Asthma and smoking-induced airway disease without spirometric COPD

Neil C Thomson MD, FRCP, FERS

Institute of Infection, Immunity & Inflammation,

University of Glasgow, Glasgow, United Kingdom

Corresponding author:

Professor Neil C Thomson, Institute of Infection, Immunity & Inflammation, University of Glasgow, Glasgow, G12 OYN, United Kingdom E- mail: neil.thomson@glasgow.ac.uk

Word count: 5599 words

ABSTRACT

Due to the high prevalence rates of cigarette smoking and asthma, current and former smokers frequently develop chronic airway disease without spirometric evidence of COPD, either alone or associated with asthma. This review considers the classification, clinical outcomes, inflammatory and imaging variables, phenotypes and management of current and former 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 former smokers with asthma and smoking-induced airway disease without COPD is a priority for future research.

Word count: 185 words

INTRODUCTION

The asthma-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 an FEV_1/FVC ratio <0.7. The overlap syndrome is associated with worse clinical outcomes compared to COPD alone, including more severe symptoms, worse quality of life, more frequent exacerbations, greater decline in lung function, increased mortality and higher health care costs [1, 2, 4, 5]. Estimates of the prevalence of ACOS range from 15% to around 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 recognized, 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 have asthma. In many countries the proportion of cigarette smokers among people with asthma is similar to the general population [9], although in the US, 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 former cigarette 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 former 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 former cigarette 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 1988-94 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 former smokers without COPD is provided from subgroups of middle age 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 former smokers with a diagnosis of asthma are 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 generalizability of the findings.

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, the methodological factors discussed above 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 former smokers [12-15, 19], suggest that 14% to 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 former smokers with normal spirometry, 11.4% and 18% respectively had a history of asthma, 12.6% and 18% had chronic bronchitis and

10.4%, and 0% had computed tomography (CT) emphysema. Among the symptomatic current and former smoker sub-groups, 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_1 [25].

A classification of chronic airway disease is proposed for symptomatic current and former 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 former 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 co-morbidities, 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 former smokers with normal spirometric lung function or with asthma. Lung disorders, such as interstitial lung disease or non-respiratory conditions, such as cardiac disease or high BMI can be alternative causes of symptoms in current and former smokers and these disorders can occur in addition to chronic airway disease.

In summary, classification of asthma and smoking-related diseases in current and former 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 former smokers with chronic airway disease without spirometric COPD or a history of asthma are compared with current and former 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 or greater in the general population, particularly in current and former smokers [12, 14, 15]. In the COPDGene and SPIROMIC cohorts, a history of wheezing, breathlessness or limitation of exercise was reported by approximately half the current and former smokers without COPD [16, 17, 30]. In the symptomatic subgroup of the SPIROMIC 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 or greater [12, 14, 15]. Chronic bronchitis was reported by 12.6% and 19% of current and former smokers with normal spirometry recruited to 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 (ECRH) survey reported prevalence rates of 39% and 42% respectively in non-smokers 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_1 [35].

Quality of life

Health-related quality of life is poorer in adults aged >40 years or greater without a diagnosis of asthma, emphysema or COPD who gave a history of exacerbations than those without exacerbations [14]. In the COPDGene cohort, current and former smokers without spirometric

COPD had worse health status as assessed by the St. George's Respiratory Questionnaire (SGRQ) 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 health care utilization

In the CanCOLD general population study, approximately 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 gender, presence of wheezing, the use of respiratory medications and self-perceived poor health. A five-year follow-up of the COPDGene cohort reported that 4.1% of current and former smokers without COPD had one or more exacerbations per year and approximately 1% has 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 SPIROMIC population, symptomatic current and former smokers more often had exacerbations (0.27 events per year) than asymptomatic current or former smokers (0.08 events per year) or never smokers (0.03 events per year) [17]. Current smoking is a risk factor for severe asthma exacerbations [27] including during pregnancy [44] and in severe disease [31], more hospitalization 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 former smokers without COPD compared with asymptomatic current or former smokers [17] and in smokers with asthma compared with never-smokers with asthma [19, 31, 46]. Small airway dysfunction occurs in current and former 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 former smokers without spirometric COPD (FEV_1/FVC greater than lower limit of normal) had abnormal forced expiratory volume in 3 and 6 seconds (FEV_3/FEV_6) ratios that identified individuals with mild COPD characterised by CT small airway disease, impaired exercise tolerance and reduced quality of life [48]. In a five year follow-up of the COPDGene cohort, the rate of FEV_1 decline was similar in current and former smokers without COPD who reported breathlessness or exacerbations compared to 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_1 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 to non-smokers 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 treatment with inhaled corticosteroids compared to non-smokers 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 (MESA) study, greater emphysema-like changes on cardiac CT were associated with increased all-cause mortality among people without airflow obstruction, particularly among smokers [66]. Co-morbidities occur frequently in smokers with asthma, with higher rates of cardiovascular disease, pneumonia and lung cancer compared to 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 (hsCRP,) had a higher pack-year history than patients without systemic inflammation or a co-morbidity [67]. The US National Health and Nutrition Examination Survey Epidemiologic Follow-up Study (NHEFS) 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 former smokers

In the COPDGene cohort, former 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 former cigarette smokers [17]. In most studies, former smokers with asthma had levels of symptom control, chronic bronchitis, quality of life and health care 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 former 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 former smokers with asthma were similar to never smokers and current smokers with asthma [19].

In summary, current and former 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-1β and IL-8, reduced epithelial integrity and increased thickness of the laminin layer in the sub-epithelium [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 former 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 to 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 former smokers without spirometric COPD had segmental CT airway wall thickening [16]. In the SPIROMIC population, symptomatic current and former 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 former smokers without spirometric COPD recruited to COPDGene [16].

In smokers with asthma, sputum airway inflammation is often reported to be non-eosinophilic, 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 former and never smokers with severe asthma [31]. Bronchial biopsy studies in smokers with mild and moderate asthma report reduced eosinophil numbers, increased sub-mucosal mast cell numbers [79] and increased $CD8^+$ T lymphocytes [80] compared to 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, $CD4^+$ lymphocyte numbers were reduced in current and former smokers compared to non-smokers 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 measure of segmental airway wall thickness are similar in smokers and never smokers with mild to severe asthma in [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 to 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 former cigarette 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 former smokers compared with severe childhood-onset asthma and the adult-onset group have a higher pack year history [89].

Allergic asthma: Total IgE concentrations in asthma are not altered by smoking status [19, 31], whereas specific IgE sensitization to some common environmental allergens is reduced in current smokers and former smokers with severe asthma compared to 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 to non-smokers [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 non-obese 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 former 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 non-smokers (<10 pack years) and smokers with asthma (≥10 pack years), suggesting that CT imaging evidence of severe sinusitis was associated with type-2 high inflammation irrespective of smoking status [102].

Psychological factors: Active cigarette smokers with severe asthma had higher Hospital Anxiety and Depression (HAD) scores than never smokers or former 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. T helper type 2 cell (Th_2)-high inflammation (Type 2 high inflammation) is

closely associated with eosinophilic inflammation and predicts a favourable therapeutic response to biological agents targeting the Th_2 cytokine pathway. A non-eosinophilic phenotype is associated with current smoking and is poorly responsive to current therapies including corticosteroids [104]. Cigarette-smoking might induce a Th_2-low inflammatory phenotype, although little is known about the prevalence or importance of Th_2-low inflammation in current or former smoker with asthma or associated clinical asthma phenotypes.

In summary, some clinical and inflammatory phenotypes of asthma are influenced by smoking status and different phenotypes of chronic airway disease occur in current and former cigarette 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 the adverse health effects caused by exposure to tobacco smoke in people with asthma and in current and former 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 co-morbidities, 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 to 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 SPROMICS 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 intension to stop smoking in the next 30 day 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 smoker or former smoker with a smoking history of >10 pack-years and studies in COPD exclude symptomatic current smoker or former 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 former 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 extrafine-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 extrafine particle hydrofluoroalkane (HFA)-beclometasone may achieve better control at lower prescribed doses than large particle inhaled corticosteroids [113], but to date, randomized 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 β_2-agonist to an inhaled corticosteroid improves clinical outcomes in smokers with asthma [61,

114, 115]. The long-acting muscarinic antagonist (LAMA) tiotropium was included in the 2015 GINA guideline as an alternative add-on therapy for people with a history of exacerbations [2]. The generalizability 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 former smokers with greater than a 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 $FEV_1 \leq 80\%$ predicted and FEV_1/FVC ratio ≤ 0.7)[116]. There is some support for the effectiveness of tiotropium in 'real-life' populations of asthma that include current and former 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 LABA and ICS 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] and 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 former 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 co-morbidities than heathy 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 former 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 exits in current and former 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 former 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 former smokers of differing ages and smoking intensity.

KEY MESSAGES

- Due to the high prevalence of cigarette smoking and asthma, current and former smokers frequently develop chronic airway disease without spirometric evidence of 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 former 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 former smokers with airway disease without spirometric evidence of COPD, either alone or in association with asthma is a priority for future research.

REFERENCES

1. Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease. 2016 http://www.goldcopd.org
2. Global Initiative for Asthma (GINA) 2016 http://www.ginasthma.org/
3. Cazzola M, Rogliani P. Do we really need asthma-COPD overlap syndrome? *J Allergy Clin Immunol* 2016: 138(4): 977-983.
4. Postma DS, Rabe KF. The Asthma–COPD Overlap Syndrome. *N Eng J Med* 2015: 373(13): 1241-1249.
5. Bateman ED, Reddel HK, van Zyl-Smit RN, Agusti A. The asthma–COPD overlap syndrome: towards a revised taxonomy of chronic airways diseases? *Lancet Respir Med* 2015: 3(9): 719-728.
6. Christenson SA, Steiling K, van den Berge M, Hijazi K, Hiemstra PS, Postma DS, Lenberg ME, Spira A, Woodruff PG. Asthma-COPD Overlap: Clinical Relevance of Genomic Signatures of Type 2 Inflammation in COPD. *Am J Resp Crit Care Med* 2015: 191(7): 758-766.
7. Alshabanat A, Zafari Z, Albanyan O, Dairi M, FitzGerald JM. Asthma and COPD Overlap Syndrome (ACOS): A Systematic Review and Meta Analysis. *PLoS ONE* 2015: 10(9): e0136065.
8. Kumbhare S, Pleasants R, Ohar JA, Strange C. Characteristics and Prevalence of Asthma/Chronic Obstructive Pulmonary Disease Overlap in the United States. *Annals ATS* 2016: 13(6): 803-810.
9. To T, Stanojevic S, Moores G, Gershon A, Bateman E, Cruz A, Boulet L-P. Global asthma prevalence in adults: findings from the cross-sectional world health survey. *BMC Public Health* 2012: 12(1): 204.
10. Percentage of People with Asthma who Smoke. 2016 http://www.cdc.gov/asthma/asthma_stats/people_who_smoke.htm

11. Mannino D, RC G, Petty T, Lydick E. Obstructive lung disease and low lung function in adults in the United States: data from the National Health and Nutrition Examination Survey, 1988-1994. *Arch Intern Med* 2000: 160(11): 1683-1689.
12. Halldin CN, Doney BC, Hnizdo E. Changes in prevalence of chronic obstructive pulmonary disease and asthma in the US population and associated risk factors. *Chron Respir Dis* 2015: 12(1): 47-60.
13. Soriano JB, Davis KJ, Coleman B, Visick G, Mannino D, Pride NB. The Proportional Venn Diagram of Obstructive Lung Disease: Two Approximations From the United States and the United Kingdom. *Chest* 2003: 124(2): 474-481.
14. Tan WC, Bourbeau J, Hernandez P, Chapman KR, Cowie R, FitzGerald JM, Marciniuk DD, Maltais F, Buist AS, O'Donnell DE, Sin DD, Aaron SD, for the Can CCRG. Exacerbation-like respiratory symptoms in individuals without chronic obstructive pulmonary disease: results from a population-based study. *Thorax* 2014: 69(8): 709-717.
15. Marsh SE, Travers J, Weatherall M, Williams MV, Aldington S, Shirtcliffe PM, Hansell AL, Nowitz MR, McNaughton AA, Soriano JB, Beasley RW. Proportional classifications of COPD phenotypes. *Thorax* 2008: 63(9): 761-767.
16. Regan EA, Lynch DA, Curran-Everett D, et al. Clinical and radiologic disease in smokers with normal spirometry. *JAMA Intern Med* 2015: 175(9): 1539-1549.
17. Woodruff PG, Barr RG, Bleecker E, Christenson SA, Couper D, Curtis JL, Gouskova NA, Hansel NN, Hoffman EA, Kanner RE, Kleerup E, Lazarus SC, Martinez FJ, Paine RI, Rennard S, Tashkin DP, Han MK. Clinical Significance of Symptoms in Smokers with Preserved Pulmonary Function. *New Engl J Med* 2016: 374(19): 1811-1821.
18. Martinez CH, Diaz AA, Meldrum C, Curtis JL, Cooper CB, Pirozzi C, Kanner RE, Paine IIIR, Woodruff PG, Bleecker ER, Hansel NN, Barr RG, Marchetti N, Criner GJ, Kazerooni EA, Hoffman EA, Ross BD, Galban CJ, Cigolle CT, Martinez FJ, Han MK. Age and Small Airway Imaging Abnormalities in Subjects With and Without Airflow in SPIROMICS. *Am J Resir Crit Care Med* 2016: Aug 26. [Epub ahead of print].

19. Çolak Y, Afzal S, Nordestgaard BG, Lange P. Characteristics and Prognosis of Never-Smokers and Smokers with Asthma in the Copenhagen General Population Study. A Prospective Cohort Study. *Am J Resp Crit Care Med* 2015: 192(2): 172-181.
20. Clatworthy J, Price D, Ryan D, Haughney J, Horne R. The value of self-report assessment of adherence, rhinitis and smoking in relation to asthma control. *Prim Care Resp J* 2009: 18(4): 300-305.
21. Thomson NC, Chaudhuri R. Asthma in smokers: challenges and opportunities. *Curr Opin Pulm Med* 2009: 15(1): 39-45.
22. Polosa R, Thomson NC. Smoking and asthma: dangerous liaisons. *Eur Respir J* 2013: 41(3): 716-726.
23. Thomson NC, Chaudhuri R, Livingston E. Asthma and cigarette smoking. *Eur Respir J* 2004: 24(5): 822-833.
24. Tan WC, Hague CJ, Leipsic J, Bourbeau J, Zheng L, Li PZ, Sin DD, Coxson HO, Kirby M, Hogg JC, Raju R, Road J, O'Donnell DE, Maltais F, Hernandez P, Cowie R, Chapman KR, Marciniuk DD, FitzGerald JM, Aaron SD, Canadian Respiratory Research N, the Can CCRg. Findings on Thoracic Computed Tomography Scans and Respiratory Outcomes in Persons with and without Chronic Obstructive Pulmonary Disease: A Population-Based Cohort Study. *PLOS ONE* 2016: 11(11): e0166745.
25. Kim T-B, Jang A-S, Kwon H-S, Park J-S, Chang Y-S, Cho S-H, Choi BW, Park J-W, Nam D-H, Yoon H-J, Cho Y-J, Moon H-B, Cho YS, Park C-S. Identification of asthma clusters in two independent Korean adult asthma cohorts. *Eur Respir J* 2013: 41(6): 1308-1314.
26. Forey BA, Thornton AJ, Lee PN. Systematic review with meta-analysis of the epidemiological evidence relating smoking to COPD, chronic bronchitis and emphysema. *BMC Pulm Med* 2011: 11: 36-36.
27. The Health Consequences of Smoking: 50 Years of Progress. A Report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, Coordinating Center for Health Promotion, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2014.

28. Coogan PF, Castro-Webb N, Yu J, O'Connor GT, Palmer JR, Rosenberg L. Active and Passive Smoking and the Incidence of Asthma in the Black Women's Health Study. *Am J Resp Crit Care Med* 2015: 191(2): 168-176.
29. Eisner MD, Anthonisen N, Coultas D, Kuenzli N, Perez-Padilla R, Postma D, Romieu I, Silverman EK, Balmes JR. An Official American Thoracic Society Public Policy Statement: Novel Risk Factors and the Global Burden of Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2010: 182(5): 693-718.
30. Elbehairy AF, Guenette JA, Faisal A, Ciavaglia CE, Webb KA, Jensen D, Ramsook AH, Neder JA, O'Donnell DE. Mechanisms of exertional dyspnoea in symptomatic smokers without COPD. *Eur Respir J* 2016: 48: 694-705.
31. Thomson NC, Chaudhuri R, Heaney LG, Bucknall C, Niven RM, Brightling CE, Menzies-Gow AN, Mansur AH, McSharry C. Clinical outcomes and inflammatory biomarkers in current smokers and exsmokers with severe asthma. *J Allergy Clin Immunol* 2013: 131(4): 1008-1016.
32. Chaudhuri R, McSharry C, McCoard A, Livingston E, Hothersall E, Spears M, Lafferty J, Thomson NC. Role of symptoms and lung function in determining asthma control in smokers with asthma. *Allergy* 2008: 63(1): 132-135.
33. Halbert RJ, Natoli JL, Gano A, Badamgarav E, Buist AS, Mannino DM. Global burden of COPD: systematic review and meta-analysis. *Eur Respir J* 2006: 28(3): 523-532.
34. Pelkonen M, Notkola I-L, 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(4): 1129-1137.
35. Lange P, Parner J, Vestbo J, Schnohr P, Jensen G. A 15-Year Follow-Up Study of Ventilatory Function in Adults with Asthma. *N Engl J Med* 1998: 339(17): 1194-1200.
36. Vonk JM, Jongepier H, Panhuysen CIM, Schouten JP, Bleecker ER, Postma DS. Risk factors associated with the presence of irreversible airflow limitation and reduced transfer coefficient in patients with asthma after 26 years of follow up. *Thorax* 2003: 58(4): 322-327.

37. Cerveri I, Cazzoletti L, Corsico A, Marcon A, Niniano R, Grosso A, Ronzoni V, Accordini S, Janson C, Pin I, Siroux V, de Marco R. The Impact of Cigarette Smoking on Asthma: A Population-Based International Cohort Study. *Int Arch Allergy Immunol* 2012: 158: 175-183.

38. Harmsen L, Thomsen SF, Ingebrigtsen T, Steffensen IE, Skadhauge LR, Kyvik KO, Backer V. Chronic mucus hypersecretion: prevalence and risk factors in younger individuals. *Int J Tuber Lung Dis* 2010: 14(8): 1052-1058.

39. Thomson N, Chaudhuri R, Messow CM, Spears M, MacNee W, Connell M, Murchison JT, Sproule M, McSharry C. Chronic cough and sputum production are associated with worse clinical outcomes in stable asthma. *Respir Med* 2013: 107(10): 1501-1508.

40. Martinez CH, Kim V, Chen Y, Kazerooni EA, Murray S, Criner GJ, Curtis JL, Regan EA, Wan E, Hersh CP, Silverman EK, Crapo JD, Martinez FJ, Han MK, the CI. The clinical impact of non-obstructive chronic bronchitis in current and former smokers. *Respir Med* 2014: 108(3): 491-499.

41. Eisner MD, Iribarren C. The influence of cigarette smoking on adult asthma outcomes. *Nicotine Tob Res* 2007: 9(1): 53 - 56.

42. Dransfield MT, Kunisaki KM, Strand MJ, Anzueto A, Bhatt SP, Bowler RP, Criner GJ, Curtis JL, Hanania NA, Nath H, Putcha N, Roark SE, Wan ES, Washko GR, Wells JM, Wendt CH, Make BJ. Acute Exacerbations and Lung Function Loss in Smokers With and Without COPD. *Am J Resir Crit Care Med* 2016: Aug 24. [Epub ahead of print].

43. Bowler RP, Kim V, Regan E, Williams AAA, Santorico SA, Make BJ, Lynch DA, Hokanson JE, Washko GR, Bercz P, Soler X, Marchetti N, Criner GJ, Ramsdell J, Han MK, Demeo D, Anzueto A, Comellas A, Crapo JD, Dransfield M, Wells JM, Hersh CP, MacIntyre N, Martinez F, Nath HP, Niewoehner D, Sciurba F, Sharafkhaneh A, Silverman EK, van Beek EJR, Wilson C, Wendt C, Wise RA. Prediction of Acute Respiratory Disease in Current and Former Smokers With and Without COPD. *Chest* 2014: 146(4): 941-950.

44. Murphy VE, Clifton VL, Gibson PG. The effect of cigarette smoking on asthma control during exacerbations in pregnant women. *Thorax* 2010: 65:: 739-744.

45. Kauppi P, Kupiainen H, Lindqvist A, Haahtela T, Laitinen T. Long-term smoking increases the need for acute care among asthma patients: a case control study. *BMC Pulm Med* 2014: 14: 119-119.

46. Thomson NC, Chaudhuri R, Spears M, Messow C-M, MacNee W, Connell M, Murchison JT, Sproule M, McSharry C. Poor symptom control is associated with reduced CT scan segmental airway lumen area in smokers with asthma. *Chest* 2015: 147(3): 735-744.

47. Bhatt SP, Soler X, Wang X, Murray S, Anzueto AR, Beaty TH, Boriek AM, Casaburi R, Criner GJ, Diaz AA, Dransfield MT, Curran-Everett D, Galbán CJ, Hoffman EA, Hogg JC, Kazerooni EA, Kim V, Kinney GL, Lagstein A, Lynch DA, Make BJ, Martinez FJ, Ramsdell JW, Reddy R, Ross BD, Rossiter HB, Steiner RM, Strand MJ, van Beek EJR, Wan ES, Washko GR, Wells JM, Wendt CH, Wise RA, Silverman EK, Crapo JD, Bowler RP, Han MK. Association between Functional Small Airway Disease and FEV1 Decline in Chronic Obstructive Pulmonary Disease. *Am J Resir Crit Care Med* 2016: 194(2): 178-184.

48. Dilektasli AG, Porszasz J, Casaburi R, Stringer WW, Bhatt SP, Pak Y, Rossiter HB, Washko G, Castaldi PJ, Estepar RSJ, Hansen JE. A Novel Spirometric Measure Identifies Mild COPD Unidentified by Standard Criteria. *Chest* 2016: 150(5): 1080-1090.

49. Aanerud M, Carsin A-E, Sunyer J, Dratva J, Gislason T, Jarvis D, deMarco R, Raherison C, Wjst M, Dharmage SC, Svanes C. Interaction between asthma and smoking increases the risk of adult airway obstruction. *Eur Respir J* 2015: 45(3): 635-643.

50. Perret JL, Dharmage SC, Matheson MC, Johns DP, Gurrin LC, Burgess JA, Marrone J, Markos J, Morrison S, Feather I, Thomas PS, McDonald CF, Giles GG, Hopper JL, Wood-Baker R, Abramson MJ, Walters EH. The Interplay between the Effects of Lifetime Asthma, Smoking, and Atopy on Fixed Airflow Obstruction in Middle Age. *Am J Respir Crit Care Med* 2013: 187(1): 42-48.

51. Hancox RJ, Gray AR, Poulton R, Sears MR. The Effect of Cigarette Smoking on Lung Function in Young Adults with Asthma. *Am J Resp Crit Care Med* 2016: 94(3): 276-284.

52. Thomson NC. Does Age of Onset of Asthma Influence the Effect of Cigarette Smoking on Lung Function? *Am J Resir Crit Care Med* 2016: 194(3): 249-250.

53. Thomson NC. Addressing corticosteroid insensitivity in adults with asthma. *Expert Rev Respir Med* 2016: 10(2): 137-156.
54. Barnes PJ. Corticosteroid resistance in patients with asthma and chronic obstructive pulmonary disease. *J Allergy Clin Immunol* 2013: 131: 636-645.
55. Heijink I, van Oosterhout A, Kliphuis N, Jonker M, Hoffmann R, Telenga E, Klooster K, Slebos D-J, ten Hacken N, Postma D, van den Berge M. Oxidant-induced corticosteroid unresponsiveness in human bronchial epithelial cells. *Thorax* 2013: 69(1): 5-13.
56. Chalmers GW, Macleod KJ, Little SA, Thomson LJ, McSharry CP, Thomson NC. Influence of cigarette smoking on inhaled corticosteroid treatment in mild asthma. *Thorax* 2002: 57(3): 226-230.
57. Tomlinson JEM, McMahon AD, Chaudhuri R, Thompson JM, Wood SF, Thomson NC. Efficacy of low and high dose inhaled corticosteroid in smokers versus non-smokers with mild asthma. *Thorax* 2005: 60(4): 282-287.
58. Chaudhuri R, Livingston E, McMahon AD, Thomson L, Borland W, Thomson NC. Cigarette smoking impairs the therapeutic response to oral corticosteroids in chronic asthma. *Am J Respir Crit Care Med* 2003: 168(11): 1308-1311.
59. Livingston E, Thomson N, Chalmers G. Impact of smoking on asthma therapy : a critical review of clinical evidence. *Drugs* 2005: 65(11): 1521-1536.
60. Telenga E, Kerstjens H, ten Hacken N, Postma D, van den Berge M. Inflammation and corticosteroid responsiveness in ex-, current- and never-smoking asthmatics. *BMC Pulm Med* 2013: 13(1): 58.
61. Pedersen SE, Bateman ED, Bousquet J, Busse WW, Yoxall S, Clark TJ. Determinants of response to fluticasone propionate and salmeterol/fluticasone propionate combination in the Gaining Optimal Asthma control study. *J Allergy Clin Immunol* 2007: 120(5): 1036-1042.
62. Dijkstra A, Vonk JM, Jongepier H, Koppelman GH, Schouten JP, ten Hacken NHT, Timens W, Postma DS. Lung function decline in asthma: association with inhaled corticosteroids, smoking and sex. *Thorax* 2006: 61(2): 105-110.

63. Lange P, Scharling H, Ulrik CS, Vestbo J. Inhaled corticosteroids and decline of lung function in community residents with asthma. *Thorax* 2006: 61(2): 100-104.

64. O'Byrne PM, Lamm CJ, Busse WW, Tan WC, Pedersen Sr. The Effects of Inhaled Budesonide on Lung Function in Smokers and Nonsmokers With Mild Persistent Asthma. *Chest* 2009: 136(6): 1514-1520.

65. Mannino DM, Davis KJ, DiSantostefano RL. Chronic respiratory disease, comorbid cardiovascular disease and mortality in a representative adult US cohort. *Respirology* 2013: 18(7): 1083-1088.

66. Oelsner EC, Hoffman EA, Folsom AR, Carr JJ, Enright PL, Kawut SM, Kronmal R, Lederer D, Lima JAC, Lovasi GS, Shea S, Barr RG. Association Between Emphysema-like Lung on Cardiac Computed Tomography and Mortality in Persons Without Airflow ObstructionA Cohort StudyEmphysema-like Lung on CT and All-Cause Mortality. *Annals of internal medicine* 2014: 161(12): 863-873.

67. Ilmarinen P, Tuomisto LE, Niemelä O, Danielsson J, Haanpää J, Kankaanranta T, Kankaanranta H. Comorbidities and elevated IL-6 associate with negative outcome in adult-onset asthma. *Eur Respir J* 2016: 48: 1052-1062.

68. Savage JH, Matsui EC, McCormack M, Litonjua AA, Wood RA, Keet CA. The association between asthma and allergic disease and mortality: 30-year follow-up study. *J Allergy Clin Immunol* 2014: 133(5): 1484-1487.

69. Boulet L, FitzGerald J, McIvor R, Zimmerman S, KR C. Influence of current or former smoking on asthma management and control. *Can Respir J* 2008: 15 (5): 275-279.

70. Westerhof GA, de Groot JC, Amelink M, de Nijs SB, ten Brinke A, Weersink EJ, Bel EH. Predictors of frequent exacerbations in (ex)smoking and never smoking adults with severe asthma. *Respir Med* 2016 118: 122-127

71. Stampfli MR, Anderson GP. How cigarette smoke skews immune responses to promote infection, lung disease and cancer. *Nat Rev Immunol* 2009: 9(5): 377-384.

72. Kuschner W, D'Alessandro A, Wong H, Blanc P. Dose-dependent cigarette smoking-related inflammatory responses in health adults. *Eur Respir J* 1996: 9: 1989-1944.

73. Amin K, Ekberg-Jansson A, Löfdah CG, Venge P. Relationship between inflammatory cells and structural changes in the lungs of asymptomatic and never smokers: a biopsy study. *Thorax* 2003: 58(2): 135-142.
74. Soltani A, Ewe YP, Lim ZS, Sohal SS, Reid D, Weston S, Wood-Baker R, Walters EH. Mast cells in COPD airways: relationship to bronchodilator responsiveness and angiogenesis. *Eur Respir J* 2012: 39(6): 1361-1367.
75. Berger KI, Pradhan DR, Goldring RM, Oppenheimer BW, Rom WN, Segal LN. Distal airway dysfunction identifies pulmonary inflammation in asymptomatic smokers. *ERJ Open Research* 2016: 2(4): 00066-02016.
76. Niewoehner DE, Kleinerman J, Rice DB. Pathologic Changes in the Peripheral Airways of Young Cigarette Smokers. *N Eng J Med* 1974: 291(15): 755-758.
77. Demarche S, Schleich F, Henket M, Paulus V, Van Hees T, Louis R. Detailed analysis of sputum and systemic inflammation in asthma phenotypes: are paucigranulocytic asthmatics really non-inflammatory? *BMC Pulm Med* 2016: 16(1): 1-13.
78. McSharry C, McKay I, Chaudhuri R, Livingston E, Fraser I, Thomson N. Short and long-term effects of cigarette smoking independently influence exhaled nitric oxide concentration in asthma. *J Allergy Clin Immunol* 2005: 116(1): 88-93.
79. Broekema M, ten Hacken NHT, Volbeda F, Lodewijk ME, Hylkema MN, Postma DS, Timens W. Airway Epithelial Changes in Smokers but Not in Ex-Smokers with Asthma. *Am J Respir Crit Care Med* 2009: 180(12): 1170-1178.
80. Ravensberg AJ, Slats AM, van Wetering S, Janssen K, van Wijngaarden S, de Jeu R, Rabe KF, Sterk PJ, Hiemstra PS. CD8+ T cells characterize early smoking-related airway pathology in patients with asthma. *Respir Med* 2013: 107(7): 959-966.
81. Price D, Kaplan A, Jones R, Freeman D, Burden A, Gould S, von Ziegenweidt J, Ali M, King C, Thomas M. Long-acting muscarinic antagonist use in adults with asthma: real-life prescribing and outcomes of add-on therapy with tiotropium bromide. *J Asthma Allergy* 2015: 8: 1-13.

82. St-Laurent J, Bergeron C, Pagé N, Couture C, Laviolette M, Boulet L. Influence of smoking on airway inflammation and remodelling in asthma. *Clin Exp Allergy* 2008: 38(10): 1582-1589.

83. Wenzel SE. Asthma phenotypes: the evolution from clinical to molecular approaches. *Nat Med* 2012: 18(5): 716-725.

84. Tuomisto LE, Ilmarinen P, Niemelä O, Haanpää J, Kankaanranta T, Kankaanranta H. A 12-year prognosis of adult-onset asthma:Seinäjoki Adult Asthma Study. *Respir Med* 2016 117: 223-229.

85. Westerhof GA, Vollema EM, Weersink EJ, Reinartz SM, de Nijs SB, Bel EH. Predictors for the development of progressive severity in new-onset adult asthma. *J Allergy Clin Immunol* 2014: 134(5): 1051-1056.e1052.

86. Tan DJ, Walters EH, Perret JL, Burgess JA, Johns DP, Lowe AJ, Lodge CJ, Hayati Rezvan P, Simpson JA, Morrison S, Thompson BR, Thomas PS, Feather I, Giles GG, Hopper JL, Abramson MJ, Matheson MC, Dharmage SC. Clinical and functional differences between early-onset and late-onset adult asthma: a population-based Tasmanian Longitudinal Health Study. *Thorax* 2016: 71 (11): 981-987.

87. Tan DJ, Walters EH, Perret JL, Lodge CJ, Lowe AJ, Matheson MC, Dharmage SC. Age-of-asthma onset as a determinant of different asthma phenotypes in adults: a systematic review and meta-analysis of the literature. *Exp Rev Respir Med* 2015: 9(1): 109-123.

88. Tommola M, Ilmarinen P, Tuomisto LE, Haanpää J, Kankaanranta T, Niemelä O, Kankaanranta H. The effect of smoking on lung function: a clinical study of adult-onset asthma. *Eur Respir J* 2016: 48(5): 1298-1306.

89. Chaudhuri R, McSharry C, Heaney LG, Niven R, Brightling CE, Menzies-Gow AN, Bucknall C, Mansur AH, Lee W, Shepherd M, Spears M, Cowan DC, Husi H, Thomson NC. Effects of older age and age of asthma onset on clinical and inflammatory variables in severe refractory asthma. *Respir Med* 2016: 118: 46-52.

90. Meghji Z, Dua B, Watson RM, Gauvreau GM, O'Byrne PM. Allergen inhalation challenge in smoking compared with non-smoking asthmatic subjects. *Clin Exp Allergy* 2011: 41: 1084-1090.

91. Cahn A, Boyce M, Mistry S, Musani N, Rambaran C, Storey J, Ventresca P, Michel O. Randomised trial of allergen-induced asthmatic response in smokers and non-smokers: effects of inhaled corticosteroids. *Clin Exp Allergy* 2015: 45(10): 1531-1541.
92. Chang JE, Ding D, Martin-Lazaro J, White A, Stevenson DD. Smoking, environmental tobacco smoke, and aspirin-exacerbated respiratory disease. *Ann Allergy Asthma Immunol* 2012: 108(1): 14-19.
93. Eriksson J, Ekerljung L, Bossios A, Bjerg A, Wennergren G, Rönmark E, Torén K, Lötvall J, Lundbäck B. Aspirin-intolerant asthma in the population: prevalence and important determinants. *Clin Exp Allergy* 2015: 45(1): 211-219.
94. Gibeon D, Batuwita K, Osmond M, Heaney LG, Brightling CE, Niven R, Mansur A, Chaudhuri R, Bucknall CE, Rowe A, Guo Y, Bhavsar PK, Chung KF, Menzies-Gow A. Obesity-associated severe asthma represents a distinct clinical phenotype: Analysis of the British Thoracic Society difficult asthma registry patient cohort according to BMI. *Chest* 2013: 143(2): 406-414.
95. Holguin F, Bleecker ER, Busse WW, Calhoun WJ, Castro M, Erzurum SC, Fitzpatrick AM, Gaston B, Israel E, Jarjour NN, Moore WC, Peters SP, Yonas M, Teague WG, Wenzel SE. Obesity and asthma, an association modified by age of asthma onset. *J Allergy Clin Immunol* 2011: 127(6): 1486-1493.e1482.
96. Yawn BP, Rank MA, Bertram SL, Wollan PC. Obesity, low levels of physical activity and smoking present opportunities for primary care asthma interventions: an analysis of baseline data from The Asthma Tools Study. *NPJ Prim Care Respir Med* 2015: 25: 15058.
97. Strine TW, Balluz LS, Ford ES. The Associations between Smoking, Physical Inactivity, Obesity, and Asthma Severity in the General US Population. *J Asthma* 2007: 44(8): 651-658.
98. Gibson PG. Obesity and Asthma. *Annals ATS* 2013: 10(Supplement): S138-S142.
99. Lemière C, Boulet L-P, Chaboillez S, Forget A, Chiry S, Villeneuve H, Prince P, Maghni K, Kennedy WA, Blais L. Work-exacerbated asthma and occupational asthma: Do they really differ? *J Allergy Clin Immunol* 2013: 131(3): 704-710.e703.

100. Maestrelli P, Schlünssen V, Mason P, Sigsgaard T. Contribution of host factors and workplace exposure to the outcome of occupational asthma. *Eur Respir Rev* 2012: 21(124): 88-96.
101. Eriksson J, Ekerljung L, Sundblad BM, Lötvall J, Torén K, Rönmark E, Larsson K, Lundbäck B. Cigarette smoking is associated with high prevalence of chronic rhinitis and low prevalence of allergic rhinitis in men. *Allergy* 2013: 68(3): 347-354.
102. Kimura H, Konno S, Nakamaru Y, Makita H, Taniguchi N, Shimizu K, Suzuki DM, Ono DJ, Ohta DS, Izuhara PK, Nishimura PM, investigators ftH-C. Sinus Computed Tomographic Findings in Adult Smoking and Non-Smoking Asthmatics: Analysis of Clinical Indices and Biomarkers. *Annals ATS* 2016 in press: 0(ja): null.
103. Taylor G, McNeill A, Girling A, Farley A, Lindson-Hawley N, Aveyard P. Change in mental health after smoking cessation: systematic review and meta-analysis. *BMJ* 2014: 348: g1151.
104. Thomson NC. Novel approaches to the management of noneosinophilic asthma. *Therap Adv Respir Dis* 2016: 10(3): 211-234.
105. Chaudhuri R, Livingston E, McMahon AD, Lafferty J, Fraser I, Spears M, McSharry CP, Thomson NC. Effects of Smoking Cessation on Lung Function and Airway Inflammation in Smokers with Asthma. *Am J Respir Crit Care Med* 2006: 174(2): 127-133.
106. Livingston E, Chaudhuri R, McMahon AD, Fraser I, McSharry CP, Thomson NC. Systemic sensitivity to corticosteroids in smokers with asthma. *Eur Respir J* 2007: 29(1): 64-71.
107. Westergaard CG, Porsbjerg C, Backer V. The effect of smoking cessation on airway inflammation in young asthma patients. *Clin Exp Allergy* 2014: 44(3): 353-361.
108. McLeish AC, Zvolensky MJ. Asthma and Cigarette Smoking: A Review of the Empirical Literature. *J Asthma* 2010: 47(4): 345-361.
109. Vozoris NT, Stanbrook MB. Smoking prevalence, behaviours, and cessation among individuals with COPD or asthma. *Respir Med* 2011: 105(3): 477-484.
110. Eisner M, Yelin E, Katz P, Shoiboski S, Henke J, Blanc P. Predictors of cigarette smoking and smoking cessation among adults with asthma. *Am J Public Health* 2000: 90(8): 1307-1311.

111. McLeish AC, Farris SG, Johnson AL, Bernstein JA, Zvolensky MJ. Evaluation of smokers with and without asthma in terms of smoking cessation outcome, nicotine withdrawal symptoms, and craving: Findings from a self-guided quit attempt. *Addict Behav* 2016: 63: 149-154.

112. Melzer AC, Feemster LC, Crothers K, Carson SS, Gillespie SE, Henderson AG, Krishnan JA, Lindenauer PK, McBurnie MA, Mularski RA, Naureckas ET, Pickard AS, Au DH. Respiratory and Bronchitic Symptoms Predict Intention to Quit Smoking among Current Smokers with, and at Risk for, Chronic Obstructive Pulmonary Disease. *Annals ATS* 2016: 13(9): 1490-1496.

113. Roche N, Postma DS, Colice G, Burden A, Guilbert TW, Israel E, Martin RJ, van Aalderen WMC, Grigg J, Hillyer EV, von Ziegenweidt J, Price DB. Differential Effects of Inhaled Corticosteroids in Smokers/Ex-Smokers and Nonsmokers with Asthma. *Am J Resp Crit Care Med* 2015: 191(8): 960-964.

114. Pilcher J, Patel M, Reddel HK, Pritchard A, Black P, Shaw D, Holt S, Weatherall M, Beasley R. Effect of smoking status on the efficacy of the SMART regimen in high risk asthma. *Respirology* 2016: 21(5): 858-866.

115. Clearie KL, McKinlay L, Williamson PA, Lipworth BJ. Fluticasone/Salmeterol Combination Confers Benefits in People With Asthma Who Smoke. *Chest* 2012: 141(2): 330-338.

116. Kerstjens HAM, Engel M, Dahl R, Paggiaro P, Beck E, Vandewalker M, Sigmund R, Seibold W, Moroni-Zentgraf P, Bateman ED. Tiotropium in Asthma Poorly Controlled with Standard Combination Therapy. *N Engl J Med* 2012: 367(13): 1198-1207.

117. Spears M, Donnelly I, Jolly L, Brannigan M, Ito K, McSharry C, Lafferty J, Chaudhuri R, Braganza G, Adcock IM, Barnes PJ, Wood S, Thomson NC. Effect of low-dose theophylline plus beclometasone on lung function in smokers with asthma: a pilot study. *Eur Respir J* 2009: 33(5): 1010-1017.

118. Price D, Popov TA, Bjermer L, Lu S, Petrovic R, Vandormael K, Mehta A, Strus JD, Polos PG, Philip G. Effect of montelukast for treatment of asthma in cigarette smokers. *J Allergy Clin Immunol* 2013: 131(3): 763-771.

119. Rodriguez-Roisin R, Han MK, Vestbo J, Wedzicha JA, Woodruff PG, Martinez FJ. Chronic Respiratory Symptoms with Normal Spirometry: A Reliable Clinical Entity? *Am J Resir Crit Care Med* 2017: 195(1): 17-22.
120. Mannino DM. Does Undiagnosed Chronic Obstructive Pulmonary Disease Matter? *Am J Resir Crit Care Med* 2016: 194(3): 250-252.
121. Pinto LM, Gupta N, Tan W, Li PZ, Benedetti A, Jones PW, Bourbeau J. Derivation of normative data for the COPD assessment test (CAT). *Respir Res* 2014: 15(1): 68-68.

Table 1. Methodological issues that influence the interpretation of studies of adults with asthma and smoking-induced airway disease without spirometric evidence of COPD

Demographic information: • 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. • Gender and race of participants may not be representative of the general population.
***Diagnosis of chronic airway disease*:** • 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 a symptomatic current and former smoker 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 (FEV_1/FVC ratio <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.
Smoking status: • Combined data from current smokers and former smokers may obscure differences in outcomes in one or another smoking group. • Findings in studies with an entry criteria of a smoking history of $\geq$10 pack-years, such as COPDGene and SPIROMICS may not be relevant to those with a less intense history of exposure to tobacco smoke. • Factors relating to smoking behavior, 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.

Assessment of clinical outcomes:

- Measures of current symptoms and quality of life in smokers with asthma, such as the Asthma Control Test (ACT), Asthma Control Questionnaire (ACQ) and Asthma Quality of Life (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 COPD Assessment Test (CAT) and St George's Respiratory Questionnaire score (SGQS). For example, the SGQS 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 former smokers [121].
- Definition of chronic bronchitis varies between studies and in some, is based on components of the SGQS.
- Definition of severe exacerbation in asthma, which is based on the use of high dose systemic corticosteroid for 3 days or longer, 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.

Generalizability of findings:

- The selection process and criteria used to recruit participants to studies of airway disease in individuals without COPD may not be generalizable to the general population, although baseline demographic and clinical variables in the COPDGene study showed some similarities to those in the NHANES study in the general population [16].

Table 2. Summary of the effects of smoking status on clinical outcomes in asthma and symptomatic smokers without spirometric COPD*

Outcome	Asthma with a smoking history and without spirometric COPD	Smoking-induced airway disease without spirometric COPD (no history of asthma)
	Current smokers with asthma compared with never smokers with asthma	Current and former smokers compared with 'healthy' never smokers
Respiratory symptoms		
Wheeze, breathlessness	Increased	Increased
Exercise tolerance	Decreased	Decreased
Chronic bronchitis	Increased	Increased
Quality of life	Decreased or similar	Decreased
Exacerbations	Increased or similar	Increased
Health care utilization	Increased	Increased
Lung function		
Baseline spirometry	Decreased	Decreased
Small airway dysfunction	Increased	Increased
Decline in FEV_1	Increased or similar	Similar
Therapeutic response to inhaled corticosteroids		
Short to medium term treatment	Decreased	-
Long-term treatment	Decreased or similar	-

Smoking-related comorbidities	Increased	Increased
All-cause mortality	Increased	Increased

*Refer to the main text for information on the published studies used to summarize the effects of smoking status on clinical outcomes in asthma and symptomatic smokers without spirometric COPD. Symbol: -, not known

FIGURE LEGEND

Figure 1: Classification of chronic airway diseases in symptomatic current and former smokers without spirometric airflow obstruction (FEV_1/FVC ratio <0.7) due to smoking-induced airway disease without a history of asthma, asthma-induced airway disease or an overlap of both diseases.

Symbol '?': It is not known whether current and former smokers with smoking-induced airway disease without evidence of COPD or a history of asthma have clinical evidence of corticosteroid insensitivity.