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Chronic cough and sputum production are associated with worse clinical outcomes in stable asthma

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Summary

Background: Chronic cough and sputum production (chronic mucus hypersecretion) is a poorly described clinical feature of asthma. Our objective was to identify clinical, immunological and computed tomography (CT) measures of airway wall dimensions associated with these symptoms in smokers and never smokers with asthma.

Methods: Cross-sectional data was analysed from 120 smokers and never smokers with asthma. Participants with and without a history of chronic mucus hypersecretion were compared for clinical outcomes, sputum differential cell counts and CT measures of airway dimensions (wall thickness, luminal area and percent wall area).

Results: Chronic mucus hypersecretion occurred in a higher proportion of smokers with asthma (56%) than never smokers with asthma (20%), ($p < 0.001$) and the proportion of patients with these symptoms increased with asthma severity ($p = 0.003$). Smokers with asthma and chronic mucus hypersecretion had worse current clinical control than smokers without those symptoms [ACQ score 2.3 versus 1.6, $p = 0.002$]. A greater proportion of never smokers with chronic mucus hypersecretion required short courses of oral corticosteroids in the last year (58% versus 19%, $p = 0.011$). Sputum neutrophil and eosinophil counts were similar in asthma patients with or without chronic mucus hypersecretion. Of those with severe asthma and chronic mucus

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hypersecretion, a CT measure of airway lumen area was reduced in smokers compared to never smokers (11.4 mm^2 versus 18.4 mm^2 ; $p = 0.017$).

Conclusions: Chronic mucus hypersecretion occurs frequently in adults with stable asthma, particularly in smokers with severe disease and is associated with worse current clinical control in smokers and more exacerbations in never smokers.

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Introduction

Chronic cough and sputum production due to airway mucus hypersecretion is an important component of several airway diseases including chronic obstructive pulmonary disease (COPD) and asthma. Cigarette smoking is one of the strongest risk factors for chronic bronchitis, also termed chronic mucus hypersecretion, in individuals with and without airflow limitation [1]. Chronic mucus hypersecretion develops in asthma [2–5], at least in part, due to the pro-inflammatory effects on airway epithelial glands of the T-helper type 2 (Th2) cytokines interleukin (IL)-9 and IL-13, as well as IL-1 β and tumour necrosis factor (TNF)- α [6].

The prevalence rates for chronic bronchitis vary between studies, due to differences in the definitions used and in the populations studied, but overall a consistent picture emerges of higher rates in airway disease and with cigarette smoking [5,7]. A systematic review of 38 studies reported a prevalence rate for chronic bronchitis of 6.4% in the general population [8] and with increased rates in smokers without airflow obstruction [2,9]. Higher rates are found in patients with COPD compared to smokers without COPD, with prevalence rates ranging from 27% [10] to over 70% [11–13]. There is more limited information on the prevalence rates for chronic cough and sputum production in asthma [2–5,14]. The Copenhagen City Heart Study and the European Community Respiratory Health (ECRH) survey reported prevalence rates of 39% and 42% respectively in non-smokers with asthma and with higher rates in smokers with asthma [2,14].

Chronic bronchitis in COPD has been associated with worse clinical outcomes [7,10] and increased mortality [9]. Less is known about the clinical features of patients with asthma who give a history of chronic mucus hypersecretion compared to those without these symptoms. Chronic mucus hypersecretion is associated with a significantly greater decline in FEV₁ among smokers with asthma [2], with more severe disease [3] and with chronic persistent airflow obstruction in non-smokers with asthma [4]. The presence of excessive airway mucus in asthma may also contribute to exacerbations and fatal attacks of asthma [15].

Taken together, these findings indicate that whilst chronic mucus hypersecretion is known to occur in asthma and that it may play a role in disease outcomes, the relationships between chronic mucus hypersecretion in smokers and never smokers with asthma with clinical, lung function, immunological outcomes and computed tomography (CT) airway dimensions are unknown. We wished to test the hypothesis that clinical outcomes are worse and/or that inflammatory biomarkers and CT measures of airway dimensions differ, in patients with asthma who give a

history of chronic mucus hypersecretion and that these outcomes are also influenced by smoking status and disease severity. We undertook an analysis of 120 subjects with asthma (smokers and never smokers) of differing severity to test this hypothesis, by examining outcomes in those with symptoms of chronic cough and sputum production compared to those without these symptoms.

Methods

Subjects and study design

A cross sectional study was performed in subjects with asthma recruited to the Glasgow COPD and Asthma Biomarker study [16]. Clinical, physiological, induced sputum cell counts and CT measurements were performed. Participants were recruited with mild, moderate and severe persistent asthma (GINA classification) [17], (both current smokers and never-smokers):

Age range 18–75 years and duration of asthma ≥ 6 months; Symptoms of episodic wheezing, chest tightness and/or dyspnoea; Objective confirmation by airway hyperactivity determined by a positive methacholine challenge or where this was not safe (when FEV₁ < 60% predicted), by evidence of airflow variability with a $\geq 12\%$ and 200 ml increase in FEV₁ following nebulised salbutamol 2.5 mg. The West Glasgow Research Ethics Committee approved the study and all patients gave written informed consent.

Patients had 3 study visits. At the first visit, the medical history was obtained and a methacholine challenge performed. At the second visit, one week later, spirometry and reversibility plus sputum induction were performed and asthma questionnaires completed. The third visit, a month later, was to assess reproducibility of sputum measurements. The CT scan and static lung volumes/diffusion capacity measurements were performed on visit 2 or 3. The participants were recruited over an 18 month period.

Measurements

Questionnaires

A history of chronic mucus hypersecretion was based on the question:

'Do you have a history of persistent sputum > 3 months per year'. Asthma control questionnaire (ACQ) score [18] was also obtained. Information was obtained from participants on the number of hospital admissions, accident and emergency visits and emergency oral corticosteroid use in the last year.

Lung function tests

Spirometry was performed according to ATS guidelines [19] and airway hyper-responsiveness to methacholine was measured [20]. Lung volumes and diffusing capacity for carbon monoxide (DLco) were performed using the body box technique (Zan500 Body Plethysmography, nSpire Health Limited, Hertford, UK).

Sputum induction

Performed using hypertonic saline and processed as previously described [16]. Samples with cell viability <40% or epithelial squamous cells >80% were discarded.

CT scan of the chest

Scans were performed at full inspiration using 16 slice Brightspeed and 64 slice Lightspeed (GE CT scanner, Milwaukee, Wisconsin, USA) with the following parameters: 120 KV, 100 mAs, collimation 1 mm, reconstruction slice thickness 0.65 mm, reconstruction slice separation 0.5 mm, pitch of 1 and the data was reconstructed with a CHST filter. All scans were evaluated centrally at the University of Edinburgh. Airway dimensions were measured using software previously described [21], which plots an airway path from which airway profiles were generated on cross-sections orthogonal to this airway path. Airway dimensions were measured at 1 mm intervals in the right lower lobe posterior basal segmental bronchus (designated RB10) from airway generation 3–6 using the full width at half maximum (FWHM) technique. The airway lumen diameter and airway wall thickness were measured and the percentage wall area (% WA) was calculated as (outer area of airway – lumen area)/outer area of airway × 100.

Statistical analysis

The study population was divided into those with and without a history of chronic mucus hypersecretion. Data were analysed using R version 2.15 [22]. Continuous variables were summarized as median (inter-quartile range). Their comparison between different patient groups was by *t*-test or one-way analysis of variance for approximately

normally distributed variables and by Wilcoxon tests or Kruskal–Wallis tests for other variables. Categorical variables were summarized by their observed frequencies and percentages within the participant subsets, and were compared using Fisher's exact probability tests including the Freeman-Halton extension for variables with more than 2 categories.

Results

Patient characteristics

Smokers with asthma and never smokers with asthma were similar for age, duration of asthma and dose of inhaled corticosteroid (Table 1). Additional therapies such as long-acting beta₂-agonists, leukotriene receptor antagonists or oral prednisolone were similar between severity groups. Smokers with asthma had a slightly lower median FEV₁/FVC ratio (median FEV₁/FVC ratio 72% versus 78%, *p* = 0.029) and lower diffusing capacity (77% versus 86%, *p* < 0.001) than never smokers with asthma.

Prevalence of chronic cough and sputum production

Chronic mucus hypersecretion was reported by a higher proportion of smokers with asthma (56%) compared with the never smokers with asthma (20%), (*p* < 0.001). The proportion of patients with chronic mucus hypersecretion increased with asthma severity (*p* = 0.003); in both smokers (*p* = 0.012) and never smokers (*p* = 0.045) [Fig. 1].

Clinical characteristics of participants according to the presence of chronic mucus hypersecretion

Smokers with asthma and chronic mucus hypersecretion had higher ACQ scores (2.29 versus 1.57, *p* = 0.002), but were similar to smokers with asthma without this symptom for other clinical characteristics (Table 2, Fig. 2). A greater

Table 1 Demographics and clinical baseline characteristics.

	Asthma		<i>p</i> -Value
	Never smoker	Smoker	
Number	59	61	
Age (years)	48.2 (39.8, 53.9)	47.5 (42.0, 52.8)	<i>p</i> = 0.941
Sex (male)	23 (39.0%)	29 (47.5%)	<i>p</i> = 0.363
Disease duration (years)	21.0 (9.5, 38.0)	20.0 (10.0, 32.0)	<i>p</i> = 0.486
FEV ₁ % predicted pre-bronchodilator	79.0 (70.0, 91.0)	78.0 (58.0, 93.2)	<i>p</i> = 0.599
FEV ₁ % predicted post-bronchodilator	91.0 (79.0, 98.0)	84.0 (70.5, 102.0)	<i>p</i> = 0.429
FEV ₁ /FVC post-bronchodilator	78.0 (69.0, 83.0)	72.5 (66.8, 79.2)	<i>p</i> = 0.029
Pack years smoked	—	33.0 (22.0, 52.0)	—
DLCO% predicted COHb	86 (80, 93)	77 (66, 86)	<i>p</i> = 0.001
Beclometasone equivalent dose of inhaled steroid	800 (400, 1000)	800 (700, 1000)	<i>p</i> = 0.384

Data depicted as Median (IQR) unless otherwise specified. Boldface *p* values indicate *p* < 0.05.

Abbreviations: FEV₁ = forced expired volume in one second, FVC = forced vital capacity, DLco% predicted = Diffusing capacity for carbon monoxide, corrected for haemoglobin and carboxyhaemoglobin (COHb) as a percentage of the predicted value.

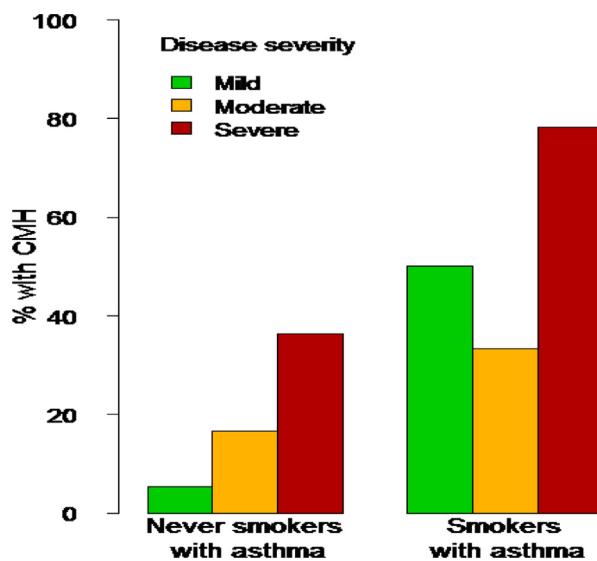


Figure 1 Proportion of patients with asthma of different disease severity and smoking status with a history of chronic mucus hypersecretion (CMH). The proportion of patients with cough and sputum production increased with asthma severity ($p = 0.003$); in both smokers ($p = 0.012$) and never smokers ($p = 0.045$).

proportion of never smokers with asthma and chronic mucus hypersecretion required emergency short courses of oral corticosteroids in the last year (58.3% versus 19.1%, $p = 0.011$), but were similar to never smokers with asthma without this symptom for all other clinical characteristics (Table 2, Fig. 3). Smokers with severe asthma with chronic mucus hypersecretion compared to never smokers with severe asthma with these symptoms had higher ACQ scores (2.9 versus 1.9, $p < 0.044$), but did not differ significantly in age, duration of disease, pre-and post-bronchodilator FEV₁, and inhaled corticosteroid dose (Table 4).

Sputum cell counts of participants according to the presence of cough and sputum production

The percentage of induced sputum neutrophil and eosinophils were similar in patients with chronic mucus hypersecretion to those without these symptoms in smokers with asthma and never smokers with asthma (Table 3). Smokers with asthma with chronic mucus hypersecretion compared to never smokers with similar symptoms did not differ in the percentage of induced sputum neutrophil or eosinophil cell counts; similar results were found in subjects with severe disease (Table 4).

Table 2 Clinical and lung function and imaging outcomes in never-smokers and smokers with asthma according to the presence of chronic cough and sputum production.

	Never smokers with asthma		<i>p</i> -Value	Smokers with asthma		<i>p</i> -Value
	CMH+ (n = 12)	CMH- (n = 47)		CMH+ (n = 34)	CMH- (n = 27)	
Age (years)	47.7 (42.1, 56.1)	48.2 (37.5, 53.5)	<i>p</i> = 0.651	48.4 (42.1, 53.2)	45.6 (41.5, 51.5)	<i>p</i> = 0.796
Gender (male)	4 (33.3%)	19 (40.4%)	<i>p</i> = 0.749	17 (50.0%)	12 (44.4%)	<i>p</i> = 0.797
Disease duration (years)	22.0 (15.0, 27.0)	21.0 (9.0, 42.0)	<i>p</i> = 0.325	15.5 (10.0, 36.0)	20.0 (11.0, 31.0)	<i>p</i> = 0.873
ACQ score	1.71 (1.00, 2.58)	1.00 (0.57, 1.68)	<i>p</i> = 0.115	2.29 (1.57, 3.00)	1.57 (1.21, 1.97)	<i>p</i> = 0.002
BMI kg/m ²	30.4 (25.5, 36.4)	28.3 (25.3, 32.5)	<i>p</i> = 0.481	26.0 (23.4, 30.2)	25.7 (22.2, 29.5)	<i>p</i> = 0.528
FEV ₁ % predicted pre bronchodilator	79.0 (62.0, 85.5)	81.0 (71.2, 91.8)	<i>p</i> = 0.310	78.0 (58.0, 93.0)	77.0 (65.0, 93.5)	<i>p</i> = 0.692
FEV ₁ % predicted post bronchodilator	91.0 (78.5, 97.0)	90.0 (79.2, 98.0)	<i>p</i> = 0.629	85.0 (69.0, 99.0)	83.0 (71.0, 102.0)	<i>p</i> = 0.953
Pack years smoked	—	—	—	31.0 (23.0, 58.0)	34.0 (19.0, 50.5)	<i>p</i> = 0.805
DL _{CO} % predicted COHb	84.0 (73.5, 91.5)	86.0 (81.0, 93.0)	<i>p</i> = 0.214	76.5 (61.0, 86.0)	77.0 (69.0, 84.0)	<i>p</i> = 0.608
Beclometasone equivalent dose of inhaled corticosteroids (μg)	1000 (600, 1600)	800 (400, 800)	<i>p</i> = 0.112	800 (800, 1000)	800 (400, 1000)	<i>p</i> = 0.188
Hospitalisation or A&E visits for asthma in the past year	2 (16.7%)	2 (4.3%)	<i>p</i> = 0.181	3 (8.8%)	0 (0.0%)	<i>p</i> = 0.248
Emergency oral steroid use in last 1 year	7 (58.3%)	9 (19.1%)	<i>p</i> = 0.011	10 (29.4%)	4 (14.8%)	<i>p</i> = 0.228
History suggestive of rhino-sinusitis	6 (50.0%)	15 (31.9%)	<i>p</i> = 0.315	10 (29.4%)	5 (18.5%)	<i>p</i> = 0.382
History suggestive of allergic rhinitis	8 (66.7%)	25 (53.2%)	<i>p</i> = 0.521	18 (52.9%)	13 (48.1%)	<i>p</i> = 0.799

Data depicted as median (IQR) or for bottom four rows as number (percent). Boldface *p* values indicate *p* < 0.05.

* *p*-Value for comparison between never smokers with asthma and CMH and smokers with asthma and CMH. Abbreviations: CMH = chronic mucus hypersecretion (chronic cough and sputum production); ACQ = asthma control questionnaire score; BMI = body mass index; FEV₁ = forced expired volume in one second, DL_{CO} % pred = Diffusing capacity for the lungs measured using carbon monoxide, corrected for haemoglobin and carboxyhaemoglobin; A&E = accident and emergency.

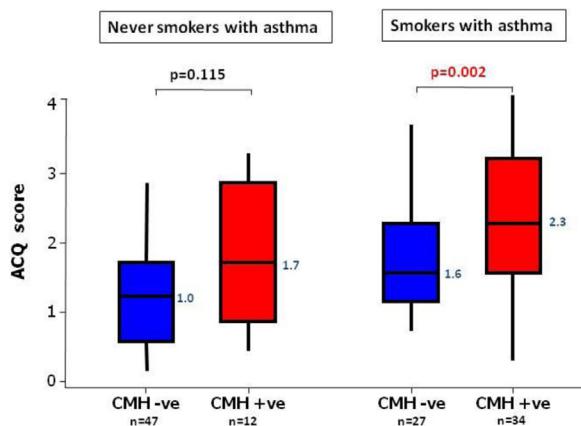


Figure 2 Asthma control questionnaire (ACQ) score in never-smokers with asthma and smokers with asthma according to the presence of chronic mucus hypersecretion. Smokers with asthma and chronic mucus hypersecretion had higher ACQ scores (2.3 versus 1.6, $p = 0.002$). Abbreviations: CMH, chronic mucus hypersecretion; –ve, CMH absent; +ve, CMH present.

CT imaging measures in participants according to the presence of cough and sputum production

CT measures of airway dimensions (RB10 wall thickness; RB10 lumen area; RB10% wall area) were similar between patient groups with and without chronic mucus hypersecretion (Table 2). RB10 lumen area was reduced in smokers with severe asthma with chronic mucus hypersecretion compared to never smokers with severe asthma (11.4 mm^2 (8.9, 13.0) versus 18.4 mm^2 (13.7, 23.0), $p = 0.017$) with chronic mucus hypersecretion (Table 4).

Discussion

In the study we determined whether clinical outcomes are worse and/or that sputum cell counts or CT measures of

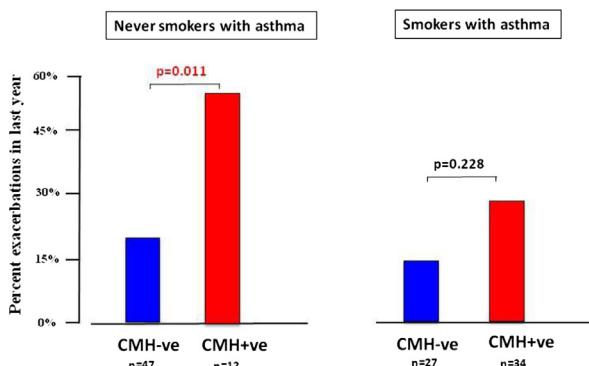


Figure 3 Emergency short courses of oral corticosteroids in the last year in never-smokers with asthma and smokers with asthma according to the presence of chronic mucus hypersecretion. A greater proportion of never smokers with asthma and chronic mucus hypersecretion required emergency short courses of oral corticosteroids in the last year (58.3% versus 19.1%, $p = 0.011$). Abbreviations: CMH, chronic mucus hypersecretion; –ve, CMH absent; +ve, CMH present.

airway dimensions differ, in patients with asthma who give a history of chronic cough and sputum production compared to those without these symptoms. The main findings were that chronic mucus hypersecretion is a common symptom in adults with stable asthma, particularly in smokers and in patients with severe disease. Chronic mucus hypersecretion was associated with worse current clinical control in smokers with asthma and a greater number of short courses of oral steroids in never smokers with asthma. Sputum cell counts did not differ significantly in the asthmatic participants in relation to symptoms of chronic mucus hypersecretion. CT lumen was reduced in smokers with severe asthma with chronic mucus hypersecretion compared to never smokers with severe asthma.

The definition of chronic mucus hypersecretion in some surveys required the presence of daily productive cough for at least three consecutive months for more than two successive years, whereas in others the presence of chronic cough and phlegm production for more than 1 year was sufficient [23]. In our study the diagnosis of chronic mucus hypersecretion omitted reference to '2 or more years' and might have overestimated the prevalence of chronic cough and sputum production. In support of our findings, when comparisons are made between groups, the same question was used in all participants. In the Copenhagen City Heart Study, 39% of the non-smokers with asthma (mean age of 52 years) gave a history of chronic mucus hypersecretion [2], a prevalence rate similar to the never smokers with severe asthma in our study (36.4%), but a much higher proportion than reported in patients with mild or moderate disease (5.3% and 16.7% respectively). We found higher rates of chronic mucus hypersecretion in smokers with asthma in all categories of disease severity compared to never smokers with asthma, but particularly in the severe group (78.3%). Overall these results indicate that chronic mucus hypersecretion is a common clinical symptom in chronic persistent asthma, particularly in smokers.

Smokers with asthma with chronic mucus hypersecretion had higher ACQ scores than smokers without these symptoms. The ACQ-6 score comprises 6 questions on different aspects of asthma control and although no specific question enquires about cough and sputum production, these symptoms impacted on the overall score. Smokers with asthma are known to have worse ACQ scores than never smokers with asthma [24] and possibly a history of chronic mucus hypersecretion adversely effects the perception of symptoms in this sub-group of smokers, particularly in those with severe disease. A similar effect on ACQ scores was not seen in the never smokers with asthma including patients with severe asthma. A greater proportion of never smokers with chronic mucus hypersecretion required emergency short courses of oral corticosteroids in the last year suggesting that these symptoms are associated with increased rates of exacerbation of asthma. In the general population, smokers that develop chronic bronchitis are at increased risk of developing COPD and increased mortality [9]. In asthma, chronic mucus hypersecretion is associated with a significantly greater decline in FEV₁ among smokers [2] and with chronic persistent airflow obstruction in non-smokers [4].

Airway mucin (MUC) is primarily produced by airway goblet cells and in asthma MUC5AC is the predominant

Table 3 Induced sputum cell counts and computed tomography (CT) measures in never smokers and smokers with asthma according to the presence of chronic cough and sputum production.

	Never smokers with asthma			Smokers with asthma		
	CMH+ (n = 12)	CMH- (n = 47)	p-Value	CMH+ (n = 34)	CMH- (n = 27)	p-Value
Sputum cell counts						
Total cell count ($10^4/\text{mL}$)	610 (541, 822)	662 (508, 866)	<i>p</i> = 0.745	583 (533, 740)	574 (473, 727)	<i>p</i> = 0.576
Neutrophils (%)	41.2 (24.5, 73.5)	49.8 (28.0, 63.6)	<i>p</i> = 0.920	50.0 (29.5, 69.5)	65.0 (43.2, 72.0)	<i>p</i> = 0.132
Eosinophils (%)	1.00 (0.25, 1.50)	0.75 (0.00, 2.25)	<i>p</i> = 0.619	0.50 (0.00, 1.50)	0.50 (0.25, 2.50)	<i>p</i> = 0.517
Macrophages (%)	24.0 (19.6, 50.8)	33.8 (16.6, 52.9)	<i>p</i> = 0.724	24.5 (18.0, 42.5)	23.0 (13.5, 37.0)	<i>p</i> = 0.672
CT imaging						
RB10 wall thickness (mm)	1.61 (1.50, 1.73)	1.50 (1.43, 1.77)	<i>p</i> = 0.372	1.66 (1.60, 1.78)	1.65 (1.54, 1.80)	<i>p</i> = 0.390
RB10 lumen area mm^2	19.4 (13.7, 22.7)	18.2 (12.4, 21.7)	<i>p</i> = 0.737	13.0 (9.3, 17.9)	15.5 (11.2, 18.9)	<i>p</i> = 0.692
RB10% wall area	64.9 (60.8, 67.4)	63.9 (60.0, 68.7)	<i>p</i> = 0.989	69.8 (62.3, 76.0)	68.6 (62.9, 73.2)	<i>p</i> = 0.442

Data depicted as median (IQR). Boldface *p* values indicate *p* < 0.05. Abbreviations: CMH = chronic mucus hypersecretion (chronic cough and sputum production); CT = Computed tomography; mm = millimetres; RB10 = right bronchial division 10.

mucin gene increased in the epithelium [25]. The effects of corticosteroids in suppressing MUC5AC gene expression in human bronchial epithelial cells is histone-deacetylase-2 (HDAC2) dependent [26] and as reduced HDAC2 activity is implicated in causing corticosteroid insensitivity in smokers with asthma and in severe asthma [27], it is possible that this mechanism accounts for the high prevalence of chronic mucus hypersecretion in these groups of patients. Smokers with asthma have more goblet cells and mucus-positive epithelium than either ex-smokers or never-smokers with asthma [28], likely due to the effects of tobacco smoke as well as increased release of elastase from subepithelial neutrophils [29], although in the present study the

proportion of induced sputum neutrophils or eosinophils was similar in smokers or never smokers with asthma irrespective of the presence or absence of a history of chronic cough and sputum production.

Here we found that CT measures of airway dimensions (RB10 wall thickness; RB10 lumen area; RB10% wall area) were similar between patients with or without a history of chronic mucus hypersecretion in smokers and never smokers with asthma. However airway lumen area was reduced in smokers with severe asthma who gave a history of chronic cough and sputum production compared to never smokers with severe asthma with similar symptoms. The difference in airway wall area was unlikely to be as a result

Table 4 Comparison of clinical, lung function, sputum cell counts and CT measures outcome in never smokers and smokers with severe asthma with a history of chronic cough and sputum production.

	Never smoker with severe asthma and CMH+	Smoker with severe asthma and CMH+	<i>p</i> Value
Number	8	18	
Age (years)	44.9 (42.1, 52.3)	51.2 (43.2, 54.8)	<i>p</i> = 0.493
Gender (male)	4 (50.0%)	7 (38.9%)	<i>p</i> = 0.683
Disease duration (years)	22.0 (15.0, 30.8)	23.5 (14.2, 36.0)	<i>p</i> = 0.912
ACQ score	1.9 (1.6, 2.6)	2.9 (2.3, 3.6)	<i>p</i> = 0.044
BMI kg/m^2	26.1 (24.8, 38.8)	27.9 (23.9, 31.5)	<i>p</i> = 0.569
FEV ₁ % predicted post bronchodilator	82.0 (61.5, 87.0)	76.0 (69.0, 97.0)	<i>p</i> = 0.554
Pack years smoked	—	34.0 (23.8, 60.0)	
DLCO% COHb	84.0 (75.0, 91.5)	67.0 (56.0, 84.0)	<i>p</i> = 0.077
Beclometasone equivalent dose of inhaled corticosteroids (μg)	1200 (800, 2250)	1000 (800, 1900)	<i>p</i> = 0.591
Sputum cell counts			
Neutrophils (%)	49.5 (19.2, 78.6)	48.5 (35.0, 66.2)	<i>p</i> = 0.931
Eosinophils (%)	1.50 (1.12, 3.75)	1.00 (0.50, 2.50)	<i>p</i> = 0.367
CT imaging			
RB10 wall thickness (mm)	1.60 (1.50, 1.73)	1.68 (1.64, 1.85)	<i>p</i> = 0.380
RB10 lumen area mm^2	18.4 (13.7, 23.0)	11.4 (8.9, 13.0)	<i>p</i> = 0.017
RB10% wall area	64.0 (60.8, 66.9)	74.3 (69.3, 76.5)	<i>p</i> = 0.106

Data depicted as median (IQR). Boldface *p* values indicate *p* < 0.05.

Abbreviations: CMH = chronic mucus hypersecretion (chronic cough and sputum production); FEV₁ = forced expired volume in one second, DLCO% pred = Diffusing capacity for the lungs measured using carbon monoxide, corrected for haemoglobin and carboxyhaemoglobin; CT = Computed tomography; mm = millimetres; RB10 = right bronchial division 10.

of variations in bronchodilator use (unpublished data). Lumen area can be influenced by mucus accumulation and this may occur to a greater extent in smokers with severe asthma.

There are several potential limitations to our findings. The cross-sectional study design used did not allow us to determine whether the prevalence of chronic mucus hypersecretion and the association between these symptoms and clinical outcomes and CT measures in the asthma groups varies over time. Potential inaccuracy of CT measurements of airway measurements might exist as no standardised methodology exists, however we used techniques where reproducibility has been previously validated [21]. Finally the main findings require to be confirmed in large prospective studies of patients with asthma.

In conclusion, chronic cough and sputum production are common symptoms in adults with chronic stable asthma, particularly in smokers and patients with severe disease. Chronic mucus hypersecretion is likely to contribute to poor current symptom control in smokers with asthma and to increased exacerbations rates in never smokers with asthma.

Conflict of interest statement

The authors have no competing interests related to the manuscript.

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