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The Presence of Chronic Mucus Hypersecretion Across Adult Life in Relation to COPD Development

James P Allinson[1], Rebecca Hardy[2], Gavin C Donaldson[1], Seif O Shaheen[3], Diana Kuh[2], Jadwiga A Wedzicha[1]

1. Airways Disease Section, National Heart and Lung Institute, Imperial College London, United Kingdom
2. MRC Unit for Lifelong Health and Ageing at UCL, University College London, United Kingdom
3. Centre for Primary Care and Public Health, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, United Kingdom

Address correspondence to:

Dr J.P. Allinson
COPD Research Group, Airways Disease Section
National Heart and Lung Institute
Guy Scadding Building, Dovehouse Street,
Imperial College London, United Kingdom
SW3 6LY
Phone: +44 207 5945665; E-mail: j.allinson@imperial.ac.uk

Author contributions:
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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 COPD phenotype associated with poor clinical outcomes and hypothesized to be a feature of developing COPD. However, how the relationships between smoking, CMH and airway disease develop across adult life is poorly understood.

What this 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 COPD. 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.

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ABSTRACT

RATIONALE: Chronic Mucus Hypersecretion (CMH) is common amongst smokers and is associated with Chronic Obstructive Pulmonary Disease (COPD) development and progression. Understanding how the relationships between smoking, CMH and COPD develop during adult life could facilitate earlier disease detection and intervention.

METHODS: We analysed data on CMH, smoking and lung function prospectively collected by the MRC National Survey of Health and Development, a nationally representative British cohort followed since birth in 1946. We analysed 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 to 60-64 years related to concurrent FEV_1 decline.

RESULTS: From 5362 individuals enrolled at birth, 4427 contributed data between ages 20 and 64 years (52% male, 63% ever-smoker). Amongst smokers CMH prevalence escalated between ages 36 and 43 from 7.6±2.0% to 13.0±2.6%. At these ages symptoms were associated with a higher risk of subsequent airflow limitation (OR (95%CI): 3.70(1.62-8.45); 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 amongst never-smokers. The longer CMH was present across 3 occasions (ages 43, 53 and 60-64 years), the greater the concurrent FEV_1 decline, corresponding to an additional decrement of 3.6±2.5ml/year per occasion that CMH was present (p=0.005).

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CONCLUSIONS: CMH amongst middle-aged smokers represents an early developmental phase of COPD. 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.

Abstract Word Count: 260

Keywords: Chronic Mucus Hypersecretion; Chronic Bronchitis; COPD; Smoking; Cough

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INTRODUCTION:

Chronic Mucus Hypersecretion (CMH), also known as chronic bronchitis, is a common symptom amongst 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 hospitalisations (7) and higher mortality (8, 9) whilst 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 smoking behaviour (1, 2). Although behavioural, 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 both COPD presence in later life and lung function decline across life may facilitate both earlier disease detection, focussed 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).

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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).

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METHODS:

Population studied

The NSHD is a study of 5362 individuals, representative of all single births to married women during one 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 to 64 years of age. At this follow up, the 2856 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: 1690 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.

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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: 1oz 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 one or more years. At 20 years of age previous smoking behaviour was recorded. Pre-bronchodilator 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 were used on each occasion. Three manoeuvres were recorded in 1989 and two in 1999 and 2006-2011 but otherwise the same protocol, developed prior to the publication of the current ATS/ERS guidelines (30), was followed at each visit. The largest of two reproducible readings, defined as within 150 millilitres of each other, of forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) was used in analyses. Height (cm) and weight (kg) 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

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(32). The questionnaire includes separate questions about chronic cough. "Chronic" refers to "at least three 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 regularly for at least one 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

Amongst those providing complete data on both symptoms and smoking behaviour 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. Amongst 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

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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 behaviour 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 either 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 carried out for the 4 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's tests were used to analyse 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 amongst 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 analyse differences in cigarette consumption at the start of each period between quitters and persistent-smokers.

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The relationship between symptoms across adult life and airflow limitation at age 60-64 years

Airflow limitation was defined as FEV_1/FVC<lower limit of normal for their age (33), as recommended for epidemiological 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 amongst active and non-smokers 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 in order to determine whether associations between being symptomatic and airflow limitation were modified by smoking behaviour. Although the fixed ratio definition of airflow limitation (FEV_1/FVC<0.70) is likely to over detect 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 analysed using multilevel models which 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 employed three approaches to representing

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symptom presence: (1) dichotomising the population according to CMH presence at age 43 years (present vs absent); (2) dichotomising the population according to CMH presence between ages 43 and 60-64 years (present ≥ once vs never-present); (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 modelled 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 trend carried out 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 amongst men and woman 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 carried out using SPSS version 22 (IBM Corporation, Armonk, NY, USA), and STATA version 14 (Stata Corporation, Texas, USA). All tests were two sided and $P<0.05$ was considered statistically significant.

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RESULTS: (Further data tables and figures are available in the online supplement)

From the 5362 individuals initially enrolled within the cohort, 4427 (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 4427 individuals 1284 (46% male, 56% ever-smokers) contributed complete data at all time-points amongst whom 350 individuals (27.3%) reported chronic sputum (CS) or chronic cough (CC) at least once. Most of those who reported chronic sputum had also reported chronic cough and vice versa (Figure 2A). 156 individuals (12.1%) reported CMH (chronic cough concurrent with chronic sputum expectoration) at least once. Symptoms were more common amongst the 561 (43.7%) ever-smokers than the 723 (56.3%) never-smokers (Figures 2A & 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 separate plots of chronic sputum expectoration presence and chronic cough presence data.

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Relationship between symptoms and smoking with age

CMH was more common amongst persistent-smokers than amongst never-smokers ($p<0.001$ at each age). Figure 4 shows that amongst 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 amongst never-smokers during these periods did not significantly change. Figure E2 (online supplement) shows similar plots for chronic sputum expectoration prevalence and chronic cough prevalence. Chronic cough amongst 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 amongst 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 behaviour with symptom prevalence trends across each period reflecting the balance between symptom onset and resolution rates (Figure E3, online supplement). 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 onwards actually decreased. Furthermore, the dose-response relationship between cigarette consumption and symptom prevalence may steepen with advancing age (Figure E4, online supplement).

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The relationship between chronic symptoms across adult life and airflow limitation at age 60-64 years

1137 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 amongst ever-smokers (8.1%) than never-smokers (2.9%) ($p<0.001$). 81.2% of those with airflow limitation were ever-smokers. Figure E5 (online supplement) demonstrates how cumulative prevalence of chronic symptoms by age 60-64 was greater amongst those with airflow limitation (56.7% 95%CI 44.1-69.2%) than those without (27.2% 95%CI 24.2 to 30.0%) but that only 28.3% (95% CI 16.9 to 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 amongst 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, amongst non-smokers, symptoms at most ages, which were rarer than amongst active-smokers and presumably due to 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 non-smokers 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.

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After separating non-smokers into never and ex-smokers (Figure E6, online supplement) we found no association between symptoms amongst ex-smokers and airflow limitation. The interaction between symptoms and smoking status (active versus 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 $FEV_1/FVC<0.70$ definition of airflow limitation (Figure E7, online supplement).

The relationship between CMH presence and concurrent FEV_1 decline

1960 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 (Table E8), but those reporting symptoms from 36 years onwards were less likely to participate at 60-64 years (Table E8). Mean FEV_1 at age 43 years = 3.00 litres with overall FEV_1 decline of 24.2 ml/year (95%CI 23.1 to 25.4 ml/year) in a model including only age. Addition of smoking status demonstrated that FEV_1 declined more rapidly amongst smokers (31.7 ml/year 95%CI: 27.2 to 36.4 ml/year) than amongst non-smokers (23.2ml/year 95%CI: 21.9-24.4 ml/year) ($p<0.001$).

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

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decline between ages 43 and 60-64 years (Table E6A, online supplement). Widening the CMH presence classification to reflect CMH presence at ages 43, 53 or 60-64 years identified a larger symptomatic group (Table E5, online supplement) and this phenotype was also associated with both lower FEV_1 and accelerated FEV_1 decline (Table E6B, online supplement). For example, reporting of CMH on at least one occasion between 43 and 60-64 years was associated with an additional 4.5 ml/year 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/year FEV_1 decline between ages 43 and 60-64 years compared to 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 males and females of average height and weight at age 43.

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DISCUSSION

This study demonstrates for the first time that middle-age amongst smokers is a period when chronic mucus hypersecretion (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 recognised that CMH is associated with smoking-related respiratory disease outcomes (1, 5-9, 35, 36), but how CMH develops and how its association with these health outcomes emerges over the adult life course, although much hypothesised, 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 both 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 towards symptomatic participants (1) or unequal participant age (7, 37).

CMH symptoms are known to be more common amongst smokers (1, 4, 37, 38) and to become increasingly common with age (1, 12), but this study also demonstrates that the

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relationship between symptoms and smoking evolves with age. In contrast to the consistent and relatively low-level of CMH we found amongst never-smokers, CMH amongst smokers began to increase significantly between the ages of 36 and 43 years and increased further between 53 and 60 to 64 years. The escalating symptom prevalence we found amongst 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 physiological 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 amongst 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 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 to

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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 to 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 re-evaluation of studies which characterise subjects based upon CMH presence later in adult life and/or at a single time-point. For example, amongst those without CMH symptoms later in life, the presence of airflow limitation may instead relate to a symptomatic phase earlier in life which has subsequently abated. With advancing age, an increasing proportion of our study sample entered symptom remission whilst the time remaining for airflow limitation development decreased. Together these observations might explain why, similar to Guerra et al (11), we found symptom presence later in life poorly identify those smokers at greater risk of having airflow limitation by age 60 to 64 years compared to 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 amongst 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 behaviour. Although smoking

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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 physiological response to such insults. Investigating how the 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 amongst 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 pathophysiological responses to smoking and their co-existence, 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.

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A limitation of this study, as with all symptom-based studies, is its reliance upon 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 amongst some individuals, particularly amongst 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 amongst asthmatics can indicate poor asthma control (50) perhaps partly explaining their association with subsequent airflow limitation within the small sub-sample 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 due to inaccurate self-reported medical conditions based upon unverifiable prior symptom interpretation (51). This study highlights the need for further research to ascertain why chronic symptoms develop amongst 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 the majority of adult life but this also introduces several limitations. Firstly, our study sample is predominantly Caucasian, being representative of those born in England, Scotland and Wales in one week in March 1946, potentially affecting the applicability of our findings to other ethnic populations. Secondly, the NSHD protocol was designed prior to publication of guidelines promoting post-bronchodilator spirometry measurements potentially leading to over detection of airflow limitation within this study sample. Finally, longer studies inevitably offer more opportunity for participant loss over time potentially

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introducing follow-up bias, for example, with the loss of sicker individuals. Although the NSHD study sample appears 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 amongst 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, emphasising the benefits of stopping smoking irrespective of life stage. CMH is traditionally regarded as a phenotype associated with poor clinical outcomes and whilst this may be true, during life CMH appears and disappears. The duration of CMH also appears to be related to the concurrent rate of FEV_1 decline independent of smoking behaviour. 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 physiological characteristics accompanying different chronic symptom courses amongst smokers, particularly in early adult life, are warranted to advance our understanding of how airway disease develops ultimately aiming to facilitate both early detection and intervention.

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1. Fletcher CM. The Natural history of chronic bronchitis and emphysema : an eight-year study of early chronic obstructive lung disease in working men in London. Oxford ; New York: Oxford University Press; 1976.

2. Kanner RE, Connett JE, Williams DE, Buist AS. Effects of randomized assignment to a smoking cessation intervention and changes in smoking habits on respiratory symptoms in smokers with early chronic obstructive pulmonary disease: the Lung Health Study. *The American journal of medicine* 1999; 106: 410-416.

3. Pelkonen M, Notkola IL, Nissinen A, Tukiainen H, Koskela H. Thirty-year cumulative incidence of chronic bronchitis and COPD in relation to 30-year pulmonary function and 40-year mortality: a follow-up in middle-aged rural men. *Chest* 2006; 130: 1129-1137.

4. Lindberg A, Jonsson AC, Ronmark E, Lundgren R, Larsson LG, Lundback B. Ten-year cumulative incidence of COPD and risk factors for incident disease in a symptomatic cohort. *Chest* 2005; 127: 1544-1552.

5. Kim V, Han MK, Vance GB, Make BJ, Newell JD, Hokanson JE, Hersh CP, Stinson D, Silverman EK, Criner GJ, Investigators CO. The chronic bronchitic phenotype of COPD: an analysis of the COPDGene Study. *Chest* 2011; 140: 626-633.

6. Seemungal TA, Donaldson GC, Paul EA, Bestall JC, Jeffries DJ, Wedzicha JA. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. *American journal of respiratory and critical care medicine* 1998; 157: 1418-1422.

7. Vestbo J, Prescott E, Lange P. Association of chronic mucus hypersecretion with FEV1 decline and chronic obstructive pulmonary disease morbidity. Copenhagen City Heart Study Group. *American journal of respiratory and critical care medicine* 1996; 153: 1530-1535.

8. Lange P, Nyboe J, Appleyard M, Jensen G, Schnohr P. Relation of ventilatory impairment and of chronic mucus hypersecretion to mortality from obstructive lung disease and from all causes. *Thorax* 1990; 45: 579-585.

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AJRCCM Articles in Press. Published on 22-December-2015 as 10.1164/rccm.201511-2210OC

9. Prescott E, Lange P, Vestbo J. Chronic mucus hypersecretion in COPD and death from pulmonary infection. *The European respiratory journal* 1995; 8: 1333-1338.

10. de Marco R, Accordini S, Cerveri I, Corsico A, Anto JM, Kunzli N, Janson C, Sunyer J, Jarvis D, Chinn S, Vermeire P, Svanes C, Ackermann-Liebrich U, Gislason T, Heinrich J, Leynaert B, Neukirch F, Schouten JP, Wjst M, Burney P. Incidence of chronic obstructive pulmonary disease in a cohort of young adults according to the presence of chronic cough and phlegm. *American journal of respiratory and critical care medicine* 2007; 175: 32-39.

11. Guerra S, Sherrill DL, Venker C, Ceccato CM, Halonen M, Martinez FD. Chronic bronchitis before age 50 years predicts incident airflow limitation and mortality risk. *Thorax* 2009; 64: 894-900.

12. Viegi G, Scognamiglio A, Baldacci S, Pistelli F, Carrozzi L. Epidemiology of chronic obstructive pulmonary disease (COPD). *Respiration; international review of thoracic diseases* 2001; 68: 4-19.

13. Vestbo J, Lange P. Can GOLD Stage 0 provide information of prognostic value in chronic obstructive pulmonary disease? *American journal of respiratory and critical care medicine* 2002; 166: 329-332.

14. Stocks J, Hislop A, Sonnappa S. Early lung development: lifelong effect on respiratory health and disease. *The lancet Respiratory medicine* 2013; 1: 728-742.

15. Ben-Shlomo Y, Kuh D. A life course approach to chronic disease epidemiology: conceptual models, empirical challenges and interdisciplinary perspectives. *International journal of epidemiology* 2002; 31: 285-293.

16. Definition and classification of chronic bronchitis for clinical and epidemiological purposes. A report to the Medical Research Council by their Committee on the Aetiology of Chronic Bronchitis. *Lancet* 1965; 1: 775-779.

17. Rose GA, Blackburn H. Cardiovascular survey methods. *Monograph series World Health Organization* 1968; 56: 1-188.

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18. Cotes JE. Medical Research Council Questionnaire on Respiratory Symptoms (1986). *Lancet* 1987; 2: 1028.

19. de Oca MM, Halbert RJ, Lopez MV, Perez-Padilla R, Talamo C, Moreno D, Muino A, Jardim JR, Valdivia G, Pertuze J, Menezes AM. The chronic bronchitis phenotype in subjects with and without COPD: the PLATINO study. *The European respiratory journal* 2012; 40: 28-36.

20. Putcha N, Drummond MB, Connett JE, Scanlon PD, Tashkin DP, Hansel NN, Wise RA. Chronic productive cough is associated with death in smokers with early COPD. *Copd* 2014; 11: 451-458.

21. Allinson JP, Hardy R, Donaldson GC, Shaheen SO, Kuh D, Wedzicha JA. The longitudinal course of chronic mucus hypersecretion (CMH) over 43 years of adult life within a nationally representative birth cohort. *The European respiratory journal Supplement* 2014; 44.

22. Allinson JPA, Hardy RH, Donaldson GCD, Shaheen SOS, Kuh DK, Wedzicha JAW. The Overlapping Prevalence of Chronic Mucus Hypersecretion (Cmh) and Chronic Cough (Cc). *Thorax* 2014; 69: A83-A83.

23. Allinson JP, Hardy R, Donaldson GC, Shaheen SO, Kuh D, Wedzicha JA. The Changing Relationship Between Cigarette Smoking And Chronic Mucus Hypersecretion (CMH) Within A Nationally Representative Birth Cohort Over 43 Years Of Adult Life. *American journal of respiratory and critical care medicine* 2015; 191: A3906.

24. Allinson JP, Hardy R, Donaldson GC, Shaheen SO, Kuh D, Wedzicha JA. The relationship between cigarette smoking intensity and chronic mucus hypersecretion (CMH) at different ages within a nationally representative birth cohort. *The European respiratory journal Supplement* 2015; 46.

25. Allinson JP, Hardy R, Donaldson GC, Shaheen SO, Kuh D, Wedzicha JA. Chronic Mucus Hypersecretion May Represent a Biomarker of Airways Disease Activity Rather Than Simply a Phenotype: A Longitudinal Study of a Nationally Representative British Birth Cohort. *Thorax* 2015; 70: A186-A186.

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AJRCCM Articles in Press. Published on 22-December-2015 as 10.1164/rccm.201511-2210OC

26. Wadsworth M, Kuh D, Richards M, Hardy R. Cohort Profile: The 1946 National Birth Cohort (MRC National Survey of Health and Development). *International journal of epidemiology* 2006; 35: 49-54.

27. Kuh D, Pierce M, Adams J, Deanfield J, Ekelund U, Friberg P, Ghosh AK, Harwood N, Hughes A, Macfarlane PW, Mishra G, Pellerin D, Wong A, Stephen AM, Richards M, Hardy R, scientific N, data collection t. Cohort profile: updating the cohort profile for the MRC National Survey of Health and Development: a new clinic-based data collection for ageing research. *International journal of epidemiology* 2011; 40: e1-9.

28. Stafford M, Black S, Shah I, Hardy R, Pierce M, Richards M, Wong A, Kuh D. Using a birth cohort to study ageing: representativeness and response rates in the National Survey of Health and Development. *European journal of ageing* 2013; 10: 145-157.

29. Cotes JE. MRC questionnaire (MRCQ) on respiratory symptoms. *Occupational Medicine* 2007; 57: 388.

30. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J, Force AET. Standardisation of spirometry. *The European respiratory journal* 2005; 26: 319-338.

31. Fletcher CM, Peto R, Tinker CM. A comparison of the assessment of simple bronchitis (chronic mucus hypersecretion) by measurements of sputum volume and by standardized questions on phlegm production. *International journal of epidemiology* 1974; 3: 315-319.

32. Samet JM. A historical and epidemiologic perspective on respiratory symptoms questionnaires. *American journal of epidemiology* 1978; 108: 435-446.

33. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *American journal of respiratory and critical care medicine* 1999; 159: 179-187.

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34. Bakke PS, Ronmark E, Eagan T, Pistelli F, Annesi-Maesano I, Maly M, Meren M, Vermeire Dagger P, Vestbo J, Viegi G, Zielinski J, Lundback B, European Respiratory Society Task F. Recommendations for epidemiological studies on COPD. *The European respiratory journal* 2011; 38: 1261-1277.

35. Anthonisen NR. The British hypothesis revisited. *The European respiratory journal* 2004; 23: 657-658.

36. Vestbo J, Hogg JC. Convergence of the epidemiology and pathology of COPD. *Thorax* 2006; 61: 86-88.

37. Krzyzanowski M, Lebowitz MD. Changes in chronic respiratory symptoms in two populations of adults studied longitudinally over 13 years. *The European respiratory journal* 1992; 5: 12-20.

38. Brown CA, Crombie IK, Smith WC, Tunstall-Pedoe H. The impact of quitting smoking on symptoms of chronic bronchitis: results of the Scottish Heart Health Study. *Thorax* 1991; 46: 112-116.

39. Ito K, Barnes PJ. COPD as a disease of accelerated lung aging. *Chest* 2009; 135: 173-180.

40. Gould NS, Min E, Gauthier S, Chu HW, Martin R, Day BJ. Aging adversely affects the cigarette smoke-induced glutathione adaptive response in the lung. *American journal of respiratory and critical care medicine* 2010; 182: 1114-1122.

41. Rojas M, Mora AL. Age and smoke: a risky combination. *American journal of respiratory and critical care medicine* 2011; 183: 423-424.

42. Lange P, Celli B, Agusti A, Boje Jensen G, Divo M, Faner R, Guerra S, Marott JL, Martinez FD, Martinez-Camblor P, Meek P, Owen CA, Petersen H, Pinto-Plata V, Schnohr P, Sood A, Soriano JB, Tesfaigzi Y, Vestbo J. Lung-Function Trajectories Leading to Chronic Obstructive Pulmonary Disease. *The New England journal of medicine* 2015; 373: 111-122.

43. Fletcher C, Peto R. The natural history of chronic airflow obstruction. *British medical journal* 1977; 1: 1645-1648.

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AJRCCM Articles in Press. Published on 22-December-2015 as 10.1164/rccm.201511-2210OC

44. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. American Thoracic Society. *American journal of respiratory and critical care medicine* 1995; 152: S77-121.

45. Willemse BW, ten Hacken NH, Rutgers B, Lesman-Leegte IG, Postma DS, Timens W. Effect of 1-year smoking cessation on airway inflammation in COPD and asymptomatic smokers. *The European respiratory journal* 2005; 26: 835-845.

46. Mullen JB, Wright JL, Wiggs BR, Pare PD, Hogg JC. Structure of central airways in current smokers and ex-smokers with and without mucus hypersecretion: relationship to lung function. *Thorax* 1987; 42: 843-848.

47. Turato G, Di Stefano A, Maestrelli P, Mapp CE, Ruggieri MP, Roggeri A, Fabbri LM, Saetta M. Effect of smoking cessation on airway inflammation in chronic bronchitis. *American journal of respiratory and critical care medicine* 1995; 152: 1262-1267.

48. Kim V, Oros M, Durra H, Kelsen S, Aksoy M, Cornwell WD, Rogers TJ, Criner GJ. Chronic bronchitis and current smoking are associated with more goblet cells in moderate to severe COPD and smokers without airflow obstruction. *PloS one* 2015; 10: e0116108.

49. Openshaw PJ, Turner-Warwick M. Observations on sputum production in patients with variable airflow obstruction; implications for the diagnosis of asthma and chronic bronchitis. *Respiratory medicine* 1989; 83: 25-31.

50. Lange P, Parner J, Vestbo J, Schnohr P, Jensen G. A 15-year follow-up study of ventilatory function in adults with asthma. *The New England journal of medicine* 1998; 339: 1194-1200.

51. Lange P, Ulrik CS, Vestbo J. Mortality in adults with self-reported asthma. Copenhagen City Heart Study Group. *Lancet* 1996; 347: 1285-1289.

52. Micallef L, Rodgers P. eulerAPE: drawing area-proportional 3-Venn diagrams using ellipses. *PloS one* 2014; 9: e101717.

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Figure Legends:

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

FIGURE 2:

The prevalence of Chronic Mucus Hypersecretion (CMH), Chronic Sputum expectoration (CS), Chronic Cough (CC) and cigarette smoking amongst those individuals providing complete data at all six time-points within the NSHD (n=1284). (A) Area proportional Venn diagram (52) representing the overlapping cumulative prevalence (%) of CS (Ever-CS), CC (Ever-CC) and cigarette smoking (Ever-smoker vs Never-smoker). Numbers shown are percentages of the included population (n=1284). **(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% Confidence Interval of CMH, CS, CC and cigarette smoking at each of six time-points between 1966 and 2009.

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FIGURE 3:

The longitudinal pattern of Chronic Mucus Hypersecretion (CMH) presence amongst those providing complete data at all six NSHD time-points (n=1284) 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); "remission" (CMH reported previously but absent currently) and "relapse" (CMH currently reported following previous remission). CMH = chronic cough with concurrent chronic mucus expectoration. Figure E1 in the online supplement displays similar separate plots of chronic sputum expectoration presence and chronic cough presence data.

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 NSHD according to concurrent cigarette smoking behaviour (Additionally, see Figures E2-3 and Tables E2-4 in the online supplement)

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FIGURE 5:

The relationship between chronic symptoms (chronic cough and/or chronic sputum expectoration) amongst smokers and non-smokers at different ages during adult life and the presence of airflow limitation (FEV_1/FVC < lower limit of normal) by age 60-64 years. Logistic regression models adjusted for sex, concurrent smoking cigarette consumption. The log odds ratio (95% CIs) of having developed airflow limitation by the time they reached 60-64 years of age amongst those with chronic symptoms at each age.

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 for (A) males (height 176cm; weight 79kg); and (B) females (height 163cm; weight 66kg) according to the number of occasions CMH was reported across the three time-points.

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Tables

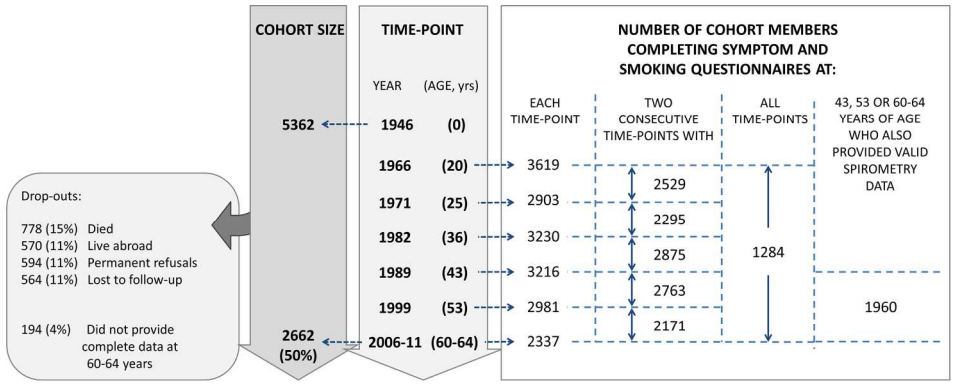
TABLE 1:

The influence of duration of Chronic Mucus Hypersecretion (CMH) presence on multilevel models estimating the relationship between CMH presence and concurrent FEV_1 decline between ages 43 and 60-64 years. Multilevel modelling included 1960 men and woman. Mean FEV_1 at age 43 years was 3.00 litres, with an unadjusted FEV_1 decline of 24.2 ml/year. 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) (Online supplement: Table E6 displays the results of separate modelling of chronic sputum expectoration and chronic cough presence).

	FEV_1 intercept (ml) at age 43 years			**FEV_1 linear change per year (ml/year) between ages 43 and 60-64 years**		
	Coefficient	(95% CI)	p value	Coefficient	(95% CI)	p value
Constant	-2328.2	(-2840.4 to -1815.9)	-	-22.3	(-23.9 to -20.8)	<0.001
Height (cm) at age 43 years	31.8	(28.5 to 35.1)	<0.001	-	-	-
Weight (Kg) at age 43 years	-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) years (0 - 3 occasions)	-162.3	(-208.5 to -116.1)	<0.001	-3.6	(-6.1 to -1.1)	0.005

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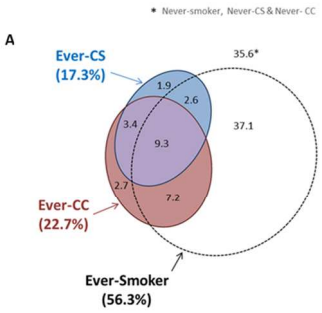
FIGURE 1



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FIGURE 2

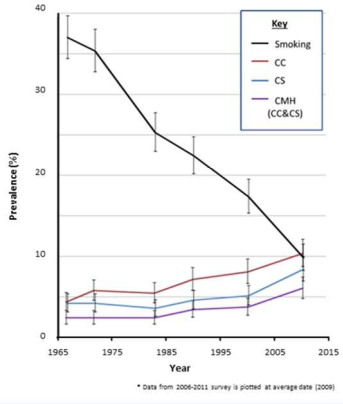


B

		PREVALENCE % (95%CI)		
		Never-Smokers (n=561)	Ever-Smokers (n=723)	OVERALL (n=1284)
SYMPTOM(S)	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 & 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 & 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		

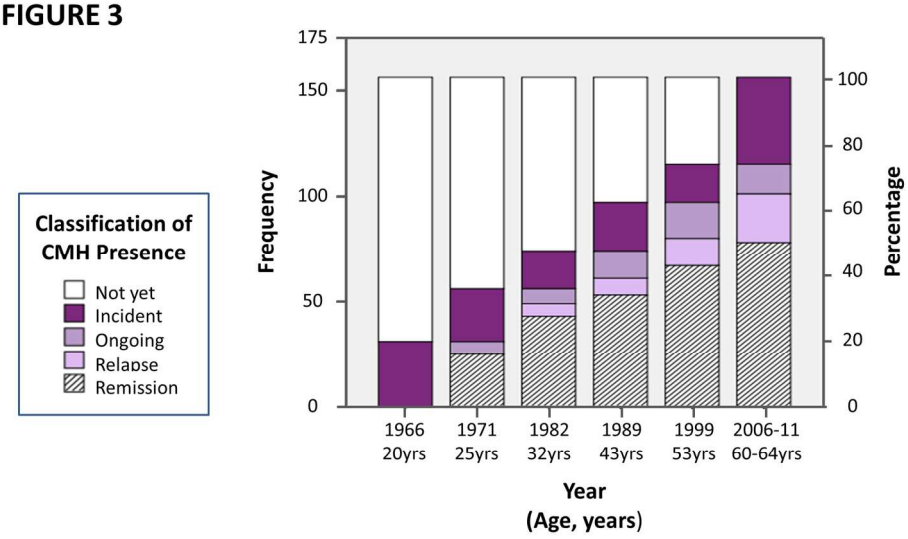
P values calculated using Chi-Square test

C



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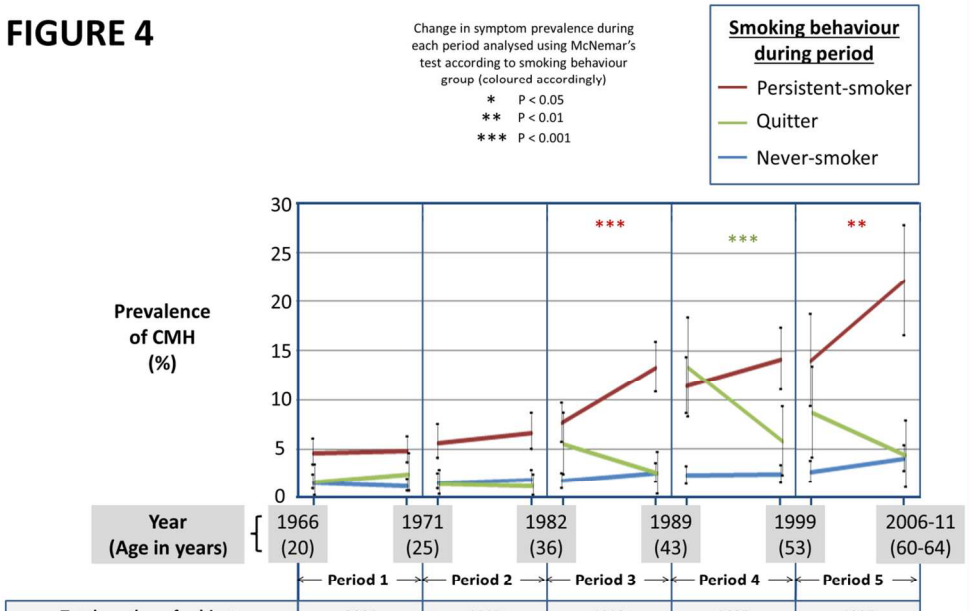
FIGURE 3



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FIGURE 4

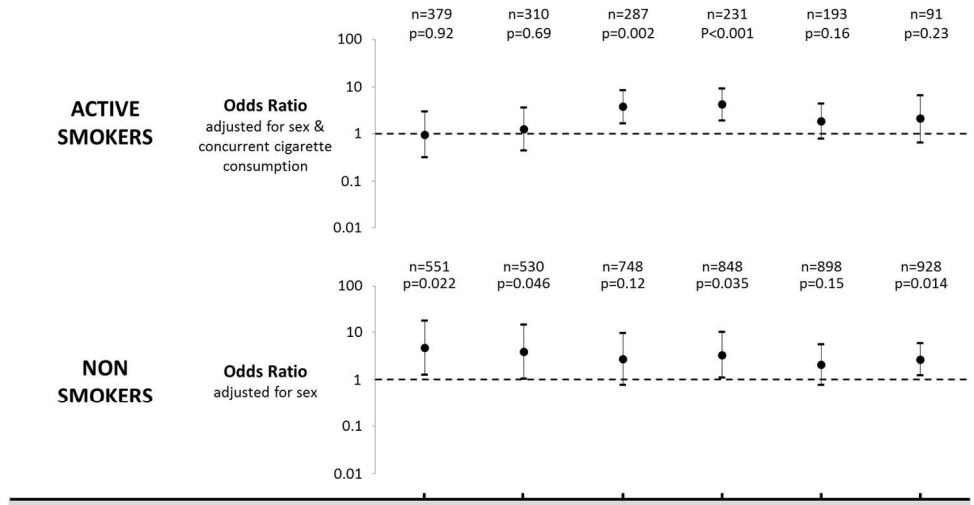


Total number of subjects			**2084**		**1815**		**1919**		**1687**	**1207**
Median cigarettes smoked/day (IQR)	Quitter	Period start †	10(5-15)	P<0.001	10(5-19)	P<0.001	15 (7-20)	P<0.001	18 (10-20)	P<0.001	15 (9-20)	P=0.006
	Persistent smoker	Period start ‡	10(10-15)	P<0.001	15(10-20)	P<0.001	20 (15-25)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

† Mann-Whitney U tests ‡ Wilcoxon Signed Rank tests

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FIGURE 5

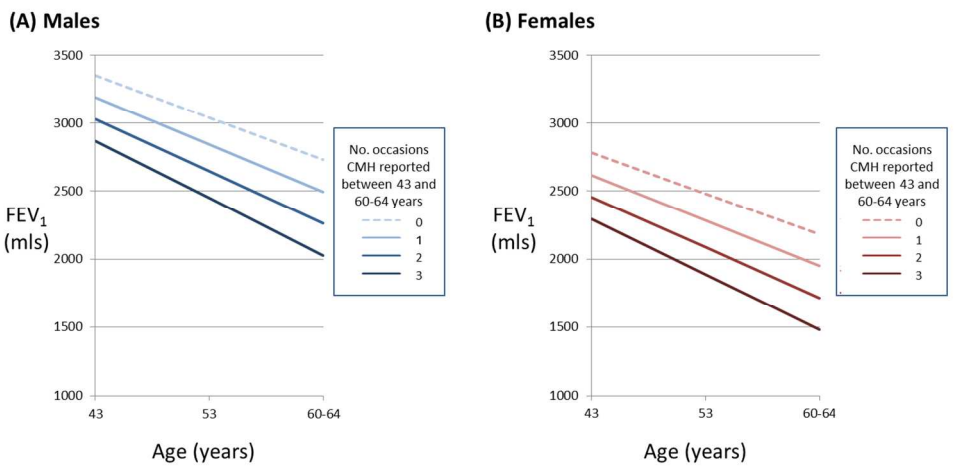


	YEAR (Age in years)	1966 (20)	1971 (25)	1982 (36)	1989 (43)	1999 (53)	2006-11 (60-64)
ACTIVE SMOKERS	Odds Ratio (95% CI)	0.95 (0.32-2.85)	1.24 (0.44-3.52)	3.70 (1.62-8.45)	4.11 (1.85-9.13)	1.82 (0.78-4.23)	2.07 (0.64-4.74)
NON SMOKERS	Odds Ratio (95% CI)	4.64 (1.25-17.22)	3.80 (1.03-14.08)	2.73 (0.78-9.55)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

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FIGURE 6



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ONLINE DATA SUPPLEMENT

The Presence of Chronic Mucus Hypersecretion Across Adult Life in Relation to COPD Development

James P Allinson, Rebecca Hardy, Gavin C Donaldson, Seif O Shaheen, Diana Kuh, Jadwiga A Wedzicha

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FIGURE E1

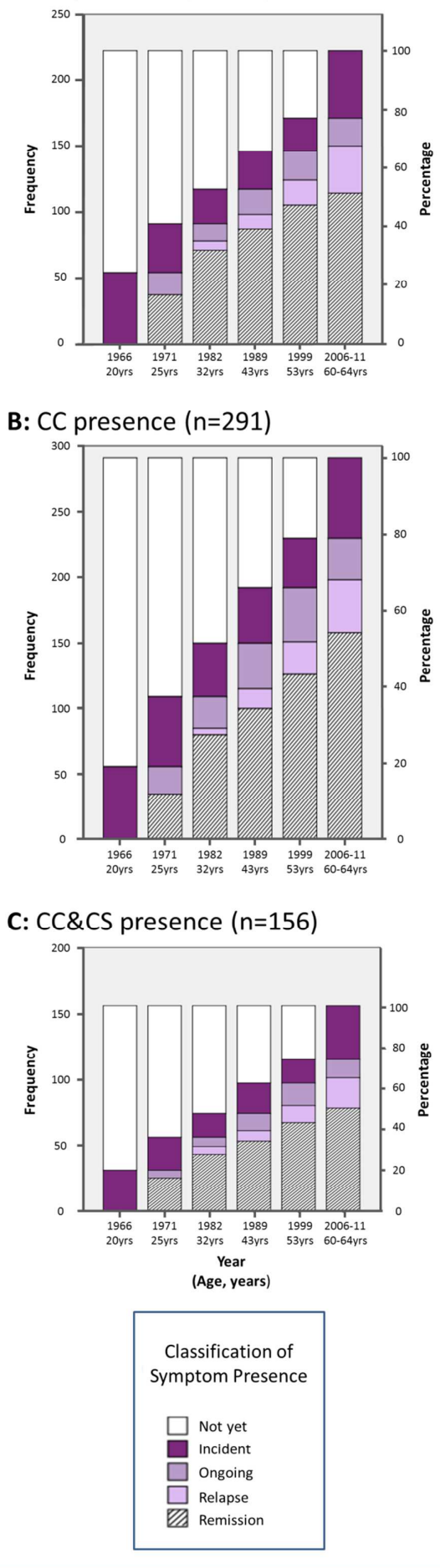
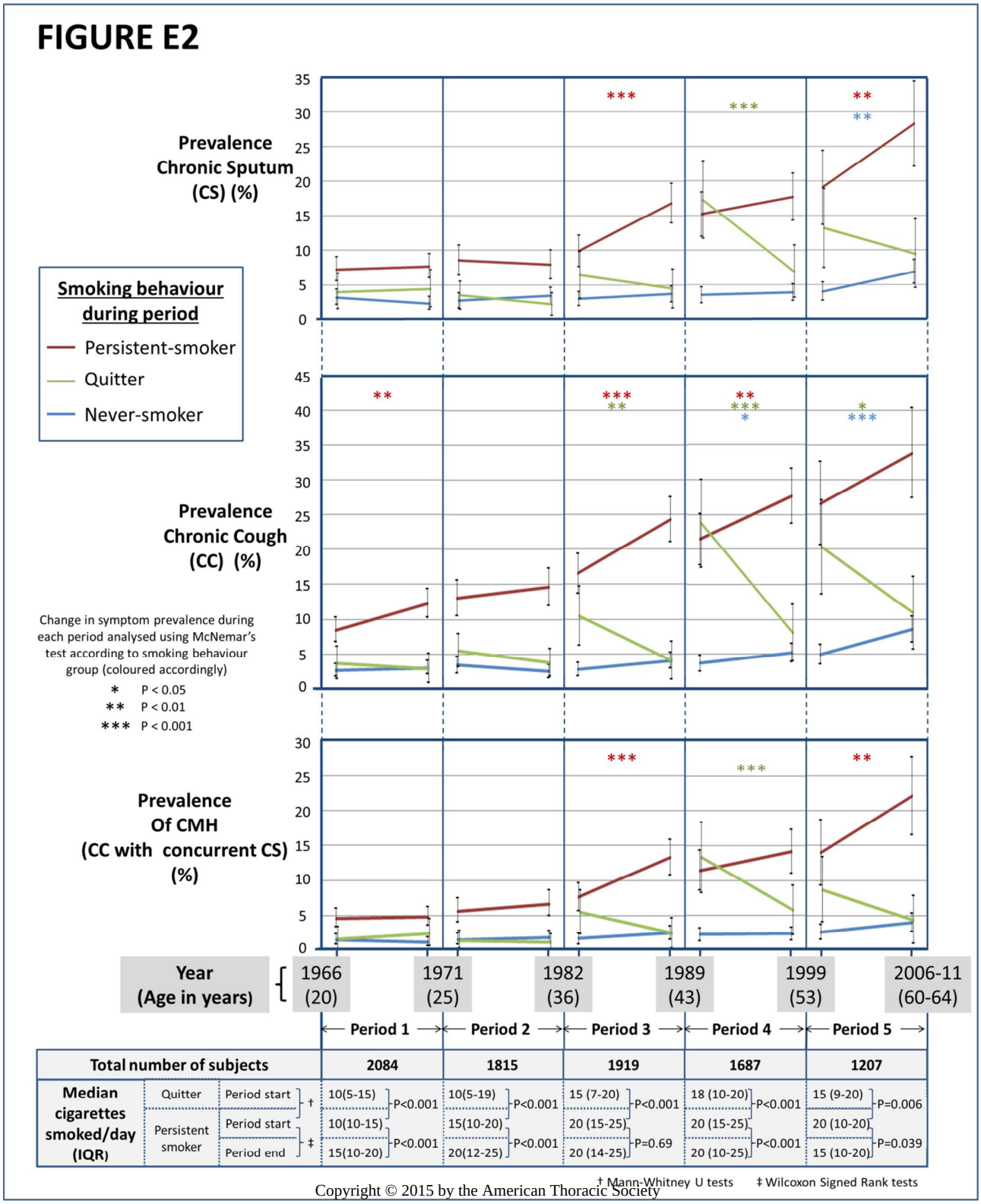


Figure E1

The longitudinal pattern of symptom presence amongst those providing complete data at all six NSHD time-points (n=1284) and reporting that symptom to be present on at least one occasion. At each time-point individuals are classified according to their previous and current reporting of respective symptom(s) as follows (and in the symptoms classification box): "not yet" (no current/previous); "incident" (first report of symptoms); "ongoing" (persistent since the incident report); "remission" (reported previously but absent currently) and "relapse" (currently reported following previous remission). **A**: Chronic Sputum (CS) presence amongst 222 individuals (17.3%) reporting CS on at least one occasion. **B**: Chronic Cough (CC) presence amongst the 22.7% (291 individuals) reporting CC on at least one occasion. **C**: Chronic Sputum with concurrent Chronic Cough (CC&CS) presence amongst the 12.1% (156 individuals) reporting CC&CS on at least one occasion.

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Figure E2 The prevalence of Chronic Sputum (CS), Chronic Cough (CC) and Chronic Sputum with concurrent Chronic Cough (CC&CS) (with 95% Confidence Intervals) and median smoking intensity during five time-periods over adult life within the NSHD according to concurrent cigarette smoking behaviour (Tables E2-4 and Figure E3).

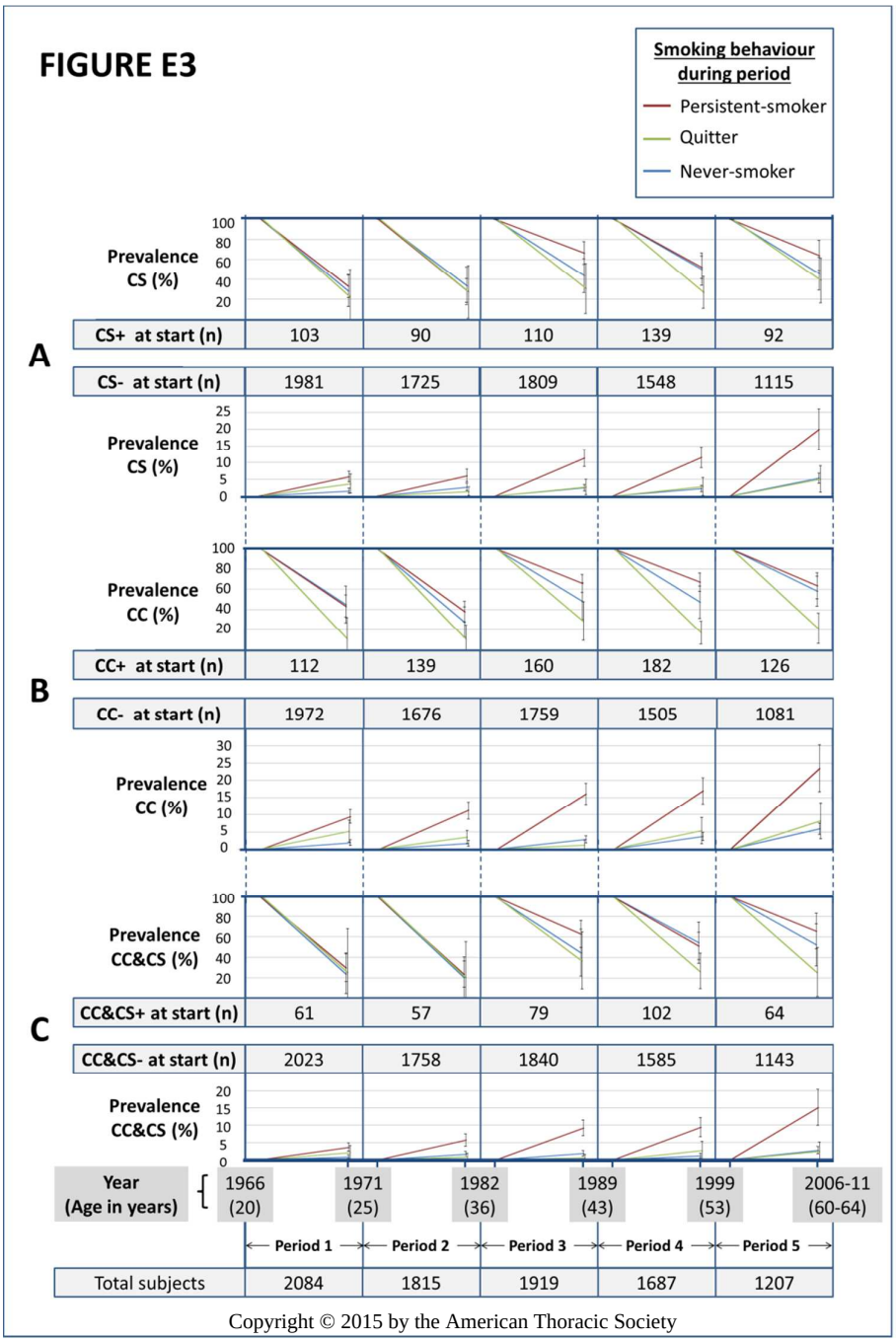


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Figure E3

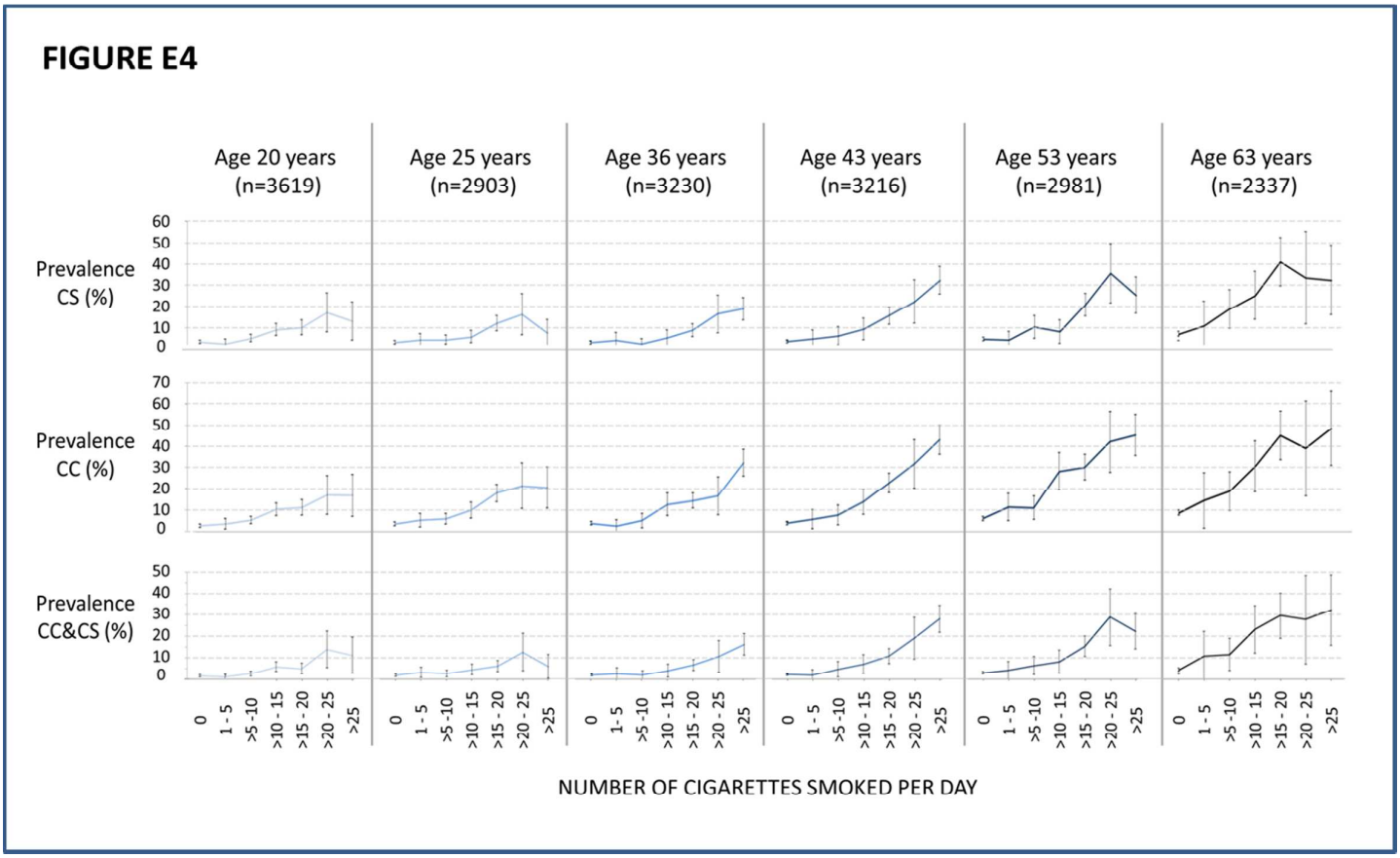
The prevalence of (A) Chronic Sputum (CS), (B) Chronic Cough (CC) and (C) Chronic Sputum with concurrent Chronic Cough (CC&CS) (with 95% Confidence Intervals) during five time-periods over adult life within the NSHD according to concurrent cigarette smoking behaviour and according to the presence or absence of respective symptom(s) at the start of the period (Tables S7-S12). CS+, CC+ and CC&CS+ denote presence of respective symptom; CS-, CC- and CC&CS- denote absence of respective symptom. See Figure 4.



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Figure E4

The prevalence pattern of Chronic Sputum (CS), Chronic Cough (CC) and Chronic Cough concurrent with concurrent Chronic Sputum (CC&CS) according to intensity of smoking (number of cigarettes smoked daily) at different ages during adult life within the NSHD.



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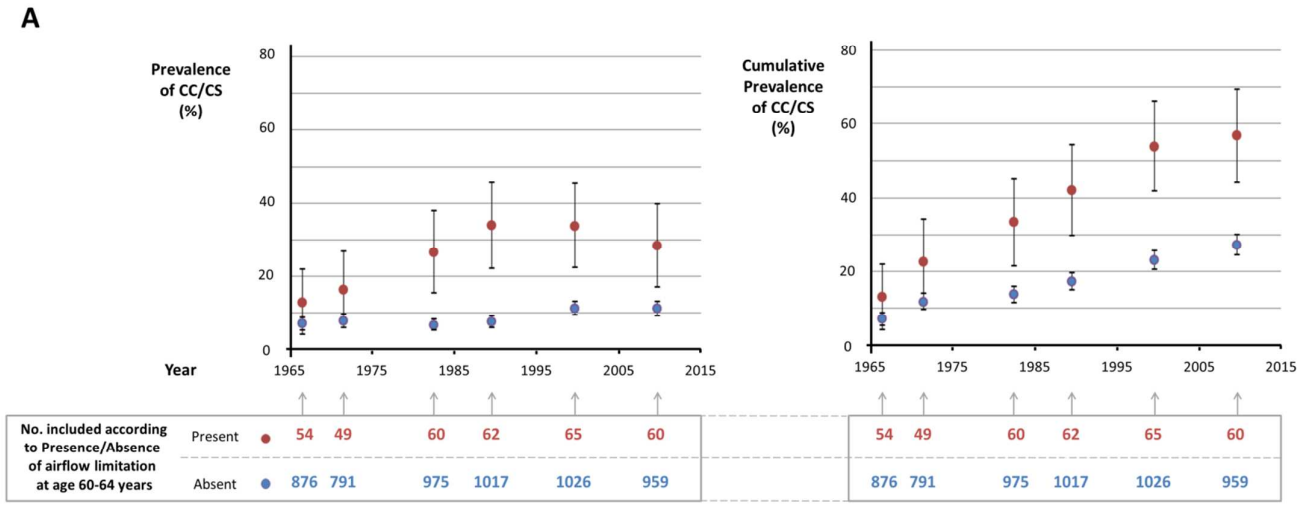
Figure E5

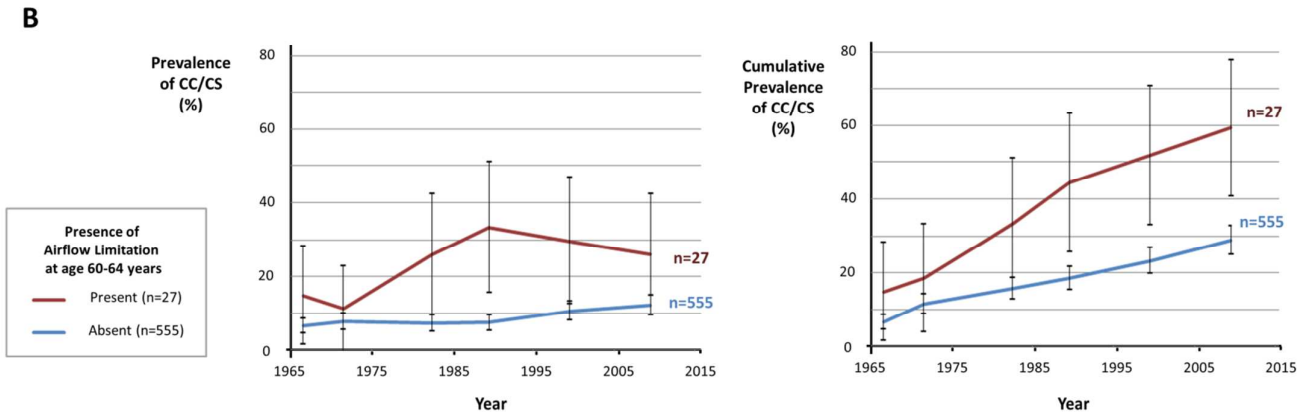
The presence of chronic cough and/or chronic sputum expectoration (CC/CS) during adult life amongst those with and without airflow limitation (FEV_1/FVC < lower limit of normal) by age 60-64 years.

(A) Prevalence and cumulative prevalence of CC/CS amongst those 1137 individuals providing complete data at ≥ one time-point and with lung function data at age 60-64 years (those included in Figure 5); (B) Prevalence and cumulative prevalence of CC/CS amongst those 582 individuals providing complete data at all time-points and with lung function data at age 60-64 years. Prevalence or cumulative prevalence is represented as a percentage with 95% confidence intervals.

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FIGURE E5





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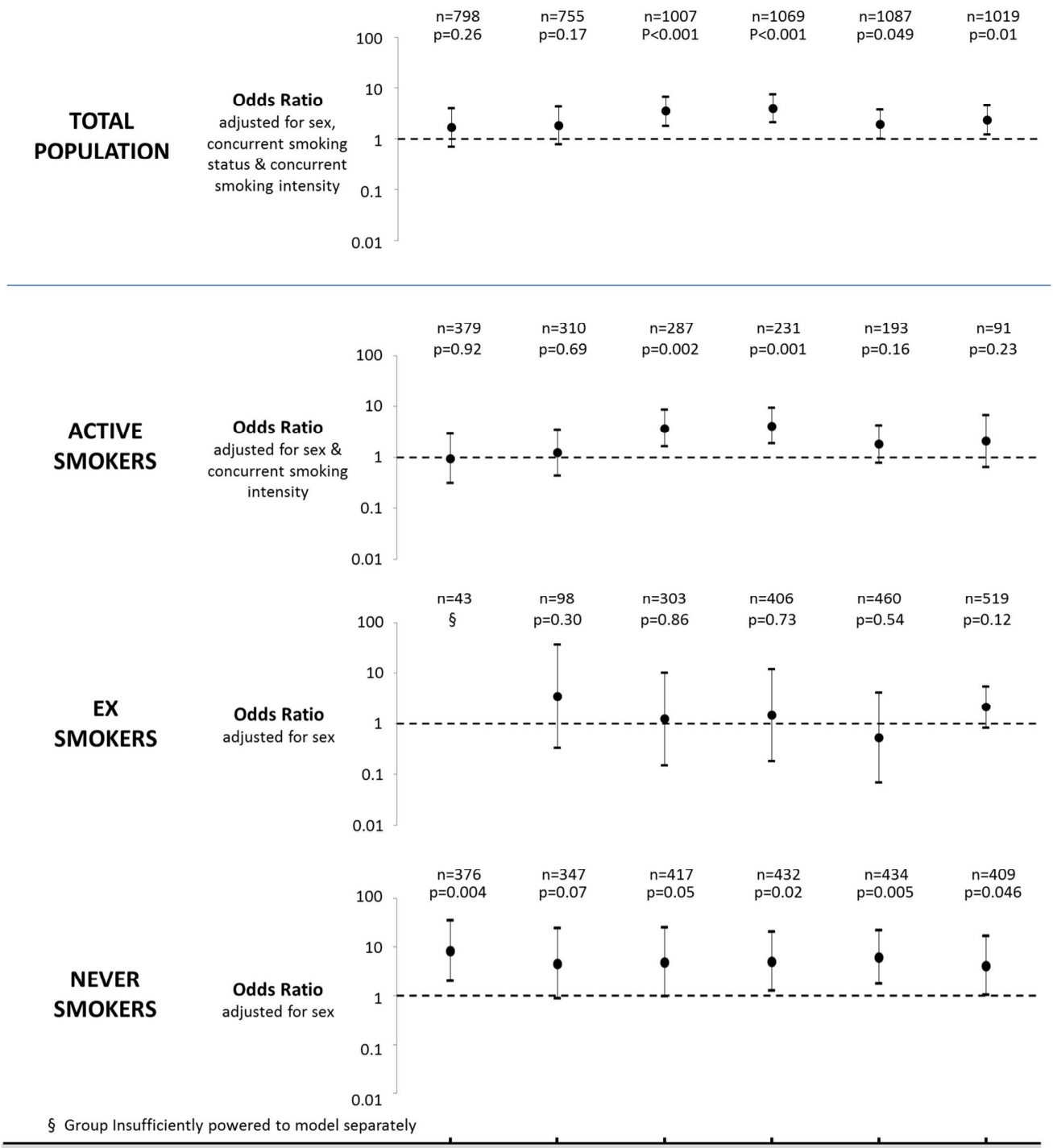
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Figure E6

The relationship between chronic symptoms (chronic cough and/or chronic sputum expectoration) amongst smokers, ex-smokers and never-smokers at different ages during adult life and the prevalence of airflow limitation (FEV_1/FVC < lower limit of normal) by age 60-64 years. Logistic regression models adjusted for sex, concurrent smoking cigarette consumption. The log odds ratio (95% CIs) of having developed airflow limitation by the time they reached 60-64 years of age amongst those with chronic symptoms at each age. A small number of individuals included in Figure 5 are excluded from this analysis as not all non-smokers could be classified as ex-smokers or never-smokers (for example, they subsequently started smoking for the first time).

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FIGURE E6



§ Group Insufficiently powered to model separately

	YEAR (Age in years)	1966 (20)	1971 (25)	1982 (36)	1989 (43)	1999 (53)	2006-11 (60-64)
TOTAL POPULATION	Odds Ratio (95% CI)	1.65 (0.69-3.92)	1.81 (0.78-4.20)	3.43 (1.74-6.74)	3.89 (2.05-7.38)	1.91 (1.00-3.65)	2.33 (1.21-4.47)
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)
EX SMOKERS	Odds Ratio (95% CI)	§ §	3.51 (0.33-36.81)	1.22 (0.15-10.09)	1.45 (0.18-11.78)	0.53 (0.69-4.05)	2.11 (0.82-5.40)
NEVER SMOKERS	Odds Ratio (95% CI)	8.34 (1.98-35.09)	4.56 (0.87-23.87)	4.90 (0.97-24.79)	5.14 (1.28-20.59)	6.15 (1.76-21.53)	4.16 (1.03-16.81)

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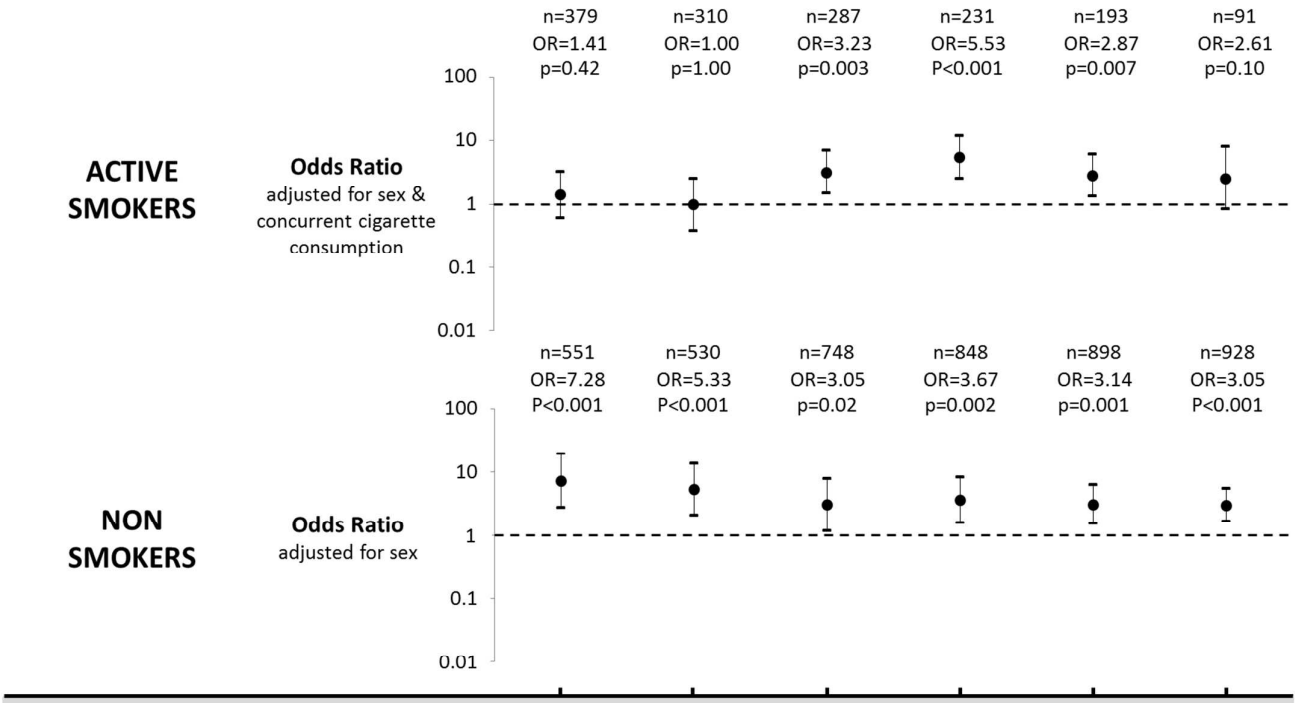
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Figure E7

The relationship between chronic symptoms (chronic cough and/or chronic sputum expectoration) amongst smokers and non-smokers at different ages during adult life and the presence of $FEV_1/FVC<0.70$ by age 60-64 years. $FEV_1/FVC<0.70$ was present in 107 (9.4%) of the 1137 individuals included, more commonly amongst ever-smokers (11.3%) than amongst never-smokers (6.5%) (p=0.007). 72.9% of those with $FEV_1/FVC<0.70$ were ever-smokers. Logistic regression models adjusted for sex, concurrent smoking cigarette consumption. The log odds ratio (95% CIs) of having developed an FEV_1/FVC ratio <0.70 by the time they reached 60-64 years of age amongst those with chronic symptoms at each age.

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FIGURE E7



	YEAR (Age in years)	1966 (20)	1971 (25)	1982 (36)	1989 (43)	1999 (53)	2006-11 (60-64)
ACTIVE SMOKERS	Odds Ratio (95% CI)	1.41 (0.61-3.25)	1.00 (0.38-2.60)	3.23 (1.50-6.95)	5.53 (2.61-11.73)	2.87 (1.33-6.23	2.61 (0.84-8.13)
NON SMOKERS	Odds Ratio (95% CI)	7.28 (2.79-19.0)	5.33 (2.10-13.51)	3.05 (1.20-7.76)	3.66 (1.61-8.35)	3.14 (1.58-6.22)	3.05 (1.69-5.51)

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Table E1

Number of times symptom(s) (Chronic Sputum (CS), Chronic Cough (CC) or CC with concurrent CS (CC&CS)) reported across six time-points by cohort members who provided complete data at all six time-points (n=1284) and reported respective symptom(s) at least once.

		SYMPTOM(S)					
		Group reporting CS at least once during the study (n=222)		Group reporting CC at least once during the study (n=291)		Group reporting CS with CC at least once during the study (n=156)	
		Count	%	Count	%	Count	%
Number of times symptom reported by subjects across six time-points	1	136	61.3	172	59.1	99	63.5
	2	42	18.9	58	19.9	26	16.7
	3	24	10.8	23	7.9	20	12.8
	4	7	3.2	25	8.6	4	2.6
	5	11	5.0	6	2.1	6	3.8
	6	2	0.9	7	2.4	1	0.6
Total		222	100.0	291	100.0	156	100.0

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Table E2

The prevalence of Chronic Sputum (CS) (with 95% Confidence Intervals) during five time-periods over adult life within the NSHD according to concurrent cigarette smoking behaviour. Chi-square tests were used to assess differences in CS prevalence between smoking groups at beginning and end of each period. McNemar's tests were used to analyse change in CS prevalence within each smoking group (Figure 4).

		BEGINNING OF PERIOD					END OF PERIOD					Significance of change in prevalence between beginning and end of period (McNemar's test)
				Chi-square test					Chi-square test			
		Prevalence of Chronic Sputum (CS) (%)	95%CI	Persistent vs Never Smoker	Persistent Smoker vs Quitter	Quitter vs Never Smoker	Prevalence of Chronic Sputum (CS) (%)	95%CI	Persistent vs Never Smoker	Persistent Smoker vs Quitter	Quitter vs Never Smoker	
Classification of smoking behaviour during period 1 (1966-1971) (n=2084)	Persistent-Smoker (n=878)	7.3	(5.6 to 9.0)	<0.001	0.08	0.46	7.7	(6.0 to 9.5)	<0.001	0.08	0.04	0.75
	Quitter (n=224)	4.0	(1.4 to 6.6)				4.5	(1.8 to 7.2)				1
	Never-Smoker (n=982)	3.1	(2 to 4.1)				2.1	(1.2 to 3.0)				0.18
Classification of smoking behaviour during period 2 (1971-1982) (n=1815)	Persistent-Smoker (n=651)	8.6	(6.4 to 10.8)	<0.001	0.004	0.42	8.0	(5.9 to 10.1)	<0.001	<0.001	0.33	0.73
	Quitter (n=307)	3.6	(1.5 to 5.7)				2.3	(0.6 to 3.9)				0.39
	Never-Smoker (n=857)	2.7	(1.6 to 3.8)				3.4	(2.2 to 4.6)				0.41
Classification of smoking behaviour during period 3 (1982-1989) (n=1919)	Persistent-Smoker (n=667)	9.9	(7.6 to 12.2)	<0.001	0.15	0.01	16.8	(14 to 19.6)	<0.001	<0.001	0.58	<0.001
	Quitter (n=199)	6.5	(3.1 to 10.0)				4.5	(1.6 to 7.4)				0.42
	Never-Smoker (n=1053)	2.9	(1.9 to 4.0)				3.7	(2.6 to 4.8)				0.28
Classification of smoking behaviour during period 4 (1989-1999) (n=1687)	Persistent-Smoker (n=481)	15.2	(12 to 18.4)	<0.001	0.50	<0.001	17.7	(14.3 to 21.1)	<0.001	<0.001	0.06	0.22
	Quitter (n=173)	17.3	(11.7 to 23)				6.9	(3.2 to 10.7)				0.001
	Never-Smoker (n=1033)	3.5	(2.4 to 4.6)				3.9	(2.7 to 5.0)				0.64
Classification of smoking behaviour during period 5 (1999-(2006-2011)) (n=1207)	Persistent-Smoker (n=204)	19.1	(13.7 to 24.5)	<0.001	0.15	<0.001	28.4	(22.2 to 34.6)	<0.001	<0.001	0.28	0.008
	Quitter (n=137)	13.1	(7.5 to 18.8)				9.5	(4.6 to 14.4)				0.33
	Never Smoker (n=866)	4.0	(2.7 to 5.4)				6.9	(5.2 to 8.6)				0.002

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Table E3

The prevalence of Chronic Cough (CC) (with 95% Confidence Intervals) during five time-periods over adult life within the NSHD according to concurrent cigarette smoking behaviour. Chi-square tests were used to assess differences in CC prevalence between smoking groups at beginning and end of each period. McNemar's tests were used to analyse change in CC prevalence within each smoking group (Figure 4).

		BEGINNING OF PERIOD					END OF PERIOD					Significance of change in prevalence between beginning and end of period (McNemar's test)
				Chi-square test					Chi-square test			
		Prevalence of Chronic Cough (CC) (%)	95%CI	Persistent vs Never Smoker	Persistent Smoker vs Quitter	Quitter vs Never Smoker	Prevalence of Chronic Cough (CC) (%)	95%CI	Persistent vs Never Smoker	Persistent Smoker vs Quitter	Quitter vs Never Smoker	
Classification of smoking behaviour during period 1 (1966-1971) (n=2084)	Persistent-Smoker (n=878)	8.8	(6.9 to 10.6)	<0.001	0.009	0.51	12.8	(10.5 to 15)	<0.001	<0.001	0.95	0.002
	Quitter (n=224)	3.6	(1.1 to 6.0)				3.1	(0.8 to 5.4)				1.00
	Never Smoker (n=982)	2.7	(1.7 to 3.8)				3.1	(2.0 to 4.1)				0.72
Classification of smoking behaviour during period 2 (1971-1982) (n=1815)	Persistent-Smoker (n=651)	13.5	(10.9 to 16.1)	<0.001	<0.001	0.07	14.9	(12.2 to 17.6)	<0.001	<0.001	0.21	0.46
	Quitter (n=307)	6.2	(3.5 to 8.9)				4.2	(2.0 to 6.5)				0.35
	Never Smoker (n=857)	3.7	(2.5 to 5.0)				2.8	(1.7 to 3.9)				0.26
Classification of smoking behaviour during period 3 (1982-1989) (n=1919)	Persistent-Smoker (n=667)	16.5	(13.7 to 19.3)	<0.001	0.04	<0.001	24.0	(20.7 to 27.2)	<0.001	<0.001	0.96	<0.001
	Quitter (n=199)	10.6	(6.3 to 14.8)				4.0	(1.3 to 6.7)				0.002
	Never Smoker (n=1053)	2.8	(1.8 to 3.7)				4.1	(2.9 to 5.3)				0.05
Classification of smoking behaviour during period 4 (1989-1999) (n=1687)	Persistent-Smoker (n=481)	21.4	(17.7 to 25.1)	<0.001	0.53	<0.001	27.7	(23.7 to 31.6)	<0.001	<0.001	0.13	0.003
	Quitter (n=173)	23.7	(17.4 to 30)				8.1	(4.0 to 12.2)				<0.001
	Never Smoker (n=1033)	3.7	(2.5 to 4.8)				5.2	(3.9 to 6.6)				0.04
Classification of smoking behaviour during period 5 (1999-(2006-2011)) (n=1207)	Persistent-Smoker (n=204)	27.0	(20.9 to 33.1)	<0.001	0.17	<0.001	34.3	(27.8 to 40.8)	<0.001	<0.001	0.35	0.06
	Quitter (n=137)	20.4	(13.7 to 27.2)				10.9	(5.7 to 16.2)				0.03
	Never Smoker (n=866)	5.0	(3.5 to 6.4)				8.5	(6.7 to 10.4)				<0.001

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Table E4

The prevalence of Chronic Cough with concurrent Chronic Sputum (CC&CS) (with 95% Confidence Intervals) during five time-periods over adult life within the NSHD according to concurrent cigarette smoking behaviour. Chi-square tests were used to assess differences in CC&CS prevalence between smoking groups at beginning and end of each period. McNemar's tests were used to analyse change in CC&CS prevalence within each smoking group (Figure 4).

		BEGINNING OF PERIOD					END OF PERIOD					
		Prevalence of Chronic Cough with concurrent Chronic Sputum (CC&CS) (%)	95%CI	Chi-square test			Prevalence of Chronic Cough with concurrent Chronic Sputum (CC&CS) (%)	95%CI	Chi-square test			Significance of change in prevalence between beginning and end of period (McNemar's test)
				Persistent vs Never Smoker	Persistent Smoker vs Quitter	Quitter vs Never Smoker			Persistent vs Never Smoker	Persistent Smoker vs Quitter	Quitter vs Never Smoker	
Classification of smoking behaviour during period 1 (1966-1971) (n=2084)	Persistent-Smoker (n=878)	4.9	(3.5 to 6.3)	<0.001	0.04	0.69	5.1	(3.7 to 6.6)	<0.001	0.12	0.07	0.90
	Quitter (n=224)	1.8	(0.1 to 3.5)				2.7	(0.6 to 4.8)				0.73
	Never Smoker (n=982)	1.4	(0.7 to 2.2)				1.1	(0.5 to 1.8)				0.63
Classification of smoking behaviour during period 2 (1971-1982) (n=1815)	Persistent-Smoker (n=651)	5.8	(4.0 to 7.6)	<0.001	0.003	1.00	6.8	(4.8 to 8.7)	<0.001	<0.001	0.44	0.53
	Quitter (n=307)	1.6	(0.2 to 3.0)				1.3	(0.0 to 2.6)				1
	Never Smoker (n=857)	1.6	(0.8 to 2.5)				2.0	(1.1 to 2.9)				0.69
Classification of smoking behaviour during period 3 (1982-1989) (n=1919)	Persistent-Smoker (n=667)	7.6	(5.6 to 9.7)	<0.001	0.31	<0.001	13.0	(10.5 to 15.6)	<0.001	<0.001	0.96	<0.001
	Quitter (n=199)	5.5	(2.4 to 8.7)				2.5	(0.3 to 4.7)				0.07
	Never Smoker (n=1053)	1.6	(0.9 to 2.4)				2.6	(1.6 to 3.5)				0.09
Classification of smoking behaviour during period 4 (1989-1999) (n=1687)	Persistent-Smoker (n=481)	11.4	(8.6 to 14.3)	<0.001	0.52	<0.001	14.1	(11 to 17.3)	<0.001	0.004	0.01	0.14
	Quitter (n=173)	13.3	(8.2 to 18.4)				5.8	(2.3 to 9.3)				0.007
	Never Smoker (n=1033)	2.3	(1.4 to 3.2)				2.4	(1.5 to 3.4)				1
Classification of smoking behaviour during period 5 (1999-(2006-2011)) (n=1207)	Persistent-Smoker (n=204)	14.2	(9.4 to 19.0)	<0.001	0.13	<0.001	22.5	(16.8 to 28.3)	<0.001	<0.001	0.85	0.008
	Quitter (n=137)	8.8	(4.0 to 13.5)				4.4	(1.0 to 7.8)				0.15
	Never Smoker (n=866)	2.7	(1.6 to 3.7)				4.0	(2.7 to 5.4)				0.06

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Table E5

Classification of population sample included in multilevel modelling of FEV_1 decline across three time-points (age 43, 53 and 60-64 years) according to concurrent symptom presence (See Table 1) as follows: (a) Symptomatic vs asymptomatic at age 43 years; (b) Symptomatic at least once vs never-symptomatic across ages 43, 53 and 60-64 years; (c) Symptom duration across ages 43, 53 and 60-64 years (scored between zero and three according to frequency of respective symptom reporting across the three time-points). CS=Chronic Sputum; CC=Chronic Cough; CC&CS=Chronic Cough with concurrent Chronic Sputum.

		Symptom group		
		CS	**CC**	**CC&CS**
Symptom/Asymptomatic at age 43 years		102/1858	144/1816	75/1885
Symptomatic ≥ once / Never-symptomatic between 43 & 60-64 years		263/1697	352/1608	187/1773
Symptom duration (No. of occasions symptoms reported between ages 43 and 60-64 years) (0 - 3 occasions)	**0**	1697	1608	1773
	1	171	237	128
	2	61	69	37
	3	31	46	22

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Table E6

The influence of longitudinal symptom pattern on multilevel models estimating the relationship between symptom presence and concurrent FEV_1 decline between ages 43 and 60-64 years. Multilevel modelling included 1960 men and woman. Mean FEV_1 at age 43 years was 3.00 litres, with an unadjusted FEV_1 decline of 24.2 ml/year. Minimally adjusted coefficients are adjusted for sex. Fully adjusted coefficients are adjusted for sex, height at age 43 years, weight at age 43 years and smoking status. Presence of symptoms (CS=Chronic Sputum; CC=Chronic Cough; and CC&CS=Chronic Cough with concurrent Chronic Sputum) is represented as follows: (A) Symptomatic vs asymptomatic at age 43 years; (B) Symptomatic at least once vs never-symptomatic across ages 43, 53 and 60-64 years; (C) Symptom duration represented by the number of occasions that symptom was reported over the three time-points (between zero and three occasions). See Table E5.

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(A) Model including phenotyping based upon sympton reporting at age 43 years (n=1960)

			FEV_1 intercept (ml) at age 43 years		FEV_1 linear change per year (ml/year) between ages 43 and 60-64 years	
			Coefficient (95% CI)	p value	Coefficient (95% CI)	p value
Symptom reported at age 43 years	CS	Minimally adjusted†	-344.7 (-449.0 to -240.5)	<0.001	-2.6 (-7.8 to 2.6)	0.32
		Fully adjusted‡	-336.6 (-434.3 to -238.9)	<0.001	-2.2 (-7.4 to 3.0)	0.41
	CC	Minimally adjusted†	-304.2 (-391.9 to -216.5)	<0.001	-5.3 (-9.6 to -1.1)	0.01
		Fully adjusted‡	-288.7 (-371.6 to -205.9)	<0.001	-4.3 (-8.6 to 0.0)	0.05
	CC&CS	Minimally adjusted†	-389.1 (-510.0 to -268.1)	<0.001	-3.7 (-9.7 to 2.4)	0.23
		Fully adjusted‡	-390.1 (-503.0 to -277.3)	<0.001	-3.3 (-9.4 to 2.7)	0.28

(B) Model including phenotyping based upon symptom reporting between 43 and 60-64 years (n=1960)

			FEV_1 intercept (ml) at age 43 years		FEV_1 linear change per year (ml/year) between ages 43 and 60-64 years	
			Coefficient (95% CI)	p value	Coefficient (95% CI)	p value
Symptom reported ≥ once between 43 & 60-64 years	CS	Minimally adjusted†	-205.3 (-273.3 to -137.2)	<0.001	-5.0 (-8.3 to -1.7)	0.00
		Fully adjusted‡	-206.1 (-270.0 to -142.2)	<0.001	-4.1 (-7.4 to -0.7)	0.02
	CC	Minimally adjusted†	-187.7 (-248.0 to -127.4)	<0.001	-4.9 (-7.8 to -2.0)	0.00
		Fully adjusted‡	-173.8 (-231.0 to -116.7)	<0.001	-4.0 (-7.0 to -1.0)	0.01
	CC&CS	Minimally adjusted†	-231.3 (-310.3 to -152.3)	<0.001	-5.5 (-9.3 to -1.6)	0.01
		Fully adjusted‡	-235.9 (-310.0 to -161.9)	<0.001	-4.5 (-8.4 to -0.7)	0.02

(C) Model including duration score based upon symptom reporting between ages 43 and 60-64 years (n=1960)

			FEV_1 intercept (ml) at age 43 years		FEV_1 linear change per year (ml/year) between ages 43 and 60-64 years	
			Coefficient (95% CI)	p value	Coefficient (95% CI)	p value
Per occasion symptom reported between ages 43 and 60-64 years (0 - 3 occasions)	CS	Minimally adjusted†	-145.9 (-187.5 to -104.3)	<0.001	-3.7 (-5.7 to -1.6)	0.00
		Fully adjusted‡	-149.0 (-188.1 to -109.9)	<0.001	-3.2 (-5.3 to -1.1)	0.00
	CC	Minimally adjusted†	-133.6 (-169.9 to -97.3)	<0.001	-3.8 (-5.6 to -2.0)	<0.001
		Fully adjusted‡	-128.5 (-163.0 to -94.0)	<0.001	-3.1 (-4.9 to -1.2)	0.00
	CC&CS	Minimally adjusted†	-156.6 (-205.9 to -107.4)	<0.001	-4.3 (-6.8 to -1.8)	0.00
		Fully adjusted‡	-162.3 (-208.5 to -116.1)	<0.001	-3.6 (-6.1 to -1.1)	0.01

† Adjusted for sex and age

‡ Adjusted for sex, age, height at age 43 years, weight at age 43 years and smoking status at ages 43, 53 and 60-64 years

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Table E7

Participation of cohort members in surveys at age 43 and 60-64 years according to prior reporting of chronic symptoms at ages 20, 25, 36, 43 and 53 years of age. (A) Chronic Sputum expectoration reporting; (B) Chronic Cough reporting; (C) Chronic Cough concurrent with Chronic Sputum expectoration reporting. P values calculated using Chi-Square test.

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(A) Participation in 1989 and 2009 according to Chronic Sputum reporting at ages 20, 25 and 36 years

		Number of Cohort Members	Participation at age 43 years		Participation at age 60-64 years	
			%	Chi-square test	%	Chi-square test
CS at age 20 years	No	3436	71.7	0.85	53.8	0.62
	Yes	183	71.0		55.7	
CS at age 25 years	No	2763	78.2	0.37	58.0	0.97
	Yes	140	75.0		57.9	
CS at age 36 years	No	3066	89.2	0.20	65.0	<0.001
	Yes	164	86.0		50.6	
CS at age 43 years	No	2985	100.0	n/a	68.9	<0.001
	Yes	231	100.0		49.4	
CS at age 53 years	No	2763	n/a	n/a	73.8	<0.001
	Yes	218			61.0	

(B) Participation in 1989 and 2009 according to Chronic Cough reporting at ages 20, 25 and 36 years

		Number of Cohort Members	Participation at age 43 years		Participation at age 60-64 years	
			%	Chi-square test	%	Chi-square test
CC at age 20 years	No	3438	71.8	0.53	54.2	0.14
	Yes	181	69.6		48.6	
CC at age 25 years	No	2702	78.3	0.22	58.2	0.41
	Yes	201	74.6		55.2	
CC At age 36 years	No	2991	89.2	0.22	65.4	<0.001
	Yes	239	86.6		49.4	
CC At age 43 years	No	2920	100.0	n/a	68.8	<0.001
	Yes	296	100.0		54.7	
CC At age 53 years	No	2658	n/a	n/a	74.3	<0.001
	Yes	323			60.7	

(C) Participation in 1989 and 2009 according to Chronic Cough with concurrent Chronic Sputum reporting at ages 20, 25 and 36 years

		Number of Cohort Members	Participation at age 43 years		Participation at age 60-64 years	
			%	Chi-square test	%	Chi-square test
CC&CS at age 20 years	No	3520	71.6	0.99	54.0	0.62
	Yes	99	71.7		51.5	
CC&CS at age 25 years	No	2817	78.1	0.77	58.0	0.84
	Yes	86	76.7		57.0	
CC&CS At age 36 years	No	3113	89.1	0.34	64.9	<0.001
	Yes	117	86.3		47.9	
CC&CS At age 43 years	No	3050	100.0	n/a	68.4	<0.001
	Yes	166	100.0		51.2	
CC&CS At age 53 years	No	2824	n/a	n/a	73.5	<0.001
	Yes	157			59.9	

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Table E8

The cumulative prevalence of Chronic Cough and/or Chronic Sputum Expectoration (CC/CC), Chronic Sputum Expectoration (CS), Chronic Cough (CC) and Chronic Productive Cough (CS&CC) by age 60-64 years according to the presence of airflow limitation (FEV1/FVC<Lower limit of normal) at age 60-64 years amongst the 1137 individuals included in Figure 5. Cumulative prevalence of each symptom complex was higher amongst those with airflow limitation at age 60-64 years (p<0.001; Chi Square tests).

		Presence of airflow limitation at age 60-64 years		Overall
		Absent (n=1068)	Present (n=69)	(n=1137)
Cumulative symptom prevalence by age 60-64 years % (95% CI)	CC/CS	27.3 (24.7 to 30)	56.5* (44.8 to 68.2)	29.1 (26.5 to 31.8)
	CS	16.5 (14.3 to 18.7)	34.8* (23.5 to 46)	17.6 (15.4 to 19.8)
	CC	22.7 (20.1 to 25.2)	50.7* (38.9 to 62.5)	24.4 (21.9 to 26.9)
	CC&CS	11 (9.2 to 12.9)	26.1* (15.7 to 36.4)	12 (10.1 to 13.8)

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