The Presence of Chronic Mucus Hypersecretion across Adult Life in Relation to Chronic Obstructive Pulmonary Disease Development

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Abstract

Rationale: Chronic mucus hypersecretion (CMH) is common among smokers and is associated with chronic obstructive pulmonary disease development and progression.

Objectives: To understand how the relationships between smoking, CMH, and chronic obstructive pulmonary disease develop during adult life, and facilitate earlier disease detection and intervention.

Methods: We analyzed data on CMH, smoking, and lung function prospectively collected by the Medical Research Council National Survey of Health and Development, a nationally representative British cohort followed since birth in 1946. We analyzed the longitudinal relationships between smoking and CMH, how symptoms during life related to airflow limitation at 60–64 years, and how CMH duration between ages 43 and 60–64 years related to concurrent FEV_1 decline.

Measurements and Main Results: From 5,362 individuals enrolled at birth, 4,427 contributed data between ages 20 and 64 years (52% male; 63% ever-smoker). Among smokers CMH prevalence escalated between ages 36 and 43 from 7.6 $\pm$ 2.0% to 13.0 $\pm$ 2.6%. At these ages, symptoms were associated with a higher risk of subsequent airflow limitation (odds ratio [95% confidence interval], 3.70 [1.62–8.45] and 4.11 [1.85–9.13], respectively). Across adult life, CMH followed a dynamic remitting–relapsing course. Symptom prevalence following smoking cessation returned to levels seen among never-smokers. The longer CMH was present across three occasions (ages 43, 53, and 60–64 yr), the greater the concurrent FEV_1 decline, corresponding to an additional decrement of 3.6 $\pm$ 2.5 ml/yr per occasion that CMH was present ($P = 0.005$).

Conclusions: CMH among middle-aged smokers represents an early developmental phase of chronic obstructive pulmonary disease. Smoking-related CMH usually resolves following smoking cessation but the longer its duration the greater the FEV_1 lost, suggesting the course of CMH across adult life may reflect the underlying course of airway disease activity.

Keywords: chronic mucus hypersecretion; chronic bronchitis; COPD; smoking; cough

Chronic mucus hypersecretion (CMH), also known as chronic bronchitis, is a common symptom among smokers (1–4). In those with chronic obstructive pulmonary disease (COPD), CMH is associated with more frequent exacerbations (5, 6), steeper lung function decline (7), more frequent hospitalizations (7), and higher mortality (8, 9), whereas in smokers without COPD, CMH may reflect greater susceptibility to COPD development (4, 10, 11).

CMH prevalence generally increases with age (1, 12). However, several longitudinal studies have suggested symptom presence within individuals fluctuates over time (1–3, 7, 10, 13) influenced, for example, by changing

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At a Glance Commentary

Scientific Knowledge on the Subject: Smoking is a major trigger of chronic mucus hypersecretion (CMH) commonly considered to identify a chronic obstructive pulmonary disease phenotype associated with poor clinical outcomes and hypothesized to be a feature of developing chronic obstructive pulmonary disease. However, how the relationships between smoking, CMH, and airway disease develop across adult life is poorly understood.

What This Study Adds to the Field: We provide evidence of an evolving relationship between smoking and CMH during middle age suggestive of an early developmental phase of chronic obstructive pulmonary disease. We show the course of CMH across adult life is more dynamic than previously appreciated, that smoking cessation at any age avoids and/or reverses CMH development, and that the longer CMH is present the greater the FEV_1 loss. These findings suggest the course of CMH reflects that of airway disease activity.

smoking behavior (1, 2). Although behavioral, genetic, and environmental factors acting throughout life may influence COPD development (14, 15), most longitudinal studies of symptoms have been relatively short in duration and consequently, how the relationship between CMH and smoking develops across adult life remains unknown. Understanding this longitudinal relationship and its association with COPD presence in later life and lung function decline across life may facilitate earlier disease detection, focused smoking cessation, and the development of novel interventions.

Some studies have defined CMH as chronic sputum expectoration (1, 16–18) and others as chronic sputum expectoration with chronic cough (7, 19). However, few studies have directly compared the clinical associations of chronic sputum, chronic cough, and chronic sputum concurrent with chronic cough, making comparisons of reported results difficult (20).

Using data from the Medical Research Council (MRC) National Survey of Health and Development (NSHD) we sought to determine (*1*) how the relationship between CMH and smoking evolves across adult life, (*2*) to what extent symptoms at different stages of life identify those smokers more likely to have airflow limitation (a cardinal feature of COPD) in later life, and (*3*) if CMH duration represents an indicator of concurrent FEV_1 decline independent of smoking.

Some of the results of this study have been previously reported in the form of abstracts (21–25).

Methods

Population Studied

The NSHD is a study of 5,362 individuals, representative of all single births to married women during 1 week in March 1946 within England, Scotland, and Wales (26). Prospective data have been collected regularly from this nationally representative cohort of men and women since birth. The most recent data collection was completed in 2006–2011 when study members reached 60–64 years of age. At this follow-up, the 2,856 participants still alive and with a known current address in mainland Britain were invited for assessment at one of six clinical research facilities; those unable or unwilling to travel were offered a home visit by a research nurse (27). Invitations were not sent to those who had died (n = 778), were living abroad (n = 570), had previously withdrawn from the study (n = 594), or had been lost to follow-up (n = 564). A total of 2,229 participants (78%) underwent assessment: 1,690 attended the clinical research facility and the remaining 539 were seen in their homes. The participating sample remains broadly representative of native-born British men and women of the same age (28). Previously, at ages 36, 43, and 53, study members were interviewed and examined in their own homes by a team of trained research nurses.

Data

Responses to the MRC respiratory symptom questionnaire (16, 17, 29) were recorded at 20, 25, 36, 43, 53, and 60–64 years of age at the nurse-led interviews or via postal questionnaires. At each age whether participants were smoking and the number of cigarettes they smoked per day was recorded. Self-rolled cigarettes were converted as follows: 1 oz tobacco = 25 manufactured cigarettes. At ages 36, 43, 53, and 60–64 years, individuals were asked if they had ever previously smoked one or more cigarettes daily for 1 or more years. At 20 years of age previous smoking behavior was recorded. Prebronchodilator lung function was measured at 43, 53, and 60–64 years supervised and quality assessed by trained nurses. The same Micro Medical Plus turbine electronic spirometer models (Micro Medical Ltd., Rochester, Kent, UK) were used on each occasion. Three maneuvers were recorded in 1989 and two in 1999 and 2006–2011 but otherwise the same protocol, developed before the publication of the current American Thoracic Society/European Respiratory Society guidelines (30), was followed at each visit. The larger of two reproducible readings, defined as within 150 ml of each other, of FEV_1 and FVC was used in analyses. Height (centimeter) and weight (kilogram) measured at age 43 years were used in analyses.

Symptom and Smoking Definitions

The MRC respiratory questionnaire-based definition of chronic bronchitis (16–18), used to detect chronic sputum expectoration, has been validated against daily sputum volume production (31) and is considered unbiased by observer, season, or administration method (32). The questionnaire includes separate questions about chronic cough. "Chronic" refers to "at least 3 months yearly." At each time point, members could report chronic sputum expectoration, chronic cough, chronic cough with concurrent chronic sputum expectoration, or no symptoms. CMH was defined as chronic cough with chronic sputum expectoration. Those smoking at least one cigarette per day regularly for at least 1 year were considered smokers. Smoking status refers to smoking activity at a given time point (active, never, or ex-smoker). Active smokers were those currently smoking. Never-smokers consistently denied ever regularly smoking throughout the study. Ex-smokers were those who had smoked previously but were not currently smoking. Cigarette consumption at each age was defined as the number of cigarettes currently smoked per day.

Statistical Analysis

Symptom and smoking patterns across adult life. Among those providing complete data on both symptoms and smoking behavior at all six ages we calculated the percentage reporting symptoms and active smoking at each age and at any age (i.e., ever-smokers, ever-CMH, ever-chronic sputum, and ever-chronic cough). Differences in ever-CMH presence by ever-smoking status were assessed using chi-square tests. Among the ever-CMH sample, CMH presence at each age was classified according to current and previous symptom reporting as follows: "not yet" (no current/previous CMH), "incident" (first report of CMH), "ongoing" (persistent CMH since the incident report), "remission" (CMH reported previously but absent currently), and "relapse" (CMH currently reported following previous remission).

Relationship between symptoms and smoking with age. We investigated how CMH prevalence changed with concurrent smoking behavior during each of the five consecutive time-periods between the six data collections. For the period from 20 to 25 years, those with complete data at both ages and classified as persistent smokers (smoking at the start and end of the period), quitters (smoking at the start but not the end of the period), or never-smokers were included. Similar analyses were performed for the four subsequent periods with quitters being excluded from subsequent periods. Chi-square tests were used to assess differences in CMH prevalence between smoking groups at beginning and end of each period. McNemar tests were used to analyze change in CMH prevalence within each smoking group. Separately, we repeated these analyses to investigate how chronic sputum expectoration prevalence and chronic cough prevalence changed over the five time periods.

To explore how changing symptom prevalence among persistent smokers might reflect changing cigarette consumption, Wilcoxon signed rank tests were used to test whether their cigarette consumption changed during each period. Mann-Whitney *U* tests were used to analyze differences in cigarette consumption at the start of each period between quitters and persistent smokers.

The relationship between symptoms across adult life and airflow limitation at age 60–64 years. Airflow limitation was defined as FEV_1/FVC less than lower limit of normal for their age (33), as recommended for epidemiologic studies (34). Multivariable logistic regression analyses were used to assess the relationship between being symptomatic (reporting chronic cough and/or chronic sputum expectoration) at each age among active and nonsmokers and the presence of airflow limitation at age 60–64 years with adjustment for sex and concurrent cigarette consumption. We tested for interactions between being symptomatic and both smoking status and cigarette consumption to determine whether associations between being symptomatic and airflow limitation were modified by smoking behavior. Although the fixed ratio definition of airflow limitation ($FEV_1/FVC < 0.70$) is likely to overdetect airflow limitation at 60–64 years (34), we repeated our analyses using this widely used definition.

The relationship between CMH presence and concurrent FEV_1 decline. The relationship between CMH presence and concurrent FEV_1 decline across ages 43, 53, and 60–64 years was analyzed using multilevel models that account for repeated measures on the same individual. Random effects for both intercept and slope were included allowing individual intercepts and slopes to vary. We used three approaches to representing symptom presence: (*1*) dichotomizing the population according to CMH presence at age 43 years (present vs. absent); (*2*) dichotomizing the population according to CMH presence between ages 43 and 60–64 years (present ⩾once vs. never-present); and (*3*) for each individual calculating the duration of CMH by scoring the number of occasions on which they reported CMH across ages 43, 53, and 60–64 years (CMH duration score across the three time points between 0 and 3).

First, FEV_1 change with age was modeled with both intercept and rate of change being allowed to vary according to sex, the intercept representing FEV_1 at age 43 years. All models were adjusted for both height and weight at 43 years of age. Both intercept and slope were then allowed to vary according to CMH presence. The CMH duration score was first fitted as a categorical variable and a test for linear

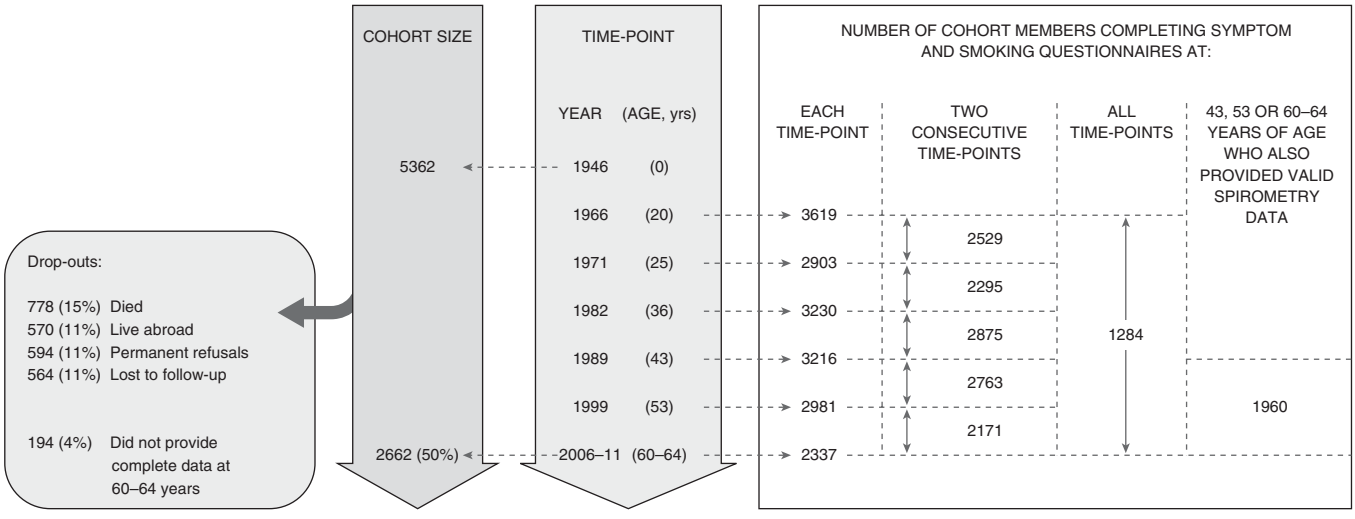


Figure 1. Timeline of cohort size and data collection during the study between recruitment in 1946 and the most recent data collection in 2006–2011.

trend performed by fitting as a continuous variable. Smoking status and cigarette consumption were included as time-varying covariates and were allowed to influence both intercept and slope. Results from these models were used to plot estimated FEV_1 decline between ages 43 and 60–64 years among men and women of average height and weight.

Separately, we repeated these analyses to investigate the respective relationships between chronic sputum expectoration presence and then chronic cough presence with concurrent FEV_1 decline across ages 43, 53, and 60–64 years.

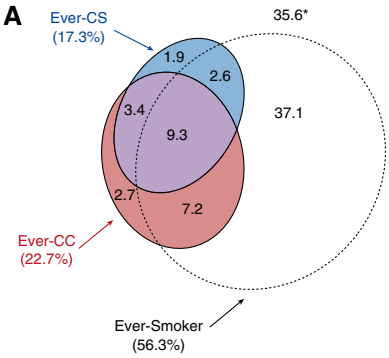
Analyses were performed using SPSS version 22 (IBM Corporation, Armonk, NY) and STATA version 14 (Stata Corporation, College Station, TX). All tests were two sided, and *P* less than 0.05 was considered statistically significant.

Results

Further data tables and figures are available in the online supplement. From the 5,362 individuals initially enrolled within the cohort, 4,427 (52% male; 63% ever-smokers) provided symptom and smoking data at one or more occasions (Figure 1).

Symptom and Smoking Patterns across Adult Life

Of these 4,427 individuals, 1,284 (46% male; 56% ever-smokers) contributed complete data at all time points among whom 350 individuals (27.3%) reported chronic sputum or chronic cough at least once. Most of those who reported chronic sputum had also reported chronic cough and vice versa (Figure 2A). A total of 156 individuals (12.1%) reported CMH (chronic cough concurrent with chronic sputum expectoration) at least once. Symptoms were more common among the 723 (56.3%) ever-smokers than the 561 (43.7%) never-smokers (Figures 2A and 2B). Although active smoking declined between ages 20 and 60–64 years (from 37.0 to 9.8%), CMH, chronic sputum expectoration, and chronic cough prevalence increased (Figure 2C). Figure 3 shows how CMH followed a remitting–relapsing course with at least 50% of the ever-CMH reporting population in symptom remission by age 60–64 years. Figure E1 in the online supplement displays similar



B

SYMPTOM(S)	PREVALENCE % (95%CI) Never-Smokers (n=561)	Ever-Smokers (n=723)	OVERALL (n=1284)
Ever-CS (n=222)	12.3 (9.6 to 15.0)	21.2 (18.2 to 24.1)	17.3 (15.2 to 19.4)
	P<0.001		
Ever-CC (n=291)	14.1 (11.2 to 17.0)	29.3 (26.0 to 32.6)	22.7 (20.4 to 25.0)
	P<0.001		
Ever-CC and Ever-CS (n=163)	7.8 (5.6 to 10.1)	16.5 (13.8 to 19.2)	12.7 (10.9 to 14.5)
	P<0.001		
Ever concurrent CC and CS (n=156)	7.7 (5.5 to 9.9)	15.6 (13.0 to 18.3)	12.1 (10.4 to 13.9)
	P<0.001		
Ever Either symptom (n=350)	18.5 (15.3 to 21.8)	34.0 (30.6 to 37.5)	27.3 (24.8 to 29.7)
	P<0.001		

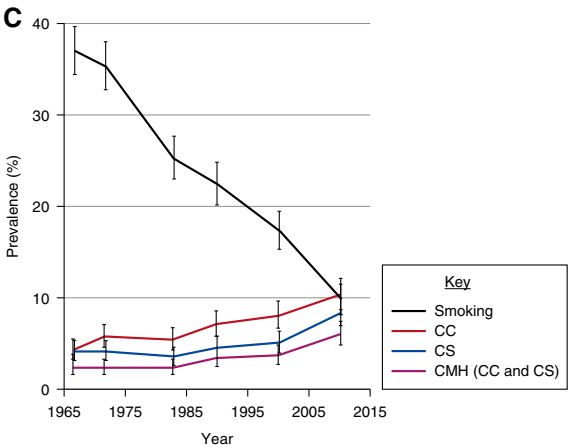


Figure 2. The prevalence of chronic mucus hypersecretion (CMH), chronic sputum expectoration (CS), chronic cough (CC), and cigarette smoking among those individuals providing complete data at all six time points within the National Survey of Health and Development (n = 1,284). (*A*) Area-proportional Venn diagram (52) representing the overlapping cumulative prevalence (%) of CS, CC, and cigarette smoking. Numbers shown are percentages of the included population (n = 1,284). *Never-smoker, never-CS, and never-CC. (*B*) Analysis of differences in cumulative-symptom prevalence between ever- and never-smoker groups (*P* values calculated using chi-square test). (*C*) Prevalence (%) with 95% CI of CMH, CS, CC, and cigarette smoking at each of six time points between 1966 and 2009. Data from the 2006–2011 survey are plotted at the average date (2009). CI = confidence interval.

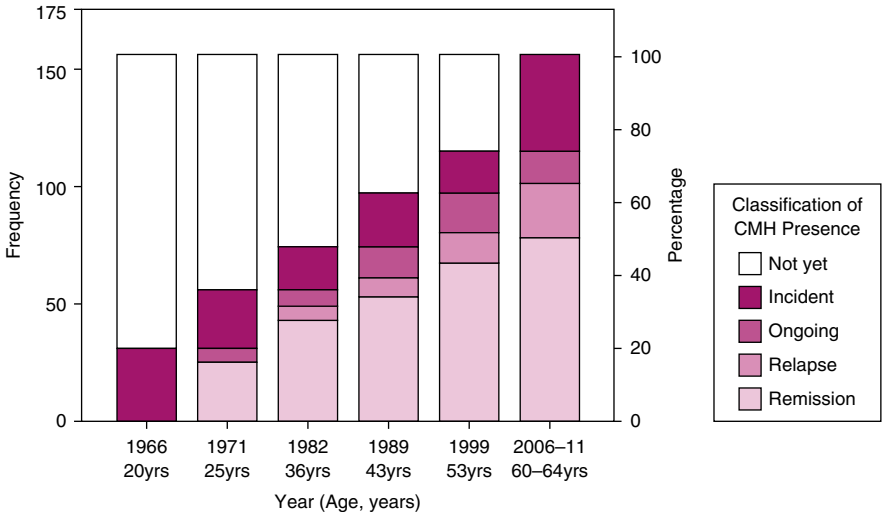


Figure 3. The longitudinal pattern of chronic mucus hypersecretion (CMH) presence among those providing complete data at all six National Survey of Health and Development time points (n = 1,284) and reporting CMH on at least one occasion (156 individuals; 12.1%). At each time point, individuals are classified according to their previous and current reporting of CMH as follows (and in the CMH presence classification box): "not yet" (no current/previous CMH), "incident" (first report of CMH), "ongoing" (persistent CMH since the incident report), "relapse" (CMH currently reported following previous remission), and "remission" (CMH reported previously but absent currently). CMH = chronic cough with concurrent chronic mucus expectoration. Figure E1 displays similar separate plots of chronic sputum expectoration presence and chronic cough presence data.

separate plots of chronic sputum expectoration presence and chronic cough presence data.

Relationship between Symptoms and Smoking with Age

CMH was more common among persistent smokers than among never-smokers ($P < 0.001$ at each age). Figure 4 shows that among smokers, CMH prevalence rose between ages 36 and 43 years ($P < 0.001$) and again between 53 and 60–64 years ($P = 0.008$). CMH prevalence among never-smokers during these periods did not significantly change. Figure E2 shows similar plots for chronic sputum expectoration prevalence and chronic cough prevalence. Chronic cough among smokers began to rise in prevalence between 20 and 25 years ($P = 0.002$), whereas chronic sputum expectoration did not start to increase until between 36 and 43 years ($P < 0.001$).

In most time periods, smoking cessation was accompanied by CMH prevalence returning to levels seen among never-smokers, avoiding and/or reversing the symptom prevalence rises experienced by persistent smokers (Figure 4). Symptom onset and remission was also detected in the absence of changes in smoking behavior with symptom prevalence trends across each period reflecting the balance between symptom onset and resolution rates (*see* Figure E3). For example, relative to never-smokers, rising persistent-smoker symptom prevalence reflected more frequent symptom onset and/or less frequent symptom resolution. Figure 4 also shows that although smoking cigarette consumption increased until age 36 years, cigarette consumption then plateaued and from age 42 years onward actually decreased. Furthermore, the dose–response relationship between cigarette consumption and symptom prevalence may steepen with advancing age (*see* Figure E4).

The Relationship between Chronic Symptoms across Adult Life and Airflow Limitation at Age 60–64 Years

A total of 1,137 individuals provided both reproducible FEV_1 and FVC measurements at age 60–64 years (42% male; 61% ever-smokers). Airflow limitation was observed in 69 individuals (6.1%) at age 60–64, more commonly among ever-smokers (8.1%) than never-smokers (2.9%) ($P < 0.001$). A total of 81.2% of those with airflow limitation were ever-smokers. Figure E5 demonstrates how cumulative prevalence of chronic symptoms by age 60–64 was greater among those with airflow limitation (56.7%; 95% confidence interval [CI], 44.1–69.2%) than those without (27.2%; 95% CI, 24.2–30.0%) but that only 28.3% (95% CI, 16.9–39.7%) of those with airflow limitation still reported chronic symptom presence at this age.

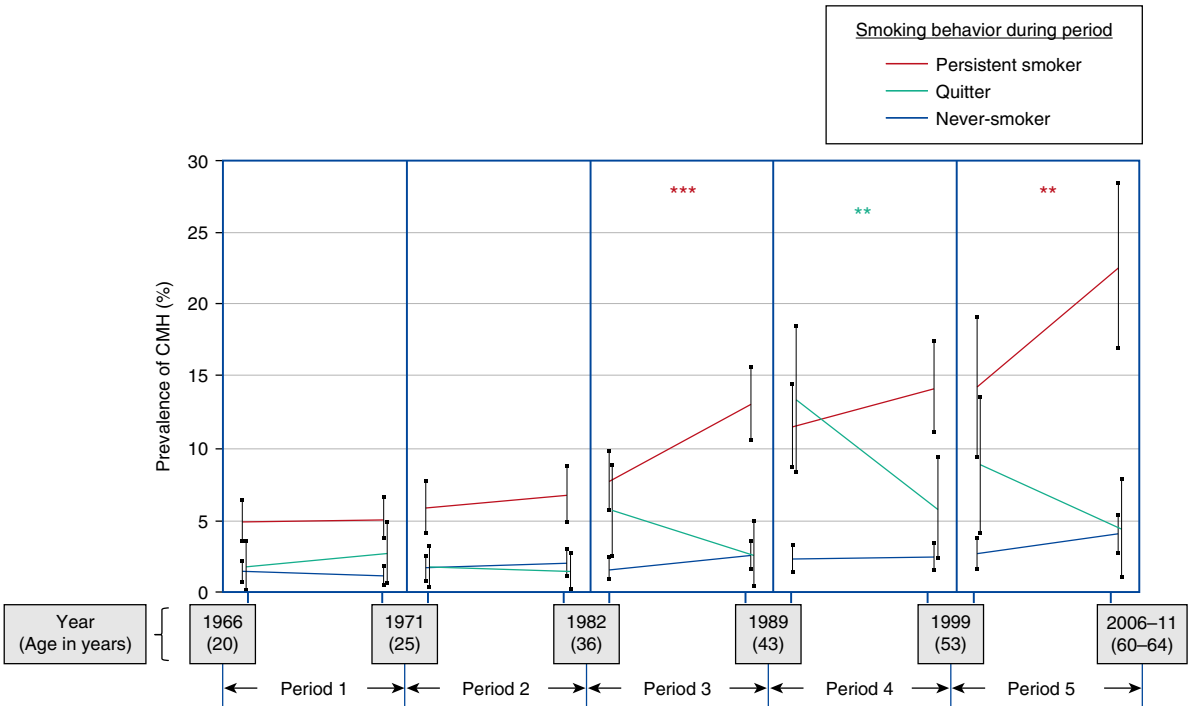
In adjusted models, symptom presence (relative to symptom absence) at ages 36 or 43 years among active smokers was associated with a significantly higher odds ratio of having airflow limitation by age 60–64, but symptom presence at ages 20, 25, 53, or 60–64 was not (Figure 5). In contrast, among nonsmokers, symptoms at most ages, which were rarer than among active smokers and presumably caused by other conditions or environmental factors, were associated with airflow limitation at age 60–64 years (Figure 5). There was a suggestion that the association between symptom presence at age 20 and airflow limitation was stronger in nonsmokers than smokers, although the test for interaction ($P = 0.07$) did not quite reach the conventional 5% significance level. There was no evidence of any interaction between smoking status and symptom presence at any of the later ages.

After separating nonsmokers into never- and ex-smokers (*see* Figure E6) we found no association between symptoms among ex-smokers and airflow limitation. The interaction between symptoms and smoking status (active vs. never-smoker) at age 20 was stronger ($P = 0.02$) than when never- and ex-smokers were grouped together, never-smokers showing a much stronger association than current smokers.

Results similar to those in Figure 5 were obtained using the FEV_1/FVC less than 0.70 definition of airflow limitation (*see* Figure E7).

The Relationship between CMH Presence and Concurrent FEV_1 Decline

A total of 1,960 individuals who provided reproducible FEV_1 measurements on at least one occasion contributed to each multilevel model (46% male; 59% ever-smoker). There was no difference in participation rates at the home visit at 43 years by prior symptom reporting (*see* Table E7), but those reporting symptoms from 36 years onward were less likely to participate at 60–64 years (*see* Table E7). Mean FEV_1 at age 43 years = 3.00 L with



Total number of subjects			2084		1815		1919		1687		1207	
Median cigarettes smoked/day (IQR)	Quitter	Period start †	10 (5–15)	P<0.001	10 (5–19)	P<0.001	15 (7–20)	P<0.001	18 (10–20)	P<0.001	15 (9–20)	P=0.006
	Persistent smoker	Period start ‡	10 (10–15)	P<0.001	15 (10–20)	P<0.001	20 (15–25)	P=0.69	20 (15–25)	P<0.001	20 (10–20)	P=0.039
		Period end ‡	15 (10–20)		20 (12–25)		20 (14–25)		20 (10–25)		15 (10–20)	

Figure 4. The prevalence of chronic mucus hypersecretion (CMH) (with 95% confidence intervals) and median smoking cigarette consumption during five time-periods over adult life within the National Survey of Health and Development according to concurrent cigarette smoking behavior (*see* Figures E2 and E3 and Tables E2–E4). $^{**}P < 0.01$; $^{***}P < 0.001$, change in symptom prevalence during each period analyzed using McNemar's test according to smoking behavior group (colored accordingly); †Mann-Whitney *U* tests; ‡Wilcoxon signed rank tests. IQR = interquartile range.

overall FEV_1 decline of 24.2 ml/yr (95% CI, 23.1–25.4 ml/yr) in a model including only age. Addition of smoking status demonstrated that FEV_1 declined more rapidly among smokers (31.7 ml/yr; 95% CI, 27.2–36.4 ml/yr) than among nonsmokers (23.2 ml/yr; 95% CI, 21.9–24.4 ml/yr; $P < 0.001$).

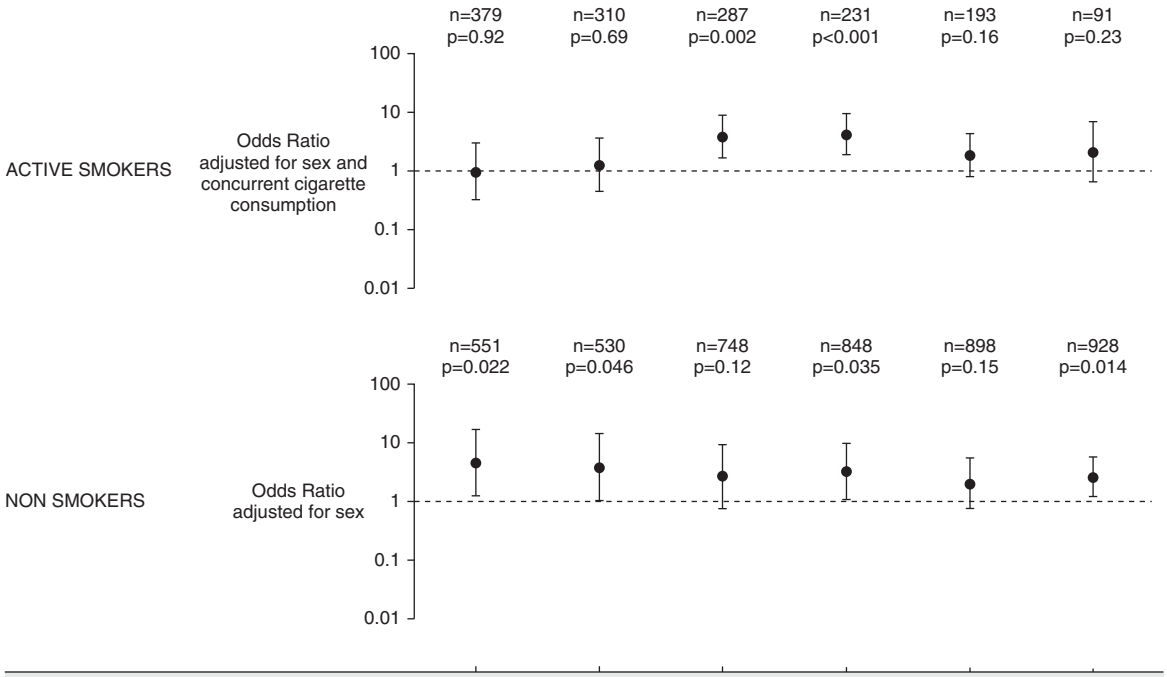
Inclusion of cigarette consumption in addition to smoking status did not alter the results of the multilevel models and was not included in the final models. CMH presence at age 43 years in fully adjusted models was associated with lower FEV_1 but not accelerated FEV_1 decline between ages 43 and 60–64 years (*see* Table E6A). Widening the CMH presence classification to reflect CMH presence at ages 43, 53, or 60–64 years identified a larger symptomatic group (*see* Table E5) and this phenotype was also associated with both lower FEV_1 and accelerated FEV_1 decline (*see* Table E6B). For example, reporting of CMH on at least one occasion between 43 and 60–64 years was associated with an additional 4.5 ml/yr decline in FEV_1 in fully adjusted models ($P = 0.03$).

A linear relationship between FEV_1 slope and CMH duration score fitted as a categorical variable was observed and thus duration score was subsequently included as a continuous variable. CMH duration score was associated with both a lower FEV_1 and faster FEV_1 decline (Table 1). For example, for each additional occasion CMH was reported there was an additional 3.6 ml/yr decline in FEV_1 ($P = 0.005$; i.e., presence of CMH on all three occasions was associated with an additional 10.8 ml/yr FEV_1 decline between ages 43 and 60–64 years compared with those without CMH on any occasion). Figure 6 shows this estimated FEV_1 decline according to CMH duration between ages 43 and 60–64 years calculated for male and female smokers of average height and weight at age 43.

Discussion

This study demonstrates for the first time that middle age among smokers is a period when CMH increasingly develops and when chronic symptoms can identify those at greater risk of having airflow limitation by their early sixties. Furthermore, this study shows that CMH followed a dynamic course across adult life. Smoking cessation at any age reversed or avoided the escalating prevalence of smoking-related CMH. We also show that the longer that CMH was present, the faster the decline in FEV_1.

It is well recognized that CMH is associated with smoking-related respiratory disease outcomes (1, 5–9, 35,



	YEAR (Age in years)	1966 (20)	1971 (25)	1982 (36)	1989 (43)	1999 (53)	2006–11 (60–64)
ACTIVE SMOKERS	Odds Ratio (95% CI)	0.95 (0.32–2.85)	1.24 (0.44–3.52)	3.70 (1.62–8.45)	4.11 (1.85–9.13)	1.82 (0.78–4.23)	2.07 (0.64–4.74)
NON SMOKERS	Odds Ratio (95% CI)	4.64 (1.25–17.22)	3.80 (1.03–14.08)	2.73 (0.78–9.55)	3.29 (1.09–9.92)	2.05 (0.77–5.47)	2.65 (1.22–5.76)

Figure 5. The relationship between chronic symptoms (chronic cough and/or chronic sputum expectoration) among smokers and nonsmokers at different ages during adult life and the presence of airflow limitation (FEV_1/FVC less than lower limit of normal) by age 60–64 years. Logistic regression models are adjusted for sex and concurrent smoking cigarette consumption. The log odds ratio (95% confidence intervals [CIs]) of having developed airflow limitation by the time they reached 60–64 years of age among those with chronic symptoms is shown at each age.

36), but how CMH develops and how its association with these health outcomes emerges over the adult life course, although much hypothesized, is little reported. The NSHD is the first study to provide prospective, longitudinal symptom prevalence data using a validated questionnaire over such an extensive period of life within a nationally representative population. Unlike many previous longitudinal studies, our study sample included both men and women (1, 3) from rural and urban areas (1, 3, 37) who were recruited following birth within the same week in March 1946, making it more generalizable and removing the need to adjust for recruitment bias toward symptomatic participants (1) or unequal participant age (7, 37).

CMH symptoms are known to be more common among smokers (1, 4, 37, 38) and to become increasingly common with age (1, 12), but this study also demonstrates that the relationship between symptoms and smoking evolves with age. In contrast to the consistent and relatively low-level of CMH we found among never-smokers, CMH among smokers began to increase significantly between the ages of 36 and 43 years and increased further between 53 and 60–64 years. The escalating symptom prevalence we found among smokers during middle age was unlikely to be explained by rising cigarette consumption, which plateaued between 36 and 43 years before subsequently decreasing. Instead, these results may indicate a rising sensitivity to the effects of active smoking during middle age, possibly reflecting an evolving physiologic response accompanying ageing (39–41) and/or the unmasking of underlying susceptibility to the effects of smoking following sufficient exposure.

The extent to which smoking-related symptoms predict future COPD development, often identified by airflow limitation presence (42), has long been debated (1, 4, 10, 11, 13, 43). We found this relationship varied according to the age of symptom reporting. In contrast to symptoms at ages 20 or 25 years, the presence of symptoms at age 36 or 43 years identified active smokers at higher risk of having airflow limitation by their early sixties. This finding taken together with the rises in symptom prevalence seen among smokers suggests that middle age is an important early phase in COPD development.

In common with others monitoring symptoms over time (1–3, 7, 10, 13, 37), we found that the reporting of CMH symptoms followed a dynamic course with changing prevalence reflecting an imbalance between rates of symptom onset

Table 1. The Influence of Duration of CMH Presence on Multilevel Models Estimating the Relationship between CMH Presence and Concurrent FEV_1 Decline between Ages 43 and 60–64 Years

	FEV_1 Intercept (*ml*) at Age 43 yr			FEV_1 Linear Change per Year (*ml/yr*) between Ages 43 and 60–64 yr		
	Coefficient	**95% CI**	***P* Value**	**Coefficient**	**95% CI**	***P* Value**
Constant	−2,328.2	−2,840.4 to −1,815.9	—	−22.3	−23.9 to −20.8	<0.001
Height at age 43 yr, cm	31.8	28.5 to 35.1	<0.001	—	—	—
Weight at age 43 yr, kg	−3.2	−5.0 to −1.5	<0.001	—	—	—
Male sex	574.9	515.5 to 634.3	<0.001	−1.4	−3.6 to 0.9	0.24
Cigarette smoking	−22.0	−62.5 to 18.5	0.29	−7.5	−10.8 to −4.3	<0.001
Per occasion chronic cough with chronic sputum reported between ages 43 and 60–64 yr (0–3 occasions)	−162.3	−208.5 to −116.1	<0.001	−3.6	−6.1 to −1.1	0.005

Definition of abbreviations: CI = confidence interval; CMH = chronic mucus hypersecretion.
Multilevel modeling included 1,960 men and women. Mean FEV_1 at age 43 years was 3.00 L, with an unadjusted FEV_1 decline of 24.2 ml/yr. Coefficients are adjusted for sex, height at age 43 years, weight at age 43 years, and smoking status. Duration of CMH is represented by the number of occasions CMH was reported over the three time points (between zero and three occasions) (Table E6 displays the results of separate modeling of chronic sputum expectoration and chronic cough presence).

and remission (2). Smoking cessation, as previously reported (2), was associated with more frequent disappearance and less frequent appearance of symptoms, resulting in lower symptom prevalence compared with persistent smokers (2, 38). However, we also show that symptom prevalence actually returned to that of never-smokers following smoking cessation at most ages, even when cessation occurred in the fifth or sixth decades of life. These findings therefore highlight both the strong relationship between active smoking and symptoms and the scope to alleviate and/or avoid respiratory symptoms at any age through smoking cessation.

Although CMH is classically considered a binary phenotype (44), within this longitudinal study, CMH presence at 60–64 years identified only 50% of those who had reported CMH during adult life. The evident instability of CMH across adult life may prompt a reevaluation of studies that characterize subjects based on CMH presence later in adult life and/or at a single time point. For example, among those without CMH symptoms later in life, the presence of airflow limitation may instead relate to a symptomatic phase earlier in life that has subsequently abated. With advancing age, an increasing proportion of our study sample entered symptom remission, whereas the time remaining for airflow limitation development decreased. Together these observations might explain why, similar to Guerra and coworkers (11), we found symptom presence later in life poorly identifies those smokers at greater risk of having airflow limitation by age 60–64 years compared with the same symptoms at earlier ages.

This study also suggests that the course of CMH is clinically relevant to lung function decline and potentially disease development. Some have already suggested the association between CMH and poor respiratory outcomes is clearest among those with persistent CMH (7, 10), but this is the first study to suggest that the longer CMH is present the greater the concurrent FEV_1 decline, even after adjusting for smoking behavior. Although smoking cessation may reduce airway inflammation (45), several studies of ex-smokers, predominantly those still reporting CMH, show airway inflammation can persist (45–47). These studies are small in size and are usually cross-sectional or short in duration. However, their findings infer that CMH presence indicates heightened airway inflammation and may reflect active disease. Hypothetically, the changes in CMH presence we demonstrate could indicate changing airway disease activity either in response to changing environmental exposure and/or altered physiologic response to such insults. Investigating how the

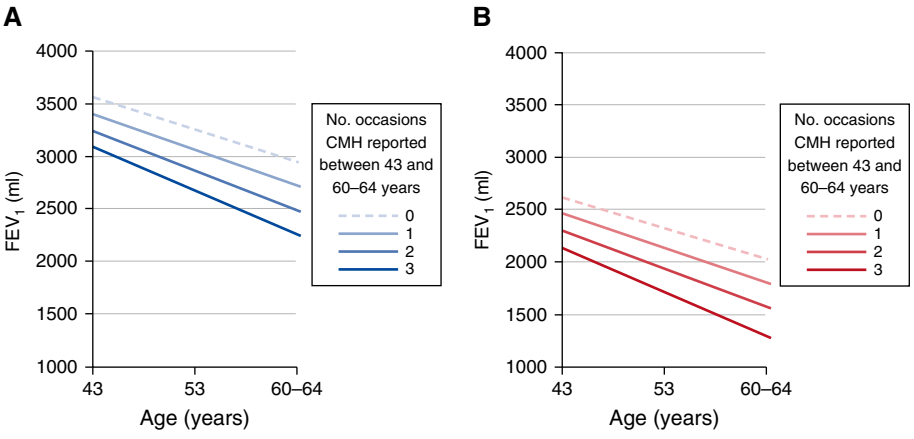


Figure 6. The influence of duration of chronic mucus hypersecretion (CMH) presence on FEV_1 decline between ages 43 and 60–64 years. Estimated FEV_1 decline between 43 and 60–64 years of age calculated using multilevel models (Table 1) including average height and weight is shown for (*A*) male (height, 176 cm; weight, 79 kg) and (*B*) female (height, 163 cm; weight, 66 kg) smokers according to the number of occasions CMH was reported across the three time points.

presence of airway inflammation associated with CMH (7, 47, 48) changes according to the appearance, persistence, and disappearance of CMH may help identify novel biomarkers useful in research or to guide therapeutic interventions.

Within our study, FEV_1 decline appeared most prominent among those concurrently reporting chronic cough and chronic sputum expectoration. A varying association between different symptom complexes and FEV_1 decline may partly explain conflicting outcomes from studies using the chronic productive cough (7) rather than the chronic sputum expectoration (1) definition of CMH. Chronic cough and chronic sputum expectoration may represent different pathophysiologic responses to smoking and their coexistence, which is associated with higher respiratory-cause mortality (20), may represent a particularly intense smoking-response. However, less than half of those reporting either chronic cough or chronic sputum expectoration during this study reported both symptoms concurrently. Therefore, although the chronic productive cough definition of CMH probably identifies those responding particularly intensely to smoking exposure, it also leaves a considerable number of smokers experiencing abnormal chronic symptoms undetected and unstudied.

A limitation of this study, as with all symptom-based studies, is its reliance on self-reporting and therefore misreporting may contribute to changing symptom status. We consistently used the extensively validated MRC questionnaire, which is one of the best tools available for accurate symptom detection on this scale. Symptoms among some individuals, particularly among our never-smoker sample, may be the result of environmental exposures, such as pollution, or diseases unrelated to smoking, such as asthma (49, 50). Chronic symptoms among people with asthma can indicate poor asthma control (50) perhaps partly explaining their association with subsequent airflow limitation within the small subsample of never-smokers reporting symptoms during this study. One of the merits, however, of this study is that we examined a sample representative of native born British men and women of the same age who were enrolled at birth (28) and this avoided potential sample bias caused by inaccurate self-reported medical conditions based on unverifiable prior symptom interpretation (51). This study highlights the need for further research to ascertain why chronic symptoms develop among some individuals but not others, and the role of asthma remains a key area of interest.

A major strength of this study is that participants were followed for a long period of time spanning most of adult life, but this also introduces several limitations. First, our study sample is predominantly white, being representative of those born in England, Scotland, and Wales in 1 week in March 1946, potentially affecting the applicability of our findings to other ethnic populations. Second, the NSHD protocol was designed before publication of guidelines promoting post-bronchodilator spirometry measurements potentially leading to overdetection of airflow limitation within this study sample. Finally, longer studies inevitably offer more opportunity for participant loss over time potentially introducing follow-up bias (e.g., with the loss of sicker individuals). Although the NSHD study sample seems to have remained broadly nationally representative (28), we found symptomatic individuals were more likely to have left the study at age 60–64 and hence we may have underestimated the association between symptoms and lung function decline.

In summary, during middle age, CMH prevalence among smokers escalates and a relationship emerges between symptoms and the subsequent presence of airflow limitation. These changes potentially represent an early phase of COPD development. Furthermore, the escalating chronic symptom prevalence experienced by smokers is avoided and reversed through smoking cessation at any age, emphasizing the benefits of stopping smoking irrespective of life stage. CMH is traditionally regarded as a phenotype associated with poor clinical outcomes and although this may be true, during life CMH appears and disappears. The duration of CMH also seems to be related to the concurrent rate of FEV_1 decline independent of smoking behavior. Therefore, the course of CMH may reflect the underlying course of airway disease activity and be a marker of COPD development. Longitudinal studies of the inflammatory and physiologic characteristics accompanying different chronic symptom courses among smokers, particularly in early adult life, are warranted to advance the understanding of how airway disease develops ultimately aiming to facilitate early detection and intervention. ■

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

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