



# Asthma and smoking-induced airway disease without spirometric COPD

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**Cigarette smokers without COPD develop chronic respiratory symptoms due to asthma and smoking-induced airway disease** <http://ow.ly/rTaS308SLLl>

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**ABSTRACT** Due to the high prevalence rates of cigarette smoking and asthma, current and ex-smokers frequently develop chronic airway disease without spirometric evidence of chronic obstructive pulmonary disease (COPD), either alone or associated with asthma. This review considers the classification, clinical outcomes, inflammatory and imaging variables, phenotypes, and management of current and ex-smokers with airway disease without COPD, focusing on overlaps in those with and without asthma. These individuals have more respiratory symptoms, worse quality of life, increased exacerbation rates, reduced lung function and more comorbidities than never-smokers with asthma or healthy never-smokers. As well as clinical features, airway inflammatory and structural changes in smoking-induced airway disease without COPD overlap with those found in smokers with asthma. Cigarette smoking is associated with worse clinical outcomes in some phenotypes of asthma. Management involves public health measures to control exposure to tobacco smoke, personal advice on smoking cessation and the use of appropriate targeted therapies, although evidence is limited on their effectiveness. Understanding the mechanisms, natural history and management of current and ex-smokers with asthma and smoking-induced airway disease without COPD is a priority for future research.

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## Introduction

Asthma–chronic obstructive pulmonary disease (COPD) overlap syndrome (ACOS) is a term recently introduced to describe people with features of both asthma and COPD [1, 2]. The definition is imprecise [3], since it is based on assessing the probability that clinical characteristics of both asthma and COPD are present in a patient with chronic airflow obstruction, defined as a forced expiratory volume in 1 s (FEV<sub>1</sub>)/forced vital capacity (FVC) ratio <0.7. The overlap syndrome is associated with worse clinical outcomes compared with COPD alone, including more severe symptoms, worse quality of life, more frequent exacerbations, greater decline in lung function, increased mortality and higher healthcare costs [1, 2, 4, 5]. Estimates of the prevalence of ACOS range from 15% to ~50% of patients with chronic airflow obstruction. ACOS is an umbrella term that describes a collection of phenotypes and endotypes of chronic airway disease, including subgroups with type 2 inflammation and eosinophilia [6]. Cigarette smoking is an important risk factor associated with the development of COPD and ACOS [7, 8]. Smoking-induced airway disease in people who do not have spirometric evidence of COPD is also recognised, either alone or in association with asthma. These subgroups of chronic airway disease with normal lung function are likely to occur commonly, due to the high prevalence rates for cigarette smoking and asthma in most populations. Worldwide, over 1 billion people are estimated to use tobacco products, mainly through smoking cigarettes, and over 300 million people have asthma. In many countries the proportion of cigarette smokers among people with asthma is similar to the general population [9], although in the USA, a higher percentage of people with asthma are smokers (21%) than among those without asthma (16.8%) [10]. Smoking-induced effects on the lungs, such as chronic bronchitis, emphysema, gas trapping and small airway disease, can occur in the absence of chronic airflow obstruction. Taken together, these findings suggest that chronic respiratory symptoms in current or ex-smokers without spirometric evidence of COPD could be due to asthma, smoking-induced airway disease or a combination of these conditions. This review considers the classification, clinical outcomes, inflammatory and imaging variables, phenotypes, and management of current and ex-smokers with airway disease without COPD, including those with and without asthma, and focuses on the overlaps between these subgroups.

## Epidemiological and clinical studies

Epidemiological studies in the general population, observational studies of volunteers recruited to large cohorts used to investigate COPD, and studies of people with asthma in primary and secondary care provide information to help classify chronic airway disease in current and ex-smokers without spirometric COPD, including those who also have asthma, and to describe clinical, inflammatory and imaging variables in these individuals. Epidemiological studies of people randomly selected from the general population include the US Third National Health and Nutrition Examination Surveys (NHANES III) in 1988–1994 and 2007–2010 [11–13], the Canadian Cohort of Obstructive Lung Disease (CanCOLD) study in nine urban sites in Canada [14], and the New Zealand Wellington Respiratory Survey [15]. Information on current and ex-smokers without COPD is provided from subgroups of middle-aged and older volunteers recruited to the Genetic Epidemiology of COPD (COPDGene) study [16] and the Subpopulations and Intermediate Outcome Measures in COPD Study (SPIROMICS) [17, 18]. Both studies included individuals with a concomitant diagnosis of asthma. Data on current and ex-smokers with a diagnosis of asthma are

### BOX 1 Key messages

- Due to the high prevalence of cigarette smoking and asthma, current and ex-smokers frequently develop chronic airway disease without spirometric evidence of chronic obstructive pulmonary disease (COPD), either alone or in association with asthma
- Adverse health-related outcomes occur due to smoking-induced airway diseases (chronic bronchitis, emphysema, small airway disease), asthma or a combination of these diseases
- Current and ex-smokers without COPD, either with or without asthma, have more respiratory symptoms, worse quality of life, increased exacerbation rates, reduced lung function and more comorbidities than never-smokers with asthma or healthy never-smokers
- As well as clinical features, airway inflammatory and structural changes in smoking-induced airway disease without COPD overlap with those found in smokers with asthma
- Cigarette smoking is associated with worse clinical outcomes in some phenotypes of asthma
- Management involves public health measures to control exposure to tobacco smoke, personal advice on smoking cessation and the use of appropriate targeted therapies, although evidence is limited on the effectiveness of therapeutic interventions
- Understanding the mechanisms, natural history and management of current and ex-smokers with airway disease without spirometric evidence of COPD, either alone or in association with asthma, is a priority for future research

based on epidemiological studies in the general population, such as the Copenhagen General Population Study [19], and studies in primary care and secondary care [20–23]. Several important issues about methodology influence the interpretation of the evidence provided by these studies (table 1), such as differences in demographic factors between study populations, uncertainty about the diagnosis of the type of chronic airway disease, variations in exposure to tobacco smoke, differences in the methods used to assess clinical outcomes and generalisability of the findings.

TABLE 1 Methodological issues that influence the interpretation of studies of adults with asthma and smoking-induced airway disease without spirometric evidence of chronic obstructive pulmonary disease (COPD)

<b>Demographic information</b>	Adult participants recruited to clinical studies of smokers with asthma are generally younger than those included in epidemiological studies in the general population and COPD cohorts were participants are middle-aged and older
<b>Diagnosis of chronic airway disease</b>	Sex and race of participants may not be representative of the general population Establishing an accurate diagnosis of asthma, smoking-induced airway disease without asthma, chronic bronchitis, emphysema or a combination of airway diseases can be difficult in symptomatic current smokers and ex-smokers without spirometric COPD Asthma and other airway diseases may be underdiagnosed or misdiagnosed in observational studies that are based on history alone and without objective tests The specificity of objective criteria used to diagnose asthma may not be sufficient to exclude people with symptomatic smoking-induced airway disease who do not have asthma Observational studies in asthma can often report outcomes that combine data from smokers with and without chronic airflow obstruction (forced expiratory volume in 1 s/forced vital capacity <0.7), making it harder to assess the findings in those without spirometric COPD Undiagnosed emphysema and air trapping can occur in cigarette smokers without spirometric COPD, and these conditions may be missed by spirometry and only become evident with additional tests of lung functions (transfer factor, whole-body plethysmography, impulse oscillatory, multiple-breath washout tests) and imaging techniques (low-dose computed tomography) Studies may include people with other chronic respiratory diseases, such as bronchiectasis Spirometric measurements can vary over time resulting in an individual being considered not to have COPD on recruitment to a study, when subsequent tests demonstrate airflow obstruction The influence of factor(s) inducing airway disease other than tobacco smoke, such as occupational agents and environmental exposures, are not controlled in most studies Symptoms due to upper airway disease can be misdiagnosed as being due to lower airway disease Combined data from current smokers and ex-smokers may obscure differences in outcomes in one or another smoking group Findings in studies with an entry criteria of a smoking history of ≥10 pack-years, such as COPDGene and SPIROMICS, may not be relevant to those with a less intense history of exposure to tobacco smoke [16–18] Factors relating to smoking behaviour, such as number of puffs per cigarette, depth of inhalation and types of cigarette, may not be reflected by history of pack-years and current smoking status
<b>Smoking status</b>	Measures of current symptoms and quality of life in smokers with asthma, such as the ACT, ACQ and AQLQ scores, can overlap with those used to measure chronic respiratory symptoms and health status in smoking-induced airway disease with or without COPD, such as the CAT and SGRQ scores. For example, the SGRQ score is associated with changes in AQLQ and by some treatments for asthma, such as mepolizumab, and concomitant asthma can confound CAT scores in current or ex-smokers [121]
<b>Assessment of clinical outcomes</b>	The definition of chronic bronchitis varies between studies and in some, is based on components of the SGRQ score The definition of severe exacerbation in asthma, which is based on the use of high-dose systemic corticosteroid for ≥3 days, either alone or associated with an emergency department visit or hospital admission, overlaps with components of the definition of exacerbation-like respiratory symptoms used in studies of smoking-induced airway disease with or without COPD In observation studies, the assessment of clinical outcomes can be influenced by recall bias Age of onset of asthma influences the effects of cigarette smoking on lung function and possibly other variables
<b>Generalisability of findings</b>	The selection process and criteria used to recruit participants to studies of airway disease in individuals without COPD may not be generalisable to the general population, although baseline demographic and clinical variables in the COPDGene study showed some similarities to those in the National Health and Nutrition Examination Survey study in the general population [16]

ACT: Asthma Control Test; ACQ: Asthma Control Questionnaire; AQLQ: Asthma Quality of Life; CAT: COPD Assessment Test; SGRQ: St George’s Respiratory Questionnaire.

### Classification of chronic airway diseases in smokers without COPD

The ability to classify smoking-induced airway disease without spirometric COPD, with or without features of asthma, is hampered by the relatively small number of published studies, by the methodological factors as discussed in the previous section, and by a limited understanding of the phenotypes, endotypes and mechanism of airway disease in these subgroups. Epidemiological studies of middle-aged and older individuals without spirometric evidence of COPD, approximately half of whom are current or ex-smokers [12–15, 19], suggest that 14–20% have chronic airway disease, mainly due to asthma, chronic bronchitis or a combination of these diseases. A small proportion have emphysema alone, although this increases to one-third in heavy cigarette smokers [24]. In the COPDGene [16] and SPIROMICS [17] cohorts of symptomatic and asymptomatic middle-aged and older current and ex-smokers with normal spirometry, 11.4% and 18% had a history of asthma, 12.6% and 18% had chronic bronchitis, and 10.4% and 0% had computed tomography (CT) emphysema, respectively. Among the symptomatic current and ex-smoker subgroups, many had airway disease not associated with a history of asthma, although around one-third had asthma, one-third had chronic bronchitis and a small proportion had a combination of these conditions. Cluster analysis performed in two Korean cohorts of patients with asthma that included current smokers identified a “smoking asthma” cluster that was predominately male and had well-preserved FEV<sub>1</sub> [25].

A classification of chronic airway disease is proposed for symptomatic current and ex-smokers without airflow obstruction (figure 1). Smoking-induced airway diseases include chronic bronchitis, emphysema, small airway disease or a combination of these diseases [26, 27] and these conditions occur in people who also have a diagnosis of asthma. Some individuals may have undiagnosed asthma or other smoking-induced abnormality not detected by current techniques. Chronic respiratory symptoms in current and ex-smokers with asthma may be due to mechanisms induced by asthma, by smoking or by a combination of both pathways. Cigarette smoking is a risk factor for cardiovascular comorbidities, increased mortality and the development of asthma in adults [27, 28]. Risk factors implicated in causing COPD other than cigarette smoking [29], including exposure to biomass fuels, occupational agents and air pollution, as well as to impaired lung growth in childhood and poverty [1, 29], may contribute to airway damage in current and ex-smokers with normal spirometric lung function or with asthma. Lung disorders, such as interstitial lung disease, or nonrespiratory conditions, such as cardiac disease or high body mass index, can be alternative causes of symptoms in current and ex-smokers, and these disorders can occur in addition to chronic airway disease.

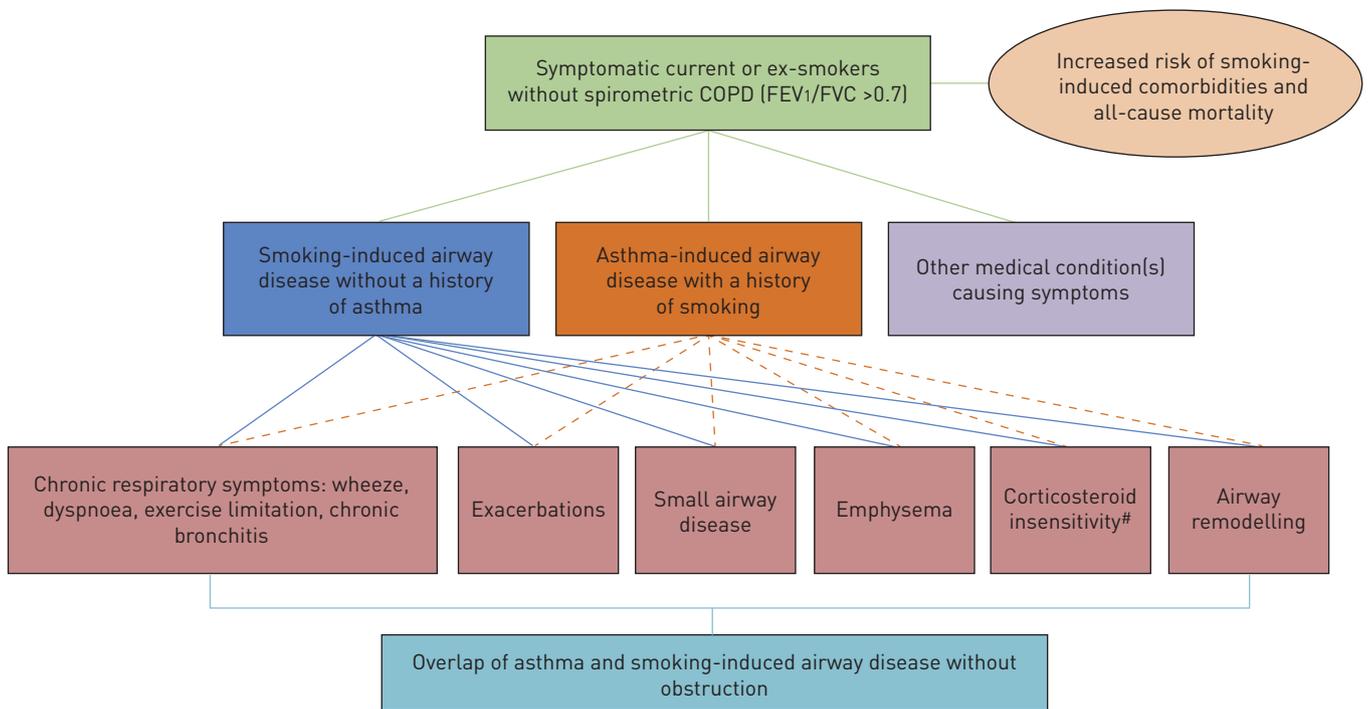


FIGURE 1 Classification of chronic airway diseases in symptomatic current and ex-smokers without spirometric airflow obstruction [forced expiratory volume in 1 s/forced vital capacity (FEV<sub>1</sub>/FVC) >0.7] due to smoking-induced airway disease without a history of asthma, asthma-induced airway disease or an overlap of both diseases. #: it is not known whether current and ex-smokers with smoking-induced airway disease without evidence of chronic obstructive pulmonary disease (COPD) or a history of asthma have clinical evidence of corticosteroid insensitivity.

In summary, classification of asthma and smoking-related diseases in current and ex-smokers without evidence of spirometric COPD will require to be revised in the light of future studies that provide a greater understanding of the underlying phenotypes and endotypes of chronic airway disease in these individuals.

**Clinical outcomes**

Similarities and differences in clinical outcomes in current and ex-smokers with chronic airway disease without spirometric COPD or a history of asthma are compared with current and ex-smokers with asthma (table 2).

**Chronic respiratory symptoms**

Chronic respiratory symptoms of wheezing and dyspnoea are experienced by between 15% and 30% of adults aged ≥40 years in the general population, particularly in current and ex-smokers [12, 14, 15]. In the COPDGene and SPIROMICS cohorts, a history of wheezing, breathlessness or limitation of exercise was reported by approximately half the current and ex-smokers without COPD [16, 17, 30]. In the symptomatic subgroup of the SPIROMICS study, a high proportion reported wheezing (69%) and had a diagnosis of asthma (27%) [17]. Surveys of people with asthma, including those with severe disease, demonstrate that current smoking is an important risk factor for poor symptom control, including wheezing and breathlessness [19, 20, 31, 32], and these individuals often report limitations in exercise tolerance.

The prevalence rate for chronic bronchitis in the general population is 6.4% [33], with higher rates in smokers without airflow obstruction [34, 35], including adults aged ≥40 years [12, 14, 15]. Chronic bronchitis was reported by 12.6% and 19% of current and ex-smokers with normal spirometry recruited to the COPDGene [16] and SPIROMICS cohorts [17], respectively, with a higher proportion reporting chronic bronchitis among symptomatic individuals (33%) [17]. There is relatively limited information on the prevalence of chronic bronchitis in asthma [35–39]. The Copenhagen City Heart Study and the European Community Respiratory Health survey reported prevalence rates of 39% and 42%, respectively, in nonsmokers with asthma [35, 37], with higher rates in smokers with asthma [35, 37], particularly those with severe disease [39]. Smoking-induced chronic bronchitis without COPD is a risk factor for respiratory exacerbations [14], and is associated with worse quality of life, reduced exercise tolerance and a higher pack-year history [40]. In smokers with asthma, chronic bronchitis is associated with worse current symptom control [39] and a greater decline in FEV<sub>1</sub> [35].

**Quality of life**

Health-related quality of life is poorer in adults aged ≥40 years without a diagnosis of asthma, emphysema or COPD who gave a history of exacerbations than those without exacerbations [14]. In the COPDGene

TABLE 2 Summary of the effects of smoking status on clinical outcomes in asthma and symptomatic smokers without spirometric chronic obstructive pulmonary disease (COPD)<sup>#</sup>

Outcome	Asthma with a smoking history and without spirometric COPD: current smokers with asthma compared with never-smokers with asthma	Smoking-induced airway disease without spirometric COPD (no history of asthma): current and ex-smokers compared with healthy never-smokers
<b>Respiratory symptoms</b>		
Wheeze, breathlessness	Increased	Increased
Exercise tolerance	Decreased	Decreased
Chronic bronchitis	Increased	Increased
<b>Quality of life</b>	Decreased or similar	Decreased
<b>Exacerbations</b>	Increased or similar	Increased
<b>Healthcare utilisation</b>	Increased	Increased
<b>Lung function</b>		
Baseline spirometry	Decreased	Decreased
Small airway dysfunction	Increased	Increased
Decline in FEV <sub>1</sub>	Increased or similar	Similar
<b>Therapeutic response to ICSs</b>		
Short- to medium-term treatment	Decreased	Not known
Long-term treatment	Decreased or similar	Not known
<b>Smoking-related comorbidities</b>	Increased	Increased
<b>All-cause mortality</b>	Increased	Increased

FEV<sub>1</sub>: forced expiratory volume in 1 s; ICS: inhaled corticosteroid. <sup>#</sup>: refer to the main text for information on the published studies used to summarise the effects of smoking status on clinical outcomes in asthma and symptomatic smokers without spirometric COPD.

cohort, current and ex-smokers without spirometric COPD had worse health status as assessed by the St George's Respiratory Questionnaire total score than healthy never-smokers [16]. In some surveys, smokers with asthma had worse levels of asthma-specific quality of life than never-smokers with asthma [41].

#### *Exacerbations and healthcare utilisation*

In the CanCOLD general population study, ~4% of individuals without evidence of COPD or a history of asthma had an exacerbation in the last year [14], and these events were associated with female sex, presence of wheezing, the use of respiratory medications and self-perceived poor health. A 5-year follow-up of the COPDGene cohort reported that 4.1% of current and ex-smokers without COPD had one or more exacerbations per year and ~1% had a severe exacerbation requiring hospital admission [42]. Risk factors for acute episode of respiratory disease in smokers without COPD are similar to those with COPD, although the rate of episodes is higher in the latter group [43]. In the SPIROMICS population, symptomatic current and ex-smokers more often had exacerbations (0.27 events-year<sup>-1</sup>) than asymptomatic current or ex-smokers (0.08 events-year<sup>-1</sup>) or never-smokers (0.03 events-year<sup>-1</sup>) [17]. Current smoking is a risk factor for severe asthma exacerbations [27] including during pregnancy [44], and in severe disease [31], more hospitalisation for asthma [41], more visits to the emergency room for asthma [45] and increased numbers of life-threatening asthma attacks. In contrast, the Copenhagen General Population Study reported that the risk of asthma exacerbations was unrelated to smoking status [19].

#### *Lung function*

Spirometric lung function tests are reduced in cigarette smokers without a history of lung disease compared with never-smokers [1], in symptomatic current or ex-smokers without COPD compared with asymptomatic current or ex-smokers [17] and in smokers with asthma compared with never-smokers with asthma [19, 31, 46]. Small airway dysfunction occurs in current and ex-smokers without COPD, irrespective of the presence or absence of respiratory symptoms [18], and its presence is associated with a more rapid decline in lung function [47]. Tests of small airway function are also impaired in smokers with asthma [46]. In the COPDGene cohort, current and ex-smokers without spirometric COPD (FEV<sub>1</sub>/FVC greater than lower limit of normal) had abnormal forced expiratory volume in 3 and 6 s (FEV<sub>3</sub>/FEV<sub>6</sub>) ratios that identified individuals with mild COPD characterised by CT small airway disease, impaired exercise tolerance and reduced quality of life [48]. In a 5-year follow-up of the COPDGene cohort, the rate of FEV<sub>1</sub> decline was similar in current and ex-smokers without COPD who reported breathlessness or exacerbations compared with those who did not [42]. Several longitudinal population-based studies report accelerated decline in lung function in adult smokers with asthma [35, 49, 50], although other studies report a similar decline in FEV<sub>1</sub> in asthma irrespective of smoking status [37]. A greater proportion of smokers with adult-onset asthma develop persistent airflow obstruction and although current smokers with a history of childhood-onset asthma can develop COPD, this occurs in association with severe disease in childhood rather than cigarette smoking in adulthood [51, 52].

#### *Corticosteroid insensitivity*

Corticosteroid insensitivity occurs in chronic inflammatory diseases including severe asthma and COPD [53, 54]. The effects of budesonide on epithelial barrier function in primary bronchial epithelial cells is impaired in asthma and COPD, and this effect is less evident in healthy smokers, suggesting that corticosteroid responsiveness in smokers without spirometric evidence of COPD might be better preserved than in those with COPD [55], although this hypothesis remains to be tested in clinical studies. Cigarette smokers with mild to moderate asthma are less sensitive to the short- and medium-term therapeutic effects of inhaled corticosteroids on symptoms and lung function compared with nonsmokers with asthma [21, 56, 57]. Smokers with chronic asthma are also less sensitive to short-term oral corticosteroid therapy [58] and to the cutaneous vasoconstrictor response to topical corticosteroids [59]. Data is conflicting on whether the long-term therapeutic effects of inhaled corticosteroids are impaired in smokers with asthma [60–64]. Taken together, these studies suggest that most smokers with asthma are less sensitive to short- and medium-term treatment with inhaled corticosteroids compared with nonsmokers with asthma, but that a small proportion of smokers can respond adequately to this treatment and that long-term treatment may have beneficial effects.

#### *Comorbidities and mortality*

Cigarette smoking is a risk factor for diseases that can impact on the health of smokers with asthma or smoking-induced airway disease without COPD, such as cardiovascular disease [65], anxiety and depression, and osteoporosis. In the US Multi-Ethnic Study of Atherosclerosis study, greater emphysema-like changes on cardiac CT were associated with increased all-cause mortality among people without airflow obstruction, particularly among smokers [66]. Comorbidities occur frequently in smokers with asthma, with higher rates of cardiovascular disease, pneumonia and lung cancer compared with never-smokers without asthma [19].

Patients with adult-onset asthma, at least one comorbidity and evidence of systemic inflammation, characterised by elevated levels of interleukin (IL)-6 and high-sensitivity C-reactive protein, had a higher pack-year history than patients without systemic inflammation or a comorbidity [67]. The NHANES I Follow-up Study reported an increased risk of respiratory mortality and all-cause mortality in asthma that may be explained by the confounding effect of cigarette smoking [68].

#### *Clinical outcomes in ex-smokers*

In the COPDGene cohort, ex-smokers had less chronic respiratory symptoms, fewer exacerbations and less airway wall area thickening plus greater emphysema and gas trapping than current smokers [16]. In the SPIROMICS cohort, the proportion of current smokers with chronic respiratory symptoms and exacerbations was similar to the ex-smokers [17]. In most studies, ex-smokers with asthma had levels of symptom control, chronic bronchitis, quality of life and healthcare use for asthma that were either similar or worse than never-smokers with asthma and that were generally better than current smokers with asthma [20, 31, 37, 41, 69]. In one study of people with severe asthma, increased blood neutrophil counts in ex-smokers with a low pack-year history were associated with frequent exacerbations, whereas elevated blood eosinophils predicted exacerbations in never-smokers [70]. The Copenhagen General Population Study reported that the frequency of any respiratory symptoms was not associated with smoking status in individuals with asthma [19]. All-cause mortality and rates of cardiovascular disease, pneumonia and lung cancer in ex-smokers with asthma were similar to never-smokers and current smokers with asthma [19].

In summary, current and ex-smokers without COPD have more chronic respiratory symptoms, worse quality of life, increased exacerbation rates, reduced lung function and more comorbidities than never-smokers without COPD. There is considerable overlap in the range and frequency of adverse clinical outcomes between those with and without a diagnosis of asthma.

#### **Inflammatory and imaging variables**

Cigarette smoking and asthma induce distinct inflammatory and structural changes to the lungs, although less is known about whether these stimuli interact. Tobacco smoke induces pro-inflammatory responses in the lungs that are mediated by alveolar macrophages, neutrophils and respiratory epithelial cells, and it also impairs innate defence mechanisms that are produced by alveolar macrophages, epithelial cells, natural killer cells and dendritic cells [71]. The risk of developing smoking-related inflammation increases with greater smoking intensity in healthy subjects [72]. The bronchial mucosa of asymptomatic smokers without COPD has increased inflammatory cells, including neutrophils, mast cells and macrophages, increased cells staining positive for IL-1 $\beta$  and IL-8, reduced epithelial integrity, and increased thickness of the laminin layer in the subepithelium [73, 74]. In smokers with normal lung function, it is likely that epithelial inflammation and glandular hyperplasia contribute to symptoms of chronic bronchitis, impaired inflammatory responses contribute to increased risk of infection and altered immunity contributes to airway damage. Published data are not available on the airway histology in symptomatic and asymptomatic smokers without spirometric COPD recruited to the COPDGene and SPIROMICS cohorts. Current smokers without COPD, but with evidence of small airway dysfunction, have evidence of distal airway inflammation [75, 76]. In the CanCOLD study of middle-aged or older current and ex-smokers with normal lung function (mean age 68 years), the prevalence of bronchial wall thickening, air trapping and emphysema on visual inspection of CT scans was 58%, 35% and 30%, respectively, compared with never-smokers with no obstruction [24]. CT emphysema was estimated to be mild, since it was not associated with worse clinical outcomes [24]. In the COPDGene cohort, approximately one-third of current and ex-smokers without spirometric COPD had segmental CT airway wall thickening [16]. In the SPIROMICS population, symptomatic current and ex-smokers without spirometric evidence of COPD, irrespective of a history of asthma, had greater CT airway wall thickening compared with asymptomatic individuals [17]. Quantitative CT and visual scoring emphysema was reported in 10.4% and 24%, respectively, of current and ex-smokers without spirometric COPD recruited to COPDGene [16].

In smokers with asthma, sputum airway inflammation is often reported to be noneosinophilic, either neutrophilic or paucigranulocytic [21, 22, 31], although a recent study found no association between smoking status and sputum inflammatory phenotypes in asthma [77]. Differences in the intensity of smoking may explain some of the discrepancies between studies. Exhaled nitric oxide concentration is reduced in current cigarette smokers with asthma [31, 78], whereas concentrations are similar in ex- and never-smokers with severe asthma [31]. Bronchial biopsy studies in smokers with mild and moderate asthma report reduced eosinophil numbers, increased submucosal mast cell numbers [79] and increased CD8<sup>+</sup> T-lymphocytes [80] compared with never-smokers with asthma. In addition, smokers with asthma have increased bronchial goblet cell numbers and more proliferation and greater thickness of the epithelium [79]. In the U-BIOPRED cohort of individuals with severe asthma, CD4<sup>+</sup> lymphocyte numbers

were reduced in current and ex-smokers compared with nonsmokers with severe asthma [81]. Airway smooth muscle mass, basement membrane thickness and submucosal gland area are similar [79, 82]. In keeping with these latter findings, CT measures of segmental airway wall thickness are similar in smokers and never-smokers with mild to severe asthma [46]. CT large airway luminal area is reduced in smokers with severe asthma [46], particularly in those who gave a history of chronic mucus hypersecretion [39], possibly due to mucus accumulation in the large airways and to structural changes to the airways. CT emphysema is an infrequent finding in smokers with asthma [46].

In summary, these observations suggest that tobacco-induced airway inflammatory and structural changes are present in smokers without spirometric COPD compared with healthy never-smokers. Airway inflammation in smokers with asthma differs from that of never-smokers with asthma; current smoking is associated with less eosinophilic airway inflammation, more mast cell numbers, increased bronchial epithelial glands and reduced segmental airway luminal area. Airway inflammatory and structural changes in smoking-induced airway disease without COPD overlap those found in smokers with asthma.

## Phenotypes

Subtypes or phenotypes of asthma are recognised, based on clinical, physiological or immunological variables, and these are used to classify asthma and to predict response to therapy [83]. Phenotypes of smoking-related disease occur in current and ex-smokers without spirometric COPD or a history of asthma, such as chronic bronchitis, emphysema and small airway disease (figure 1). Current and former cigarette smoking in asthma is associated with worse outcomes in certain clinical phenotypes discussed earlier, such as chronic bronchitis, chronic persistent airflow obstruction and corticosteroid insensitivity. There is limited and, in some cases, conflicting information on the influence of current and former cigarette smoking on clinical and inflammatory phenotypes of asthma.

### *Clinical phenotypes*

#### *Adult-onset asthma*

Greater pack-year history is a predictor of uncontrolled asthma, increased disease severity and greater decline in lung function in people with adult-onset asthma [84–88]. A higher proportion of people with severe adult-onset asthma are current and ex-smokers compared with severe childhood-onset asthma, and the adult-onset group has a higher pack-year history [89].

#### *Allergic asthma*

Total IgE concentrations in asthma are not altered by smoking status [19, 31], whereas specific IgE sensitisation to some common environmental allergens is reduced in current smokers and ex-smokers with severe asthma compared with never-smokers with severe asthma [31]. Smoking status of individuals with mild atopic asthma does not influence the magnitude of the allergen-induced early response [90, 91], whereas the magnitude of the late response is reported to be reduced [91] or similar [90] in current smokers compared with nonsmokers [91].

#### *Aspirin-exacerbated respiratory disease*

Active smoking in adulthood and exposure to second-hand smoke in childhood are associated with an increased risk of developing aspirin-exacerbated respiratory disease [92, 93].

#### *Obesity-related asthma*

The prevalence and intensity of current or former cigarette smoking in obese or nonobese individuals with severe asthma are similar [94, 95]. Both smoking and obesity are independent risk factors for poor asthma control and increased exacerbations [96]. A survey of US adults reported that current smoking increased the risk of symptoms, emergency room visits and missing work days due to asthma associated with obesity or physical inactivity [97]. It is postulated that obesity and cigarette smoking modify the clinical expression of asthma in women by increasing systemic inflammation [98].

#### *Occupational asthma*

In a Canadian prospective observational study, the proportion of current and ex-smokers was similar between people with occupational asthma and with non-work-related asthma [99]. Cigarette smoking at the time of diagnosis does not adversely influence the outcome of occupational asthma [100].

#### *Chronic rhinosinusitis*

In the Swedish general population, cigarette smoking is associated with a high prevalence of chronic rhinitis in both men and women and a low prevalence of allergic rhinitis in men [101]. Increased severity of sinusitis on CT imaging is associated with higher blood eosinophil counts, serum IgE levels, exhaled

nitric oxide and serum periostin concentrations in both adult nonsmokers (<10 pack-years) and smokers with asthma ( $\geq 10$  pack-years), suggesting that CT imaging evidence of severe sinusitis was associated with T-helper cell type 2 (Th2)-high inflammation irrespective of smoking status [102].

#### *Psychological factors*

Active cigarette smokers with severe asthma had higher Hospital Anxiety and Depression Scale scores than never-smokers or ex-smokers with severe asthma, suggesting that these subjects were experiencing a greater degree of emotional distress [31]. In the general population, smoking cessation is associated with reduced depression, anxiety and stress, and improved positive mood and quality of life, compared with continuing to smoke [103].

#### *Inflammatory phenotypes*

Eosinophilic inflammation is a risk factor for exacerbations and predicts a beneficial response to corticosteroids. Th2-high inflammation is closely associated with eosinophilic inflammation and predicts a favourable therapeutic response to biological agents targeting the Th2 cytokine pathway. A noneosinophilic phenotype is associated with current smoking and is poorly responsive to current therapies including corticosteroids [104]. Cigarette smoking might induce a Th2-low inflammatory phenotype, although little is known about the prevalence or importance of Th2-low inflammation in current or ex-smoker with asthma or associated clinical asthma phenotypes.

#### *Summary*

Some clinical and inflammatory phenotypes of asthma are influenced by smoking status, and different phenotypes of chronic airway disease occur in current and ex-smokers without spirometric COPD or a history of asthma. Establishing the overlap between the phenotypes and endotypes of asthma and smoking-induced airway disease with normal lung function and their influence in directing therapy requires future investigation.

#### **Management**

The management of adverse health effects caused by exposure to tobacco smoke in people with asthma and in current and ex-smokers without spirometric evidence of COPD involves interventions ranging from public health measures to control exposure to tobacco smoke, personal advice on smoking cessation and the use of appropriate targeted therapies. Beyond advice on smoking cessation, there is limited information on drug treatment of smokers with asthma and symptomatic smokers with normal lung function [1, 2]. The management of systemic smoking-induced comorbidities, such as cardiovascular disease, should be as guided by national and local recommendations.

#### *Smoking cessation*

Smoking cessation is an important goal in the management of all cigarette smokers, including those with asthma and symptomatic smokers with normal lung function. There is limited evidence of the effectiveness of smoking cessation on clinical outcomes in asthma, and most studies include small numbers of participants and are of short duration. In some studies, symptoms, lung function or corticosteroid sensitivity improve and sputum neutrophils decrease in those who quit smoking successfully [22, 105–108]. Former smokers with asthma have better symptom control than current smokers with asthma [20, 69]. Despite the known adverse effects of active smoking in asthma, these individuals are no more likely to receive physician counselling regarding smoking cessation nor smoking cessation pharmacotherapy compared with the general smoking population [109]. Smokers with asthma have poor smoking cessation rates [110], and slower rates of decline in nicotine withdrawal symptoms and craving during smoking quit attempts [111]. The effect of smoking cessation on clinical variables in symptomatic smokers recruited to the COPDGene or SPIROMICS cohorts is not reported, although smoking cessation was associated with older age of participants recruited to COPDGene [16]. In a population of current smokers with and without COPD, chronic respiratory symptoms, including bronchitis, were associated with the intention to stop smoking in the next 30 days, suggesting that the presence of respiratory symptoms could be used to aid smoking cessation advice in smokers with normal lung function [112].

#### *Current pharmacological treatments*

Evidence is limited on the effectiveness of therapeutic interventions directed at improving clinical outcomes due to their exclusion from most clinical trials. Studies in asthma usually exclude current smokers or ex-smokers with a smoking history of >10 pack-years and studies in COPD exclude symptomatic current smokers or ex-smokers without spirometric evidence of COPD or with a smoking history of <10 pack-years. Clinical trials in smokers with asthma may provide some limited guidance on drug treatment for current and ex-smokers with chronic airway disease without COPD or asthma. Despite the presence of reduced

sensitivity to low-dose inhaled corticosteroids, higher doses improve lung function [57], although many patients remain symptomatic. Targeting the small airways with extra-fine-particle inhaled corticosteroids may potentially impact favourably on the safety and efficacy of inhaled corticosteroids through improved total lung deposition and improved asthma control at lower daily doses than large-particle inhaled corticosteroid. Observational studies suggest that extra-fine-particle hydrofluoroalkane beclometasone may achieve better control at lower prescribed doses than large-particle inhaled corticosteroids [113], but to date, randomised controlled trials have not clearly demonstrated that equipotent doses of small-particle inhaled corticosteroids are more effective than large-particle inhaled corticosteroids. The addition of a long-acting  $\beta_2$ -agonist to an inhaled corticosteroid improves clinical outcomes in smokers with asthma [61, 114, 115]. The long-acting muscarinic antagonist tiotropium was included in the 2015 Global Initiative for Asthma guideline as an alternative add-on therapy for people with a history of exacerbations [2]. The generalisability of the findings of clinical trials of tiotropium to smokers with asthma and smoking-related airway disease with normal lung function is uncertain, since current smokers and ex-smokers with >10 pack-years were excluded from clinical trials of tiotropium in asthma and in some studies, participants had to have chronic airflow obstruction (post-bronchodilator FEV<sub>1</sub> % pred  $\leq$ 80% and FEV<sub>1</sub>/FVC  $\leq$ 0.7) [116]. There is some support for the effectiveness of tiotropium in “real-life” populations of asthma that include current and ex-smokers [81]. In an exploratory clinical trial in smokers with asthma, low-dose theophylline added to inhaled corticosteroid resulted in improvement in lung function, suggesting the restoration of corticosteroid sensitivity in those treated with the combination [117]. In one controlled trial, asthmatic patients with a smoking history of  $\leq$ 11 pack-years tended to show greater symptom control with inhaled fluticasone propionate over a 6-month period, whereas those with a smoking history of >11 pack-years tended to show greater benefit with the leukotriene receptor antagonist montelukast [118].

There are no clinical trials of drug treatments in symptomatic smokers with normal lung function to guide management. It remains to be established whether therapies shown to be effective in the treatment of smokers with asthma, such as long-acting  $\beta_2$ -agonist and inhaled corticosteroid combinations, will also benefit symptomatic smokers with normal lung function. Despite the uncertainty around drug treatment in this group, many symptomatic volunteers without COPD recruited to large COPD cohorts were taking respiratory medications. In SPIROMICS, 42% were taking bronchodilators and 23% were taking inhaled corticosteroids [17]; in COPDGene, 20% used respiratory medications [16]. There is an unmet need for effective treatments for smokers without COPD as this group experience considerable disability from chronic respiratory symptoms and are at increased risk of exacerbations.

### Conclusions and future directions

In conclusion, chronic respiratory symptoms occur in current and ex-smokers without spirometric evidence of COPD due to smoking-induced airway diseases including chronic bronchitis, emphysema, small airway disease or asthma, or a combination of these diseases. These individuals are more likely to experience wheezing, breathlessness, limitation in exercise, chronic bronchitis, poorer quality of life, exacerbations and smoking-related comorbidities than healthy never-smokers. Corticosteroid insensitivity and a greater decline in lung function are features of the smokers with asthma subgroup. Airway inflammatory and structural changes in smoking-induced airway disease without COPD overlap with those found in smokers with asthma. Cigarette smoking is associated with worse clinical outcomes in some phenotypes of asthma. The management of the adverse health effects caused by exposure to tobacco smoke involves public health measures to control exposure to tobacco smoke, personal advice on smoking cessation and the use of appropriate targeted therapies. Evidence is limited on the effectiveness of therapeutic interventions directed at improving clinical outcomes in these groups of patients due to their exclusion from most clinical trials.

There are many uncertainties about this chronic airway group, including their classification, mechanisms, natural history and management [119]. Future research needs to establish what proportions of symptomatic current and ex-smokers with normal spirometry have smoking-induced airway disease alone or also have asthma or a mixture of subtypes of smoking-induced airway disease (figure 1). In addition to the considerable overlap in clinical features that exists in current and ex-smokers with asthma and smoking-related airway disease without spirometric COPD, it will be important to understand the overlap in inflammatory mechanisms. Studies will require to recruit large numbers of current and ex-smokers from the general population and for these individuals to undergo detailed clinical, imaging and immunological phenotyping and endotyping, including the employment of system biological approaches. Different subtypes may have different mechanisms for exacerbations and other clinical outcomes and require individualised targeted therapies. The natural history of different subtypes of smoking-induced airway disease with normal lung function may differ. It is important to know whether subtypes are predictive of the development of COPD. Interestingly, a 5-year follow-up of the COPDGene cohort with normal lung

function found that acute respiratory events did not increase the decline in lung function [42]. Current smokers with adult-onset asthma are at risk of developing COPD, whereas although current smokers with a history of childhood-onset asthma can develop COPD, this appears not to be due to the effects of cigarette smoking [51, 52], suggesting that different clinical phenotypes of asthma may differ in the effects of tobacco smoke on lung function. It remains to be established whether the identification of asymptomatic patients with smoking-induced airway diseases and normal lung function will lead to improved outcomes [120]. Research is required to determine the benefit of therapeutic interventions in this symptomatic population, particularly those at increased risk of exacerbations. Drugs that could be assessed for efficacy in symptomatic smokers with normal lung function include therapies currently used in the treatment of COPD, such as long-acting bronchodilators, azithromycin and roflumilast as well as other novel therapies under development [106]. In the future, the entry criteria for clinical trials should reflect “real-life” populations that including current and ex-smokers of differing ages and smoking intensity.

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