR (95% CI)**	**P-value**	
All-cause	2,425 (34.3)	1.6 (1.2, 2.1)	0.003	1,476 (37.3)	1.5 (1.2, 1.8)	0.0004	0.83

© 2020 American Medical Association. All rights reserved.

Respiratory [a]	106 (1.7)	0.7 (0.1, 5.0)	0.71	81 (2.1)	2.6 (1.3, 5.4)	0.008	0.23

CI = Confidence interval; COPD = Chronic obstructive pulmonary disease; Cum. Inc. = Cumulative Incidence; FEV1 = Forced expiratory volume in one second; FVC = Forced vital capacity, HR = Hazard ratio

For analysis of lung function (A), linear mixed models with cohort-specific unstructured covariance matrix were used. The coefficient for the multiplicative interaction term (non-obstructive chronic bronchitis*age) was interpreted as the longitudinal association with rate of change in lung function. Models were adjusted for age, age-squared, height-squared, 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.

For analysis of chronic lower respiratory diseases-related hospitalization and mortality (B and C), associations were tested via proportional-hazards regression. Time-to-event was treated as age-at-event, with left truncation at age when non-obstructive 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 FEV1/FVC.

[a] Since respiratory mortality follow-up was not available in Framingham Offspring Cohort, the number of former smokers at risk was 6,385, and the number of current smokers at risk was 3,891.

[b] P-value for interaction term between current and former smokers.

© 2020 American Medical Association. All rights reserved.

eTable 7. Associations Between Nonobstructive Chronic Bronchitis and Severe Chronic Lower Respiratory Disease Events for Which Chronic Lower Respiratory Disease was the Principal Cause of Admission/Mortality

	Never-smokers				**Ever-smokers**			
	At risk	**Events (Cum. Inc.)**	**HR (95% CI)**	**P-value**	**At risk**	**Events (Cum. Inc.)**	**HR (95% CI)**	**P-value**
Severe chronic lower respiratory disease events	7,486	117 (1.6)	3.4 (1.5, 7.8)	0.005	7,768	256 (3.3)	2.4 (1.5, 3.9)	0.0003
Severe COPD events	7,486	61 (0.8)	3.9 (1.4, 11.1)	0.011	7,768	196 (2.5)	2.7 (1.6, 4.6)	0.0001
Severe Asthma events	7,486	53 (0.7)	4.0 (1.2, 13.1)	0.025	7,768	54 (0.7)	1.4 (0.3, 6.1)	0.620

CI = Confidence interval; COPD = Chronic obstructive pulmonary disease; Cum. Inc. = Cumulative Incidence; HR= Hazards ratio

Excludes participants with self-reported asthma at time of chronic bronchitis ascertainment.

Associations between non-obstructive chronic bronchitis and incident airflow obstruction, incident chronic lower respiratory disease events, and mortality were tested via 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 non-obstructive chronic bronchitis was defined. Study was treated as a stratum term, allowing for cohort-specific differences in the underlying survival function. In addition to the covariates included in the mixed models, proportional-hazards models were adjusted for the baseline FEV1/FVC.

© 2020 American Medical Association. All rights reserved.

eTable 8. Associations Between Nonobstructive Chronic Bronchitis, Defined as Chronic Cough With or Without Chronic Phlegm, (A) Lung Function Decline, (B) Chronic Lower Respiratory Disease-related Hospitalizations and Mortality, and (C) Respiratory and All-cause Mortality

A. Lung function decline						
	Never-smokers (n=11,243)			**Ever-smokers (n=11,082)**		
	Without non-obstructive chronic bronchitis n=10,815	**With non-obstructive chronic bronchitis n=428**		**Without non-obstructive chronic bronchitis n=10,376**	**With non-obstructive chronic bronchitis n=706**	
		Estimate (95% CI)	**P-value**		**Estimate (95% CI)**	**P-value**
FEV1, mL/year	Ref.	-0.4 (-2.1, 1.2)	0.597	Ref.	-2.4 (-3.8, -1.0)	0.001
FVC, mL/year	Ref.	-0.4 (-2.5, 1.7)	0.701	Ref.	-2.5 (-4.3, -0.8)	0.005
FEV1/FVC, %/year	Ref.	-0.01 (-0.03, 0.02)	0.488	Ref.	-0.01 (-0.03, 0.01)	0.318
B. Chronic lower respiratory disease-related hospitalization and mortality						
	Never-smokers (n=7,544)			**Ever-smokers (n=7,829)**		
	Events (Cum. Inc.)	**HR (95% CI)**	**P-value**	**Events (Cum. Inc.)**	**HR (95% CI)**	**P-value**
Chronic lower respiratory disease-related events	689 (9.1)	2.4 (1.8, 3.1)	<.0001	1,416 (18.1)	1.9 (1.6, 2.2)	<.0001
COPD-related events	383 (5.1)	2.0 (1.3, 2.9)	0.001	1,144 (14.6)	1.7 (1.5, 2.1)	<.0001
Asthma-related events	309 (4.1)	2.8 (1.9, 4.0)	<.0001	281 (3.6)	2.6 (1.8, 3.7)	<.0001
C. Mortality						
	Never-smokers (n=11,255)			**Ever-smokers (n=11,102)**		
	Events (Cum. Inc.)	**HR (95% CI)**	**P-value**	**Events (Cum. Inc.)**	**HR (95% CI)**	**P-value**
All-cause	3,262 (29.0)	1.0 (0.9, 1.2)	0.673	3,952 (35.6)	1.3 (1.2, 1.5)	<.0001

© 2020 American Medical Association. All rights reserved.

Respiratory [a]	108 (1.0)	1.4 (0.6, 3.1)	0.387	191 (1.8)	2.5 (1.6, 3.8)	<.0001

CI = Confidence interval; COPD = Chronic obstructive pulmonary disease; Cum. Inc. = Cumulative Incidence; FEV1 = Forced expiratory volume in one second; FVC = Forced vital capacity, HR = Hazard ratio

Chronic cough was defined as production of phlegm for ≥3 months in ≥2 consecutive years.

Chronic phlegm was defined as production of phlegm for ≥3 months in ≥2 consecutive years.

For analysis of lung function (A), linear mixed models with cohort-specific unstructured covariance matrix were used. The coefficient for the multiplicative interaction term (non-obstructive chronic bronchitis*age) was interpreted as the longitudinal association with rate of change in lung function. Models were adjusted for age, age-squared, height-squared, 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.
For analysis of chronic lower respiratory diseases-related hospitalization and mortality (B and C), associations were tested via proportional-hazards regression. Time-to-event was treated as age-at-event, with left truncation at age when non-obstructive 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 FEV1/FVC.

[a] Since respiratory mortality follow-up was not available in Framingham Offspring Cohort, the number of never-smokers at risk was 10,688, and the number of ever-smokers at risk was 10,337.

© 2020 American Medical Association. All rights reserved.

eTable 9. Associations Between Non-obstructive Chronic Bronchitis, Defined as Chronic Phlegm With or Without Chronic Cough, (A) Lung Function Decline, (B) Chronic Lower Respiratory Disease-related Hospitalizations and Mortality, and (C) Respiratory and All-cause Mortality

A. Lung function decline						
	Never-smokers (n=11,243)			**Ever-smokers (n=11,082)**		
	Without non-obstructive chronic bronchitis n=10,770	**With non-obstructive chronic bronchitis n=473**		**Without non-obstructive chronic bronchitis n=10,273**	**With non-obstructive chronic bronchitis n=809**	
		Estimate (95% CI)	**P-value**		**Estimate (95% CI)**	**P-value**
FEV1, mL/year	Ref.	-0.3 (-1.7, 1.1)	0.685	Ref.	-2.1 (-3.3, -0.9)	0.001
FVC, mL/year	Ref.	-0.3 (-1.4, 2.1)	0.698	Ref.	-2.3 (-3.8, -0.8)	0.002
FEV1/FVC, %/year	Ref.	-0.02 (-0.04, 0.002)	0.0739	Ref.	-0.01 (-0.02, 0.01)	0.518
B. Chronic lower respiratory disease-related hospitalization and mortality						
	Never-smokers (n=7,514)			**Ever-smokers (n=7,799)**		
	Events (Cum. Inc.)	**HR (95% CI)**	**P-value**	**Events (Cum. Inc.)**	**HR (95% CI)**	**P-value**
Chronic lower respiratory disease-related events	685 (9.1)	1.8 (1.3, 2.4)	<.0001	1,414 (18.1)	1.7 (1.5, 2.0)	<.0001
COPD-related events	381 (5.1)	2.0 (1.3, 2.8)	0.0004	1,142 (14.6)	1.5 (1.3, 1.8)	<.0001
Asthma-related events	307 (4.1)	1.5 (0.9, 2.3)	0.093	281 (3.6)	2.7 (1.9, 3.8)	<.0001
C. Mortality						
	Never-smokers (n=11,226)			**Ever-smokers (n=11,065)**		

© 2020 American Medical Association. All rights reserved.

	Events (Cum. Inc.)	HR (95% CI)	P-value	Events (Cum. Inc.)	HR (95% CI)	P-value
All-cause	3,240 (28.9)	1.0 (0.8, 1.1)	0.709	3,930 (35.5)	1.2 (1.1, 1.3)	0.004
Respiratory [a]	106 (1.0)	1.6 (0.8, 3.3)	0.175	188 (1.8)	1.3 (0.8, 2.1)	0.258

CI = Confidence interval; COPD = Chronic obstructive pulmonary disease; Cum. Inc. = Cumulative Incidence; FEV1 = Forced expiratory volume in one second; FVC = Forced vital capacity, HR = Hazard ratio

Chronic cough was defined as production of phlegm for ≥3 months in ≥2 consecutive years.

Chronic phlegm was defined as production of phlegm for ≥3 months in ≥2 consecutive years.

For analysis of lung function (A), linear mixed models with cohort-specific unstructured covariance matrix were used. The coefficient for the multiplicative interaction term (non-obstructive chronic bronchitis*age) was interpreted as the longitudinal association with rate of change in lung function. Models were adjusted for age, age-squared, height-squared, 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.
For analysis of chronic lower respiratory diseases-related hospitalization and mortality (B and C), associations were tested via proportional-hazards regression. Time-to-event was treated as age-at-event, with left truncation at age when non-obstructive 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 FEV1/FVC.

[a] Since respiratory mortality follow-up was not available in Framingham Offspring Cohort, the number of never-smokers at risk was 10,658, and the number of ever-smokers at risk was 10,308.

© 2020 American Medical Association. All rights reserved.

eTable 10. Associations Between Nonobstructive Chronic Bronchitis, Defined as Chronic Cough or Chronic Phlegm, (A) Lung Function Decline, (B) Chronic Lower Respiratory Disease-related Hospitalizations and Mortality, and (C) Respiratory and All-cause Aortality

A. Lung function decline						
	Never-smokers (n=11,243)			**Ever-smokers (n=11,082)**		
	Without non-obstructive chronic bronchitis n=10,493	**With non-obstructive chronic bronchitis n=750**		**Without non-obstructive chronic bronchitis n=9,867**	**With non-obstructive chronic bronchitis n=1,215**	
		Estimate (95% CI)	**P-value**		**Estimate (95% CI)**	**P-value**
FEV1, mL/year	Ref.	-0.5 (-1.7, 0.6)	0.383	Ref.	-1.8 (-2.9, -0.8)	0.001
FVC, mL/year	Ref.	-0.1 (-1.6, 1.3)	0.843	Ref.	-1.9 (-3.2, -0.6)	0.004
FEV1/FVC, %/year	Ref.	-0.01 (-0.03, 0.003)	0.113	Ref.	-0.01 (-0.02, 0.01)	0.203
B. Chronic lower respiratory disease-related hospitalization and mortality						
	Never-smokers (n=7,572)			**Ever-smokers (n=7,860)**		
	Events (Cum. Inc.)	**HR (95% CI)**	**P-value**	**Events (Cum. Inc.)**	**HR (95% CI)**	**P-value**
Chronic lower respiratory disease-related events	691 (9.1)	1.9 (1.5, 2.4)	<.0001	1,431 (18.3)	1.7 (1.5, 2.0)	<.0001
COPD-related events	384 (5.1)	1.9 (1.4, 2.6)	<.0001	1,155 (14.7)	1.6 (1.3, 1.8)	<.0001
Asthma-related events	310 (4.1)	1.8 (1.3, 2.5)	0.001	285 (3.6)	2.5 (1.9, 3.4)	<.0001
C. Mortality						
	Never-smokers (n=11,290)			**Ever-smokers (n=11,142)**		
	Events (Cum. Inc.)	**HR (95% CI)**	**P-value**	**Events (Cum. Inc.)**	**HR (95% CI)**	**P-value**

© 2020 American Medical Association. All rights reserved.

All-cause	3,287 (29.1)	1.0 (0.8, 1.1)	0.499	3,981 (35.7)	1.2 (1.1, 1.3)	0.001
Respiratory [a]	109 (1.0)	1.6 (0.9, 2.9)	0.090	192 (1.9)	1.8 (1.2, 2.6)	0.002

CI = Confidence interval; COPD = Chronic obstructive pulmonary disease; Cum. Inc. = Cumulative Incidence; FEV1 = Forced expiratory volume in one second; FVC = Forced vital capacity, HR = Hazard ratio

Chronic cough was defined as production of phlegm for ≥3 months in ≥2 consecutive years.

Chronic phlegm was defined as production of phlegm for ≥3 months in ≥2 consecutive years.

For analysis of lung function (A), linear mixed models with cohort-specific unstructured covariance matrix were used. The coefficient for the multiplicative interaction term (non-obstructive chronic bronchitis *age) was interpreted as the longitudinal association with rate of change in lung function. Models were adjusted for age, age-squared, height-squared, 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.
For analysis of chronic lower respiratory diseases-related hospitalization and mortality (B and C), associations were tested via proportional-hazards regression. Time-to-event was treated as age-at-event, with left truncation at age when non-obstructive 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 FEV1/FVC.

[a] Since respiratory mortality follow-up was not available in Framingham Offspring Cohort, the number of never-smokers at risk was 10,716, and the number of ever-smokers at risk was 10,369.

© 2020 American Medical Association. All rights reserved.

eTable 11. Associations Between Nonobstructive Chronic Bronchitis as Defined by FEV_1/FVC < lower-limit-normal, (A) Lung Function Decline, (B) Chronic Lower Respiratory Disease-related Hospitalizations and Mortality, and (C) Respiratory and All-cause Mortality

A. Lung function decline						
	Never-smokers (n=11,893)			**Ever-smokers (n=12,515)**		
	Without non-obstructive chronic bronchitis n=11,725	**With non-obstructive chronic bronchitis n=168**		**Without non-obstructive chronic bronchitis n=12,171**	**With non-obstructive chronic bronchitis n=344**	
		Estimate (95% CI)	**P-value**		**Estimate (95% CI)**	**P-value**
FEV1, mL/year	Ref.	-0.2 (-4.0, 3.7)	0.932	Ref.	-4.3 (-6.8, -1.7)	0.001
FVC, mL/year	Ref.	-1.0 (-2.6, 4.5)	0.597	Ref.	-3.9 (-6.4, -1.4)	0.002
FEV1/FVC, %/year	Ref.	-0.03 (-0.07, 0.01)	0.127	Ref.	-0.01 (-0.04, 0.01)	0.361
B. Chronic lower respiratory disease-related hospitalization and mortality						
	Never-smokers (n=8,146)			**Ever-smokers (n=9,055)**		
	Events (Cum. Inc.)	**HR (95% CI)**	**P-value**	**Events (Cum. Inc.)**	**HR (95% CI)**	**P-value**
Chronic lower respiratory disease-related events	797 (9.8)	3.0 (2.2, 4.2)	<.0001	1,756 (19.4)	2.0 (1.6, 2.5)	<.0001
COPD-related events	467 (5.7)	2.5 (1.6, 4.0)	<.0001	1,449 (16.0)	1.8 (1.5, 2.3)	<.0001
Asthma-related events	333 (4.1)	3.3 (2.0, 5.4)	<.0001	320 (3.5)	3.0 (1.9, 4.7)	<.0001
C. Mortality						
	Never-smokers (n=11,836)			**Ever-smokers (n=12,438)**		
	Events (Cum. Inc.)	**HR (95% CI)**	**P-value**	**Events (Cum. Inc.)**	**HR (95% CI)**	**P-value**

© 2020 American Medical Association. All rights reserved.

All-cause	3,636 (30.7)	1.2 (0.9, 1.5)	0.200	4,819 (38.7)	1.3 (1.1, 1.6)	0.000
Respiratory [a]	131 (1.2)	1.6 (0.6, 4.3)	0.384	241 (2.1)	1.8 (1.1, 3.2)	0.030

CI = Confidence interval; COPD = Chronic obstructive pulmonary disease; Cum. Inc. = Cumulative Incidence; FEV1 = Forced expiratory volume in one second; FVC = Forced vital capacity, HR = Hazard ratio

For analysis of lung function (A), linear mixed models with cohort-specific unstructured covariance matrix were used. The coefficient for the multiplicative interaction term (non-obstructive chronic bronchitis*age) was interpreted as the longitudinal association with rate of change in lung function. Models were adjusted for age, age-squared, height-squared, 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.

For analysis of chronic lower respiratory diseases-related hospitalization and mortality (B and C), associations were tested via proportional-hazards regression. Time-to-event was treated as age-at-event, with left truncation at age when non-obstructive 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 FEV1/FVC.

[a] Since respiratory mortality follow-up was not available in Framingham Offspring Cohort, the number of never-smokers at risk was 11,177, and the number of ever-smokers at risk was 11,470.

© 2020 American Medical Association. All rights reserved.

eTable 12. Associations Between Nonobstructive Chronic Bronchitis, (A) Lung Function Decline, (B) Chronic Lower Respiratory Disease-related Hospitalizations and Mortality, and (C) Respiratory and All-cause Mortality, in Sample Including Baseline Self-reported Physician-diagnosed Asthma

A. Lung function decline						
	Never-smokers (n=11,767)			**Ever-smokers (n=11,574)**		
	Without non-obstructive chronic bronchitis n=11,592	**With non-obstructive chronic bronchitis n=175**		**Without non-obstructive chronic bronchitis n=11,233**	**With non-obstructive chronic bronchitis n=341**	
		Estimate (95% CI)	**P-value**		**Estimate (95% CI)**	**P-value**
FEV1, mL/year	Ref.	-0.2 (-2.3, 2.8)	0.86	Ref.	-4.3 (-6.2, -2.4)	<.001
FVC, mL/year	Ref.	-0.8 (-4.0, 2.5)	0.65	Ref.	-4.6 (-7.0, -2.2)	<.001
FEV1/FVC, %/year	Ref.	0.01 (-0.02, 0.05)	0.46	Ref.	-0.01 (-0.04, 0.02)	0.48
B. Chronic lower respiratory disease-related hospitalization and mortality						
	Never-smokers (n=7,779)			**Ever-smokers (n=8,048)**		
	Events (Cum. Inc.)	**HR (95% CI)**	**P-value**	**Events (Cum. Inc.)**	**HR (95% CI)**	**P-value**
Chronic lower respiratory disease-related events	784 (10.1)	2.9 (2.0, 4.1)	<.001	1,522 (18.9)	2.5 (2.0, 3.0)	<.001
COPD-related events	397 (5.1)	2.2 (1.3, 3.8)	0.004	1,193 (14.8)	2.1 (1.6, 2.6)	<.001
Asthma-related events	394 (5.1)	3.4 (2.2, 5.2)	<.001	341 (4.2)	3.9 (2.6, 5.7)	<.001
C. Mortality						
	Never-smokers (n=11,709)			**Ever-smokers (n=11,515)**		
	Events	**HR**	**P-value**	**Events**	**HR**	**P-value**

© 2020 American Medical Association. All rights reserved.

	(Cum. Inc.)	(95% CI)		(Cum. Inc.)	(95% CI)	
All-cause	3,355 (28.7)	1.3 (0.9, 1.6)	0.05	4,066 (35.3)	1.6 (1.3, 1.8)	<.001
Respiratory [a]	116 (1.0)	0.9 (0.2, 4.0)	0.98	198 (1.8)	2.3 (1.3, 4.1)	0.004

CI = Confidence interval; COPD = Chronic obstructive pulmonary disease; Cum. Inc. = Cumulative Incidence; FEV1 = Forced expiratory volume in one second; FVC = Forced vital capacity, HR = Hazard ratio

For analysis of lung function (A), linear mixed models with cohort-specific unstructured covariance matrix were used. The coefficient for the multiplicative interaction term (non-obstructive chronic bronchitis*age) was interpreted as the longitudinal association with rate of change in lung function. Models were adjusted for age, age-squared, height-squared, 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.

For analysis of chronic lower respiratory diseases-related hospitalization and mortality (B and C), associations were tested via proportional-hazards regression. Time-to-event was treated as age-at-event, with left truncation at age when non-obstructive 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 FEV1/FVC.

[a] Since respiratory mortality follow-up was not available in Framingham Offspring Cohort, the number of never-smokers at risk was 11,126, and the number of ever-smokers at risk was 10,737.

© 2020 American Medical Association. All rights reserved.

eTable 13. Associations Between Nonobstructive Chronic Bronchitis, (A) Lung Function Decline, (B) Chronic Lower Respiratory Disease-related Hospitalizations and Mortality, and (C) Respiratory and All-cause Mortality, in a Sample Excluding Incident Airflow Obstruction

A. Lung function decline						
	Never-smokers (n=8,171)			**Ever-smokers (n=7,217)**		
	Without non-obstructive chronic bronchitis n=8,075	**With non-obstructive chronic bronchitis n=96**		**Without non-obstructive chronic bronchitis n=7,030**	**With non-obstructive chronic bronchitis n=187**	
		Estimate (95% CI)	**P-value**		**Estimate (95% CI)**	**P-value**
FEV1, mL/year	Ref.	-1.5 (-1.5, 4.6)	0.32	Ref.	-3.6 (-5.9, -1.3)	0.002
FVC, mL/year	Ref.	-1.5 (-2.3, 5.4)	0.44	Ref.	-4.8 (-7.7, -2.0)	0.001
FEV1/FVC, %/year	Ref.	-0.01 (-0.1, 0.04)	0.70	Ref.	0.02 (-0.01, 0.05)	0.16
B. Chronic lower respiratory disease-related hospitalization and mortality						
	Never-smokers (n=6,975)			**Ever-smokers (n=6,897)**		
	Events (Cum. Inc.)	**HR (95% CI)**	**P-value**	**Events (Cum. Inc.)**	**HR (95% CI)**	**P-value**
Chronic lower respiratory disease-related events	623 (8.9)	2.8 (1.9, 4.3)	<.001	1,176 (17.1)	2.4 (1.9, 3.1)	<.001
COPD-related events	352 (5.0)	2.2 (1.2, 4.0)	0.01	952 (13.8)	2.2 (1.7, 2.9)	<.001
Asthma-related events	274 (3.9)	3.3 (1.9, 5.8)	<.001	234 (3.4)	3.9 (2.4, 6.4)	<.001
C. Mortality						
	Never-smokers (n=10,462)			**Ever-smokers (n=9,809)**		
	Events (Cum. Inc.)	**HR (95% CI)**	**P-value**	**Events (Cum. Inc.)**	**HR (95% CI)**	**P-value**

© 2020 American Medical Association. All rights reserved.

All-cause	3,078 (29.4)	1.2 (0.9, 1.5)	0.27	3,583 (36.5)	1.6 (1.3, 1.9)	<.001
Respiratory [a]	100 (1.0)	1.2 (0.3, 4.8)	0.84	153 (1.7)	2.9 (1.5, 5.6)	0.001

CI = Confidence interval; COPD = Chronic obstructive pulmonary disease; Cum. Inc. = Cumulative Incidence; FEV1 = Forced expiratory volume in one second; FVC = Forced vital capacity, HR = Hazard ratio

For analysis of lung function (A), linear mixed models with cohort-specific unstructured covariance matrix were used. The coefficient for the multiplicative interaction term (non-obstructive chronic bronchitis*age) was interpreted as the longitudinal association with rate of change in lung function. Models were adjusted for age, age-squared, height-squared, 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.

For analysis of chronic lower respiratory diseases-related hospitalization and mortality (B and C), associations were tested via proportional-hazards regression. Time-to-event was treated as age-at-event, with left truncation at age when non-obstructive 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 FEV1/FVC.

[a] Since respiratory mortality follow-up was not available in Framingham Offspring Cohort, the number of never-smokers at risk was 9,929, and the number of ever-smokers at risk was 9,099

© 2020 American Medical Association. All rights reserved.

eTable 14. Associations Between Nonobstructive Chronic Bronchitis, (A) Lung Function Decline, (B) Chronic Lower Respiratory Disease-related Hospitalizations and Mortality, and (C) Respiratory and All-cause Mortality, Stratified by Sustained Smoking Status

A. Lung function decline									
	Sustained never-smokers (n=9,918)			**Sustained former smokers (n=5,691)**			**Sustained current smokers (n=2,064)**		
	Without non-obstructive chronic bronchitis (n=9,779)	**With non-obstructive chronic bronchitis (n=139)**		**Without non-obstructive chronic bronchitis (n=5,612)**	**With non-obstructive chronic bronchitis (n=79)**		**Without non-obstructive chronic bronchitis (n=1,942)**	**With non-obstructive chronic bronchitis (n=122, 5.9%)**	
		Estimate (95% CI)	**P-value**		**Estimate (95% CI)**	**P-value**		**Estimate (95% CI)**	**P-value**
FEV1, mL/year	Ref.	-0.1 (-2.9, 2.7)	0.95	Ref.	-5.4 (-10.0, -0.8)	0.02	Ref.	-7.6 (-11.3, -3.9)	<.001
FVC, mL/year	Ref.	0.2 (-3.4, 3.8)	0.92	Ref.	-6.4 (-12.2, -0.6)	0.03	Ref.	-9.4 (-14.0, -4.7)	<.001
FEV1/FVC, %/year	Ref.	-0.02 (-0.1, 0.03)	0.42	Ref.	-0.001 (-0.1, 0.1)	0.98	Ref.	0.02 [a] (-0.04, 0.1)	0.60
B. Chronic lower respiratory disease-related hospitalization and mortality									
	Sustained never-smokers (n=6,618)			**Sustained former smokers (n=4,741)**			**Sustained current smokers (n=1,345)**		
	Events (Cum. Inc.)	**HR (95% CI)**	**P-value**	**Events (Cum. Inc.)**	**HR (95% CI)**	**P-value**	**Events (Cum. Inc.)**	**HR (95% CI)**	**P-value**
Chronic lower respiratory disease-related events	592 (8.9)	3.4 (2.3, 5.1)	<.001	623 (13.1)	4.1 (2.7, 6.2)	<.001	426 (31.7)	1.5 (1.1, 2.2)	0.016
COPD-related events	325 (4.9)	2.7 (1.5, 4.7)	0.001	456 (9.6)	2.7 (1.5, 4.9)	0.001	391 (29.1)	1.5 (1.1, 2.1)	0.027
Asthma-related events	269 (4.1)	3.8 (2.2, 6.5)	<.001	168 (3.5)	7.2 (3.8, 13.6)	<.001	39 (2.9)	4.0 (1.4, 11.5)	0.009
C. Mortality									
	Sustained never-smokers (n=9,871)			**Sustained former smokers (n=5,666)**			**Sustained current smokers (n=2,058)**		
	Events (Cum. Inc.)	**HR (95% CI)**	**P-value**	**Events (Cum. Inc.)**	**HR (95% CI)**	**P-value**	**Events (Cum. Inc.)**	**HR (95% CI)**	**P-value**
All-cause	2,843 (28.8)	1.2 (0.9, 1.6)	0.13	2,188 (38.6)	1.6 (1.2, 2.2)	0.004	987 (4.8)	1.4 (1.1, 1.8)	0.013

© 2020 American Medical Association. All rights reserved.

Respiratory [b]	94 (1.0)	1.2 (0.3, 5.1)	0.77	99 (1.8)	0.9 (0.1, 6.3)	0.88	53 (2.6)	4.1 (1.8, 9.3)	0.001

CI = Confidence interval; COPD = Chronic obstructive pulmonary disease; Cum. Inc. = Cumulative Incidence; FEV1 = Forced expiratory volume in one second; FVC = Forced vital capacity, HR = Hazard ratio

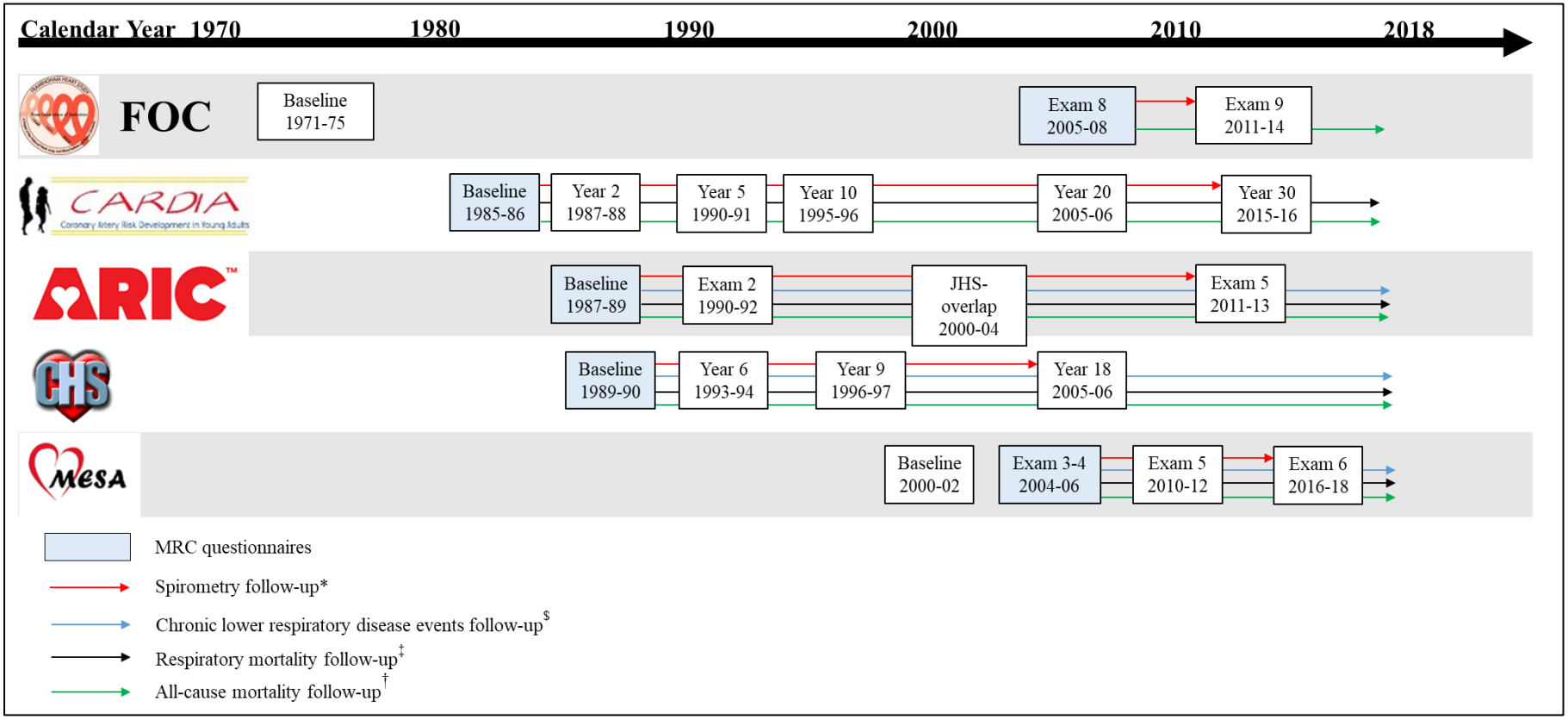
For analysis of lung function (A), linear mixed models with cohort-specific unstructured covariance matrix were used. The coefficient for the multiplicative interaction term (non-obstructive chronic bronchitis*age) was interpreted as the longitudinal association with rate of change in lung function. Models were adjusted for age, age-squared, height-squared, 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.
For analysis of chronic lower respiratory diseases-related hospitalization and mortality (B and C), associations were tested via proportional-hazards regression. Time-to-event was treated as age-at-event, with left truncation at age when non-obstructive 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 FEV1/FVC.

[a] Since model for FEV1/FVC decline did not converge, participants from the Cardiovascular Health Study (n=74) and Framingham Heart Study- Offspring (n=44) were excluded. So, the total number of current-smokers for this analysis were 1,964, among whom 115 had non-obstructive chronic bronchitis.

[b] Since respiratory mortality follow-up was not available in Framingham Offspring Cohort, the number of never-smokers, former-smokers and current-smokers at risk were 9,310, 5,446, and 2,029, respectively.

© 2020 American Medical Association. All rights reserved.

eFigure 1. Follow-up for Chronic Bronchitis and Respiratory Outcomes in the NHLBI Pooled Cohorts Study



ARIC = Atherosclerosis Risk In Communities Study; CARDIA = Coronary Artery Risk Development in Young Adults Study; CHS = Cardiovascular Health Study; FOC = Framingham Offspring Cohort; MESA = Multi-Ethnic Study of Atherosclerosis; MRC = Medical Research Council

* Longitudinal lung function were measured in five cohorts: ARIC, CARDIA, CHS, FOC, and MESA.

© 2020 American Medical Association. All rights reserved.

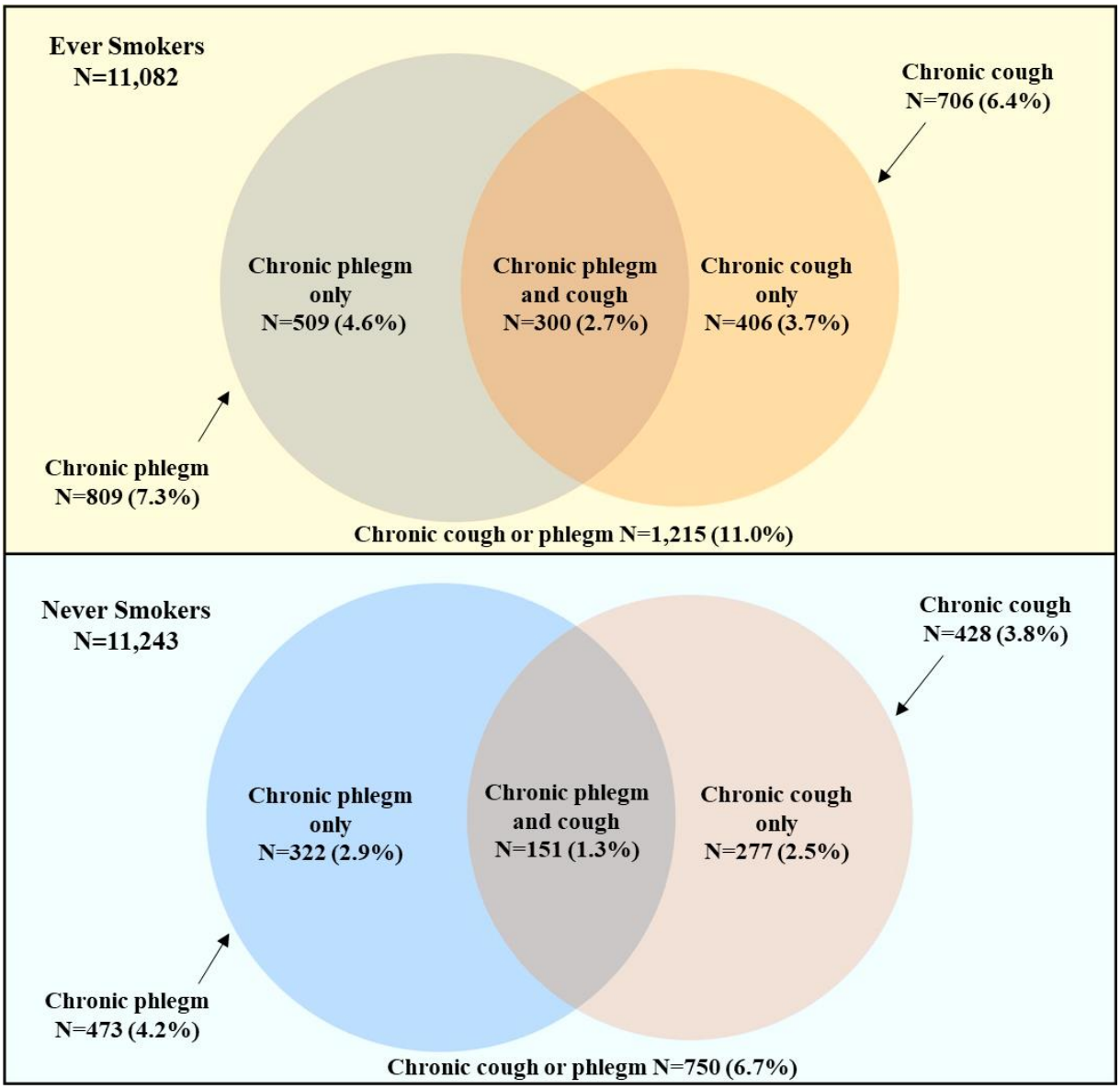
[$] Administrative criteria were used to classify chronic lower respiratory disease-related mortality (ARIC and MESA) and hospitalizations (ARIC, CHS and MESA) following a previously validated protocol using International Classification of Diseases (ICD) codes for chronic lower respiratory diseases (asthma [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]). Chronic lower respiratory disease-related events were defined as hospitalizations or deaths for which chronic lower respiratory diseases were classified as a primary/underlying or contributing cause. Chronic lower respiratory disease-related events were further sub-stratified into events attributed to asthma versus COPD, the latter of which was defined to include COPD, emphysema, and chronic bronchitis. Severe chronic lower respiratory disease events were defined as the subset of chronic lower respiratory disease -related events for which chronic lower respiratory diseases was a primary/underlying cause.

[‡] Respiratory deaths were adjudicated in two cohorts (CARDIA, CHS) and defined using administrative criteria (ICD-10, J1-J99) in two cohorts (ARIC, MESA).

[†] All-cause mortality was ascertained via follow-up calls, supplemented by the National Death Index in all five cohorts.

© 2020 American Medical Association. All rights reserved.

eFigure 2. Alternative Definitions of Nonobstructive Chronic Bronchitis

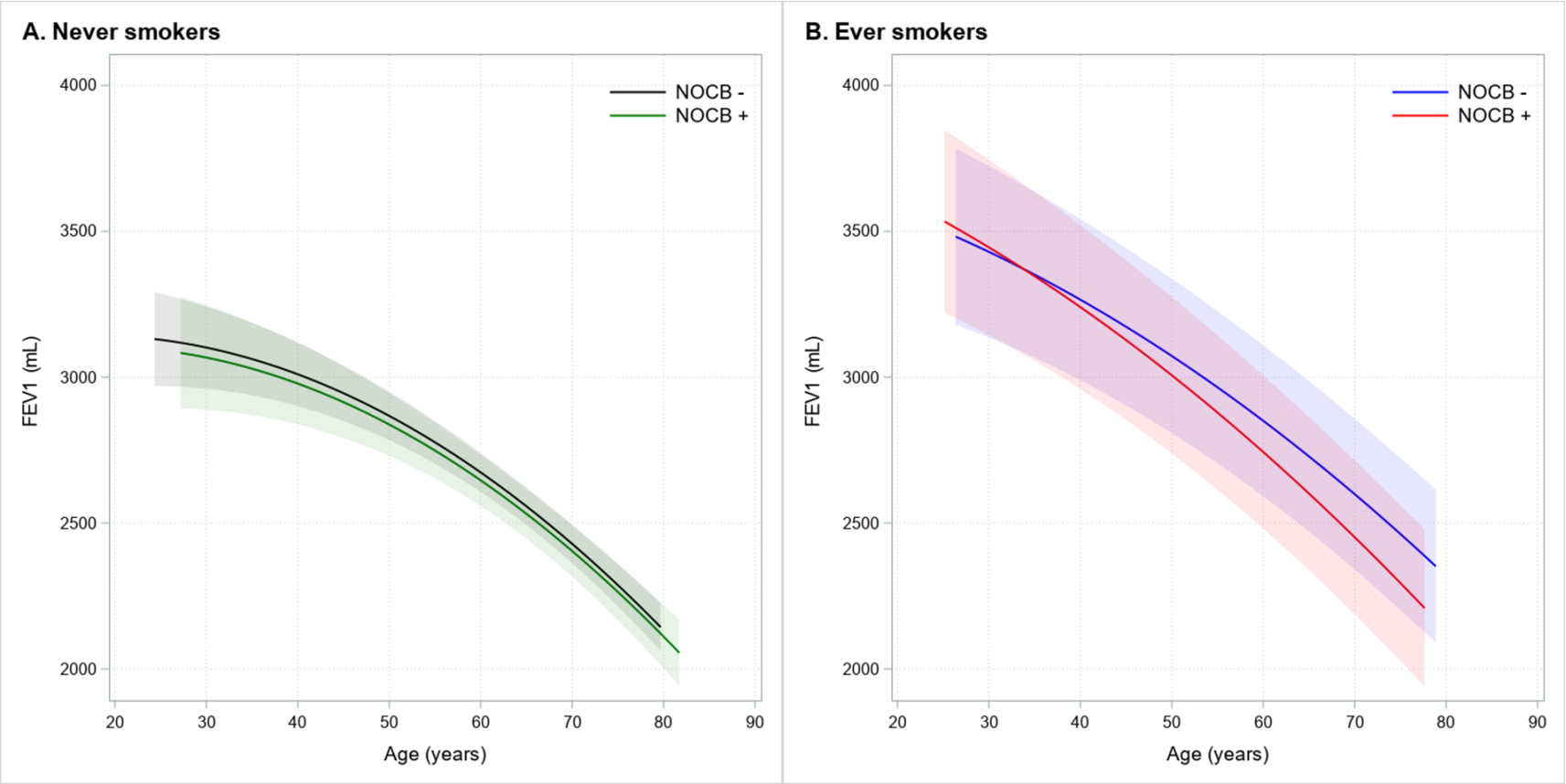


Chronic phlegm was defined as production of phlegm for ≥3 months in ≥2 consecutive years.

Chronic cough was defined as production of phlegm for ≥3 months in ≥2 consecutive years.

© 2020 American Medical Association. All rights reserved.

eFigure 3. Associations Between Nonobstructive Chronic Bronchitis and Lung Function Decline in (A) Never-smokers and (B) Ever-smokers



Excludes participants with self-reported asthma at time of chronic bronchitis ascertainment.

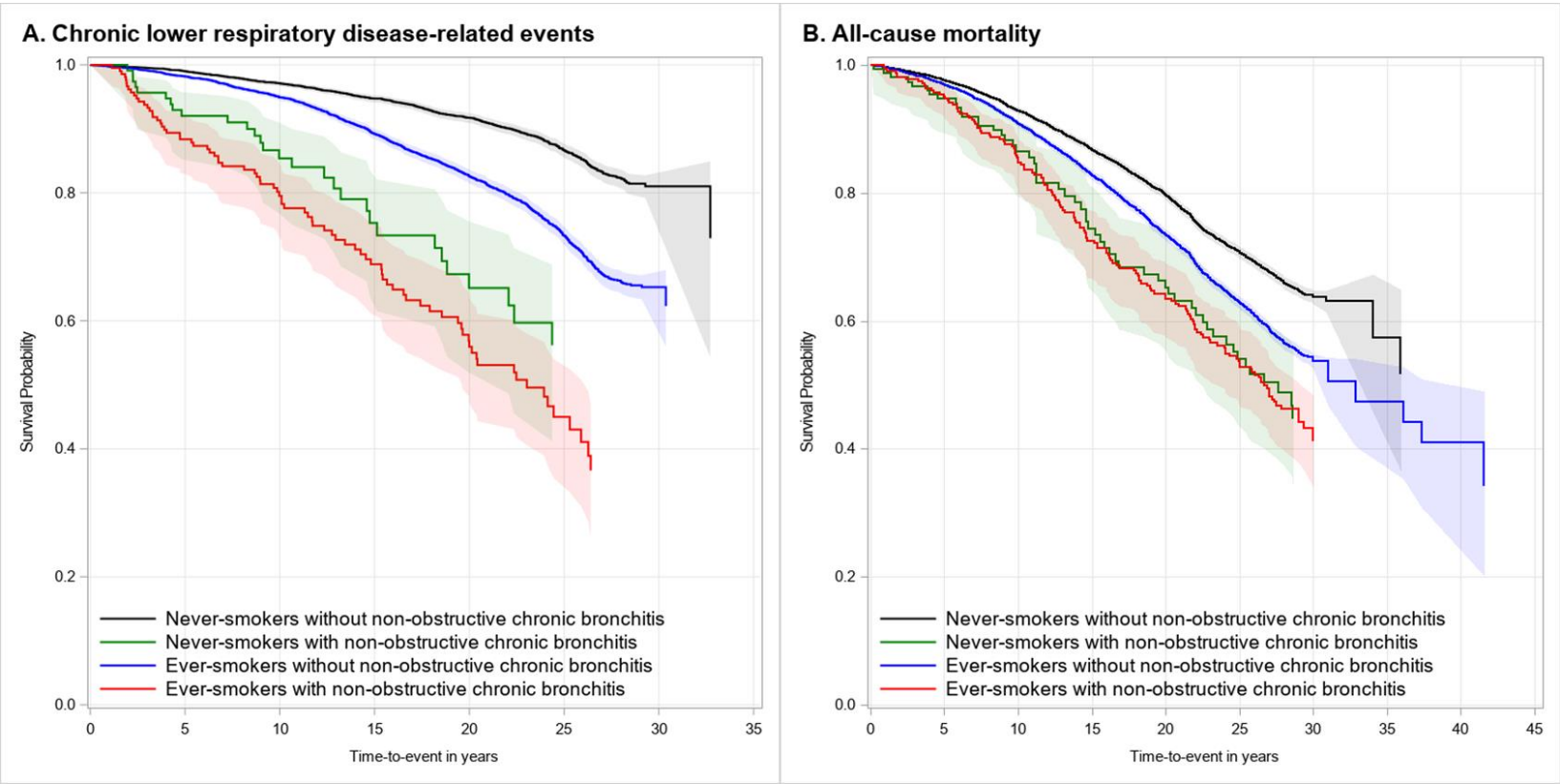
© 2020 American Medical Association. All rights reserved.

The sample includes adults of ages 18-95 years with mean 10 years (range 0-31 years) of follow-up for spirometry. The FEV1 function decline predictions beyond the 95th percentile of the distribution of age were censored.

Linear mixed models with cohort-specific unstructured covariance matrix were used. The coefficient for the multiplicative interaction term (non-obstructive chronic bronchitis*age) was interpreted as the longitudinal association with rate of change in lung function. Models were adjusted for age, age-squared, height-squared, 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.

© 2020 American Medical Association. All rights reserved.

eFigure 4. Unadjusted Kaplan-Meier Curve to Illustrate the Differences in Observed (A) Chronic Lower Respiratory Disease-related Events and (B) All-cause Mortality, According to Nonobstructive Chronic Bronchitis and Smoking Status

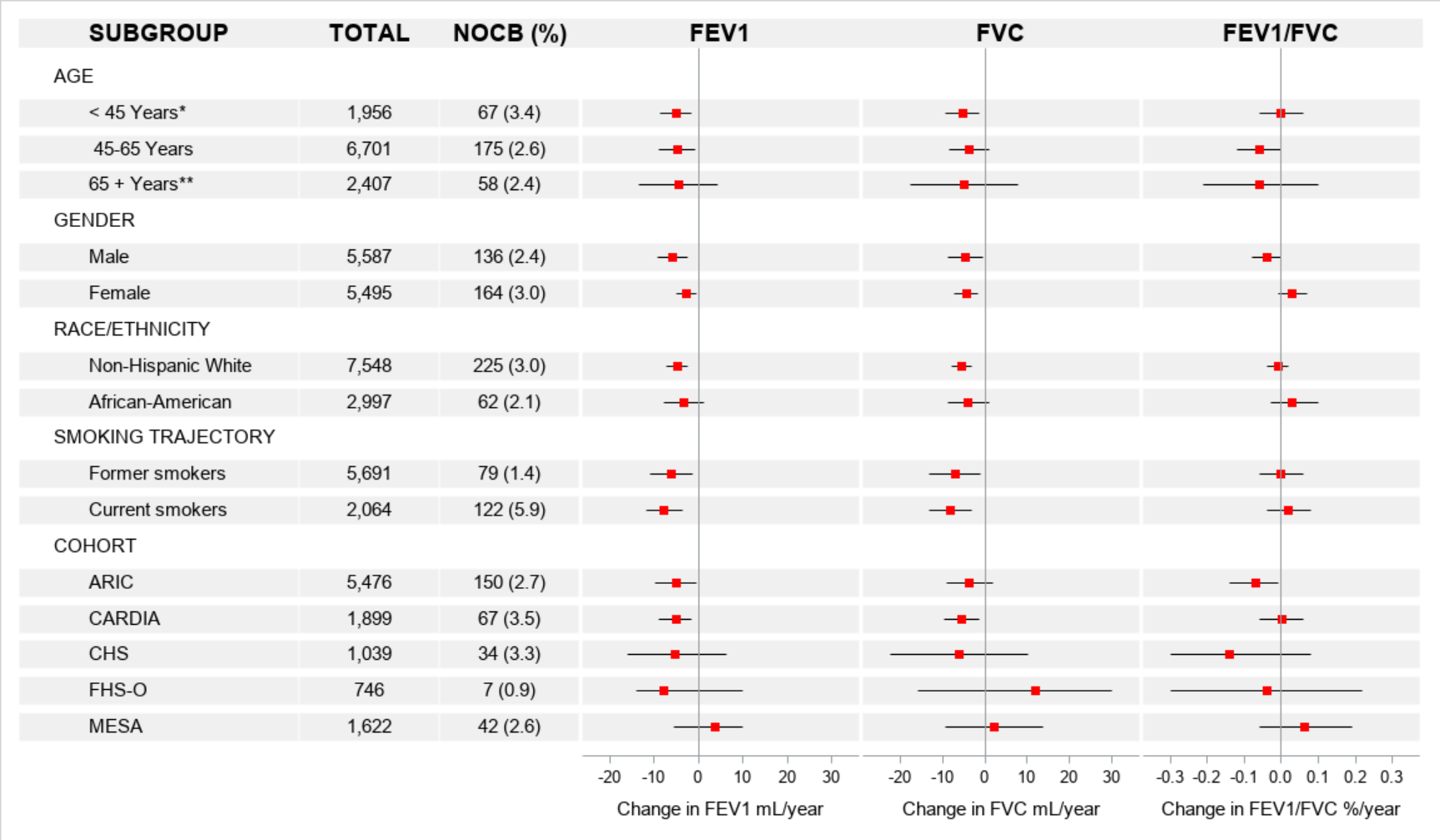


Excludes participants with self-reported asthma at time of chronic bronchitis ascertainment.

The sample includes adults of ages 18-95 years with mean 17 years (maximum 42 years) of follow-up for chronic lower respiratory disease events.

© 2020 American Medical Association. All rights reserved.

eFigure 5. Associations Between Nonobstructive Chronic Bronchitis and Decline in the FEV_1, FVC, and FEV_1/FVC, Stratified by Sociodemographic Factors Among Ever-smokers



FEV1 = Forced expiratory volume in second; FVC = Forced vital capacity

© 2020 American Medical Association. All rights reserved.

Excludes participants with self-reported asthma at time of chronic bronchitis ascertainment.

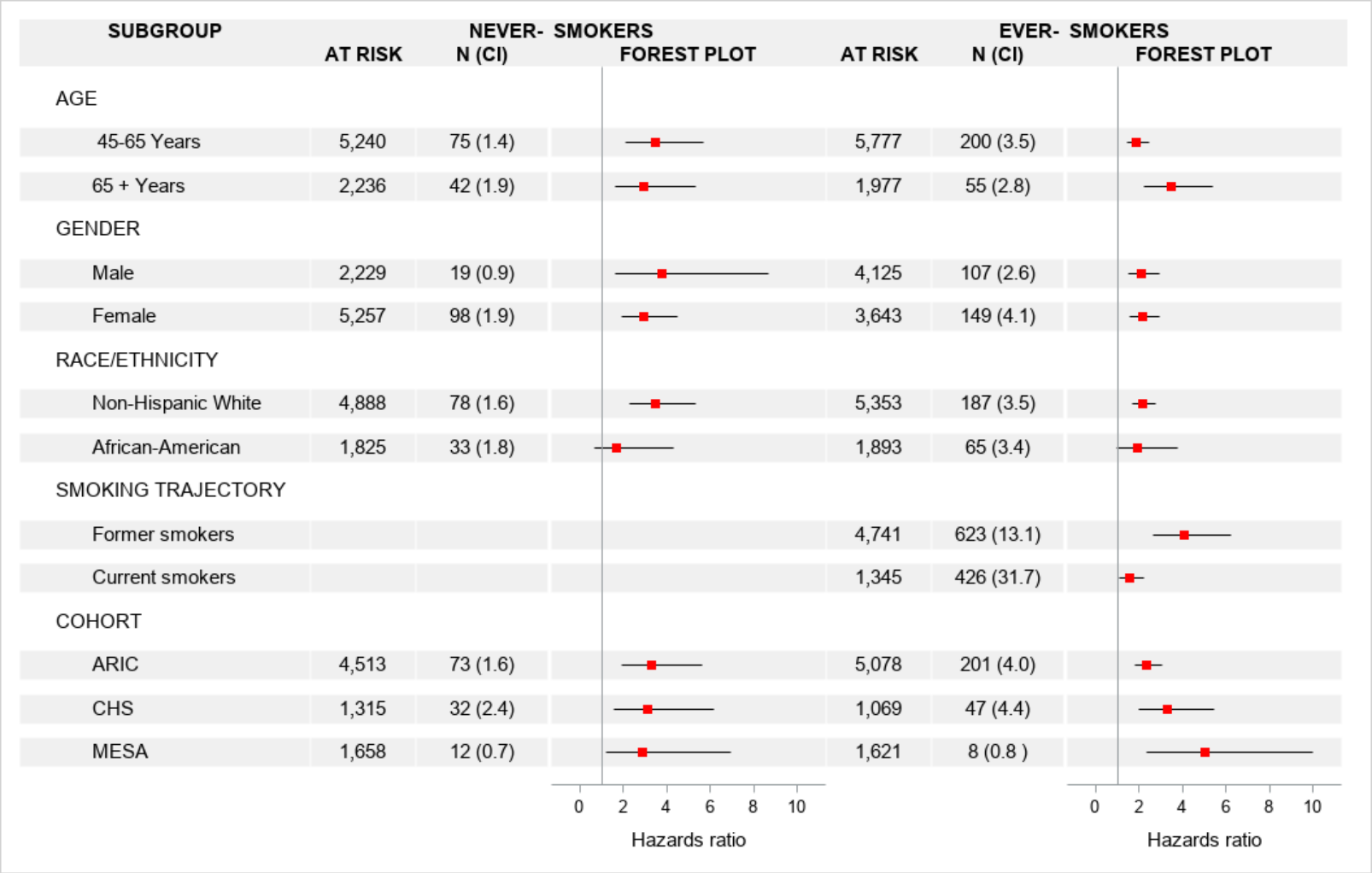
*To meet the convergence criteria for the model among ever-smokers with baseline age < 45 years, participants from ARIC (N=17) and FHS-O (N=5) were excluded.

** To meet the convergence criteria for the model among ever-smokers with baseline age > 65 years, participants from ARIC (N=105) were excluded.

Linear mixed models with cohort-specific unstructured covariance matrix were used. The coefficient for the multiplicative interaction term (non-obstructive chronic bronchitis*age) was interpreted as the longitudinal association with rate of change in lung function. Models were sequentially adjusted for *a priori* confounders and precision variables: age, age-squared, height-squared, weight, sex, race/ethnicity, educational attainment, and, among ever-smokers, smoking status and pack-years. In the context of socio-demographic differences across pooled cohorts, models were also adjusted for baseline age, birth-year, and clinical site. To account for potential confounding of associations with slope, multiplicative interaction terms with age were included for all time-invariant covariates.

© 2020 American Medical Association. All rights reserved.

eFigure 6. Associations Between Nonobstructive Chronic Bronchitis and Incident Chronic Lower Respiratory Disease-related events, Stratified by Sociodemographic Factors Among Never-smokers and Ever-smokers



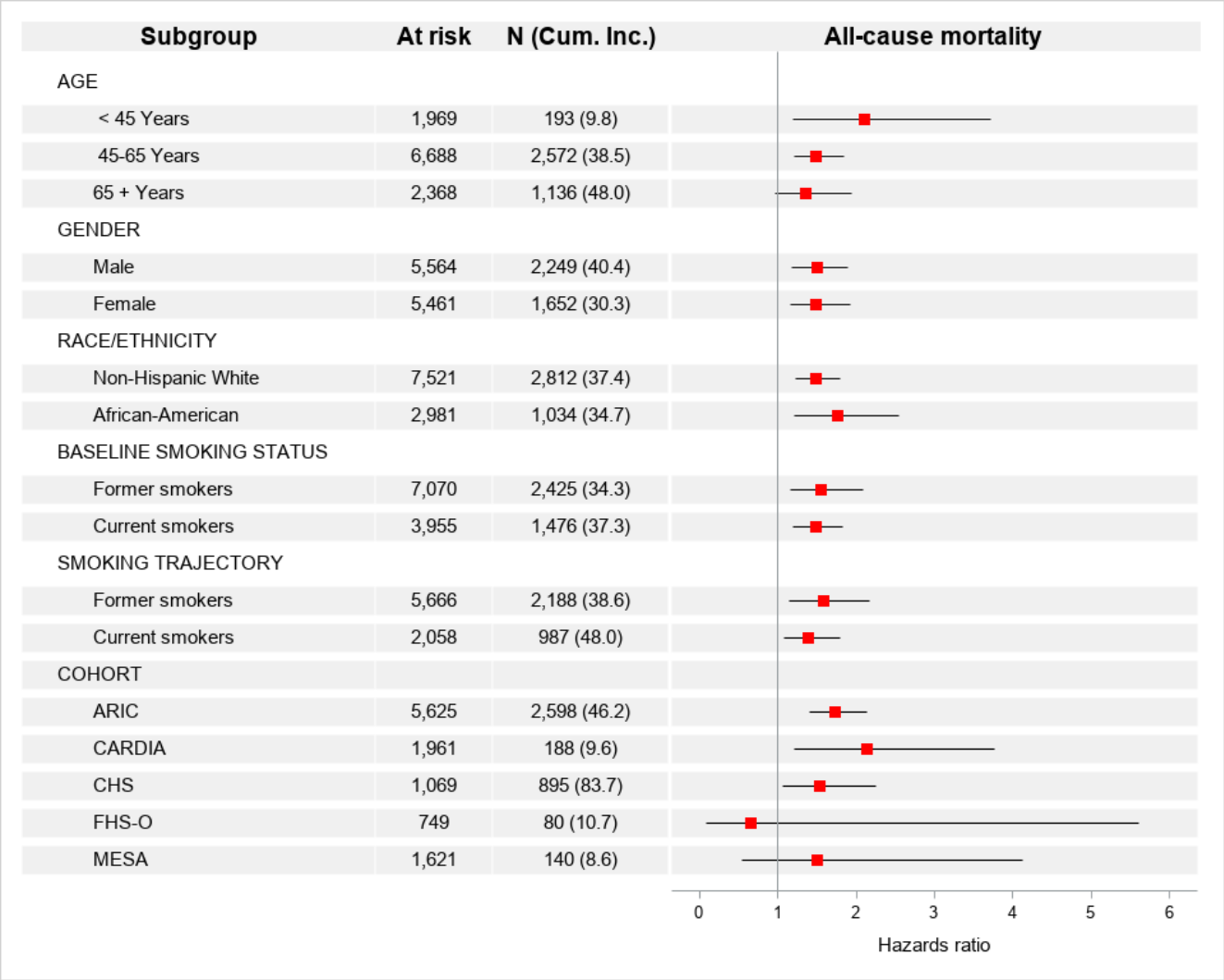
Excludes participants with self-reported asthma at time of chronic bronchitis ascertainment.

© 2020 American Medical Association. All rights reserved.

Associations between non-obstructive chronic bronchitis and incident chronic lower respiratory disease-related events were tested via 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 non-obstructive chronic bronchitis was defined. Study was treated as a stratum term, allowing for cohort-specific differences in the underlying survival function. In addition to the covariates included in the mixed models, proportional-hazards models were adjusted for the baseline FEV1/FVC.

© 2020 American Medical Association. All rights reserved.

eFigure 7. Associations Between Nonobstructive Chronic Bronchitis and All-cause Mortality Among Ever-smokers, Stratified by Sociodemographic Factors



© 2020 American Medical Association. All rights reserved.

Excludes participants with self-reported asthma at time of chronic bronchitis ascertainment.

Associations between non-obstructive chronic bronchitis and mortality were tested via 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 non-obstructive chronic bronchitis was defined. Study was treated as a stratum term, allowing for cohort-specific differences in the underlying survival function. In addition to the covariates included in the mixed models, proportional-hazards models were adjusted for the baseline FEV1/FVC.

© 2020 American Medical Association. All rights reserved.