

Asthma and Chronic Obstructive Pulmonary Disease Similarities and Differences

Dirkje S. Postma, MD, PhD^{a,*}, Helen K. Reddel, MD, PhD^b,
Nick H.T. ten Hacken, MD, PhD^a,
Maarten van den Berge, MD, PhD^a

KEYWORDS

• Asthma • COPD • Inflammation • Remodeling • Overlap phenotype

KEY POINTS

- Asthma in childhood and chronic obstructive pulmonary disease (COPD) in smokers are easily distinguishable disease entities.
- There exist overlap phenotypes of asthma and COPD, such as asthma with neutrophilia and/or without bronchodilator response, and COPD with eosinophilia and/or some bronchodilator response.
- Differences in physiology, symptoms, inflammation, and remodeling between asthma and COPD are obscured by smoking. Hence asthma in a smoker and COPD appear similar (ie, they show phenotypic mimicry).
- A key component of overlap between asthma and COPD is the effect of aging.
- Some of the mechanisms driving airway obstruction and hyperresponsiveness are similar in asthma and COPD, and some are different.
- There is an unmet need to assess optimal treatment effects and safety in subphenotypes of asthma and COPD; phenotypes that have so far been excluded from pharmacologic studies.

INTRODUCTION

Asthma and chronic obstructive pulmonary disease (COPD) are both highly prevalent diseases worldwide. This issue of *Clinics in Chest Medicine* discusses different aspects of COPD, but in addition, the present article on overlap and differential signs and symptoms with asthma has been included. This is appropriate because it is often difficult to differentiate asthma from COPD, particularly at older ages. At that time in life, patients with asthma may have developed persistent airway obstruction, a characteristic that is a prerequisite for diagnosis of COPD according to the GOLD (Global Initiative for Chronic Obstructive Lung Disease) criteria.¹ This feature would not be

a problem if asthma and COPD had the same clinical prognosis and response to pharmacologic treatment, and required similar management of the disease in clinical practice. However, this is often not the case.²

Asthma and COPD have been defined over the years in many different ways, and the heterogeneity in definitions in the literature contributes to the difficulty of evaluating evidence about the extent to which they overlap. The problem is confounded by the necessary reliance in many epidemiologic studies on self-reported diagnosis of asthma and COPD, and because, in clinical practice, these diagnoses are often assigned without lung function testing having been performed.

^a University of Groningen, Department of Pulmonology, GRIAC research institute, University Medical Center Groningen, Hanzeplein 1, 9713 GZ Groningen, The Netherlands; ^b Department of Medicine, Woolcock Institute of Medical Research, University of Sydney, 431 Gleve Point Road, Gleve NSW 2037, Australia

* Corresponding author.

E-mail address: d.s.postma@umcg.nl

Research on the clinical characterization, pathophysiology, prognosis, and management of asthma and COPD commenced with investigation of the extremes of the two conditions, namely:

1. Atopic individuals with asthma, never smokers or ex-smokers with less than 10 pack-year exposure, with significant bronchodilator reversibility at the time of study. These populations usually had an average age around 35 years.
2. Current or ex-smokers with fixed airway obstruction, generally with an age greater than 55 years.

This approach in research gave new insights into how best to treat the extreme phenotypes of asthma and COPD. However, many patients with asthma were excluded from these studies, particularly when they were smokers and showed no bronchodilator response at screening. Also excluded were many patients with COPD, especially when they showed an important reduction in airway obstruction after inhaling a bronchodilator.³ As a result, such studies have not provided good insight into the management of asthma and COPD in daily practice, because it has been recognized that many patients do not fulfill the criteria of either asthma or COPD and show a mixture of both: the so-called overlap phenotype.² In the past, this concept was dismissed as representing the Dutch hypothesis,⁴ but in more recent years the presence of overlap phenotypes has been widely accepted.⁵⁻⁷

When comparing asthma with COPD, it is important to realize that age has to be taken into account in every setting, because age induces changes in inflammation, immunologic responses, and mechanical properties of the lung.⁸ Likewise, current smoking must be taken into account, because smoking induces inflammatory and remodeling changes in the lung and affects treatment response.^{9,10} Hence it is not useful to compare young nonsmoking individuals with asthma and older smoking patients with COPD in their (dis)similarities in inflammatory cells and cytokines and in treatment response, because this is driven in both situations by differences in age and smoking status. Many studies in the past have overlooked the effects of both age and smoking and are therefore hampered in their interpretation as to whether asthma and COPD have comparable or distinct underlying mechanisms and treatment approaches.

This article discusses current knowledge on clinical features, inflammation and remodeling, genetics, and therapeutic response in asthma and COPD and discusses the overlap phenotypes.

DEFINITIONS

Asthma is currently defined as a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread, but variable, airflow obstruction within the lung that is often reversible either spontaneously or with treatment.^{11,12} In contrast, COPD has for decades been defined as a preventable and treatable disease characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. The following was added to this definition: "Exacerbations and comorbidities contribute to the overall severity in individual patients."¹ This definition of COPD is so vague that it fits many types of patients with distinct clinical characteristics, prognosis, and treatment response.¹² One of the important aspects here is that the airway obstruction in asthma, although often reversible, may be progressive in nature in a subset of patients with asthma,¹³ leading to an overlap phenotype with COPD.

The definitions of asthma and COPD have been made to have a high sensitivity, but apparently their specificity is low. The problem is well acknowledged nowadays and recent studies suggest that 13% to 20% of patients with COPD have an overlap phenotype with asthma.¹⁴ These patients have respiratory symptoms, have persistent airway obstruction, but some reversibility is still present after inhaling a bronchodilator and inflammatory markers are similar to those in asthma. Conversely, even 20% of patients with asthma at older ages have been given a diagnosis of COPD.¹⁵

CLINICAL FEATURES

Symptoms

It is difficult to differentiate asthma and COPD based on respiratory symptoms.¹⁶ In the extremes with a sudden attack of wheeze and dyspnea after allergen exposure, it is clear that this is compatible with asthma. However, in the chronic forms, symptoms are many times more diffuse and patients with asthma may have symptoms of chronic cough and/or sputum production^{17,18} formerly thought to imply COPD, especially when irreversible airway obstruction has developed.¹⁹ In contrast, patients with COPD may have wheeze, a symptom formerly attributed solely to asthma.²⁰

Moreover, an increase in the number of cigarettes smoked is associated with development of wheeze in COPD.²⁰ Thus, symptoms alone cannot rule out one or the other condition. Chronic cough and sputum production are associated with worse outcome in COPD,²¹ but how this affects asthma has not been evaluated yet. Interestingly, atopic patients with COPD more frequently develop symptoms of cough and sputum production over time than nonatopic patients.²²

Airway Obstruction and Reversibility

Bronchodilator response has been assumed to be a key differential parameter between asthma and COPD. However, bronchodilator response is frequently observed in patients with COPD in clinical practice, as well as in more recently designed clinical trials and in observational studies in patients with COPD.²³ Up to 50% of patients with COPD in the Understanding Potential Long-term Impacts on Function with Tiotropium (UPLIFT) study showed some bronchodilator response.²⁴ In another study, patients with COPD without a history of asthma showed a prevalence of bronchodilator response of 44%, with bronchodilator response being more frequently present in more severe disease.²⁵ This pattern is compatible with findings in the Evaluation of COPD longitudinally to Identify Surrogate Endpoints (ECLIPSE) cohort investigating 1831 patients with COPD tested before and after salbutamol inhalation.²⁶ In this study, it was concluded that the magnitude of postsalbutamol forced expiratory volume in 1 second (FEV₁) change is comparable between patients with COPD and smoking controls, but is lower with more severe airway obstruction and in the presence of emphysema.²⁶ Bronchodilator response status varied temporally in the latter study, but patients with consistent bronchodilator response ($n = 227$) did not differ in mortality, hospitalization, or exacerbation frequency from those with a lack of bronchodilator response, after adjustment for differences in baseline FEV₁.²⁶ One study suggested that the bronchodilator response in COPD is associated with eosinophilia, whereas absence of this response is associated with neutrophilia, possibly also explaining why some studies suggest a better inhaled corticosteroid (ICS) response in patients with reversible COPD.²⁷ In addition, it is debatable whether significant airway obstruction needs to be a prerequisite to define COPD, because emphysema may exist even without the presence of airway obstruction.²⁸

When investigating a group of 228 patients with asthma followed for 26 years, it was shown that asthmatic patients may develop irreversible airway

obstruction.¹⁹ Although all of this cohort had reversible airway obstruction at baseline, at follow-up, 16% had developed irreversible airway obstruction, 23% had reduced carbon monoxide transfer coefficient, and 5% had both. Persistent airway obstruction was predicted by lower lung function, lower bronchodilator response, and milder hyperresponsiveness at baseline and was accompanied by the development of symptoms of chronic cough and sputum production. Patients with asthma with low transfer factor at follow-up had a higher total lung capacity and residual volume at baseline, but in multiple regression analysis this was no longer significant when pack-years of smoking were entered; higher pack-years significantly contributed to a lower transfer factor, but smoking was not independently associated with persistent airway obstruction. These observations may suggest that subtle signs of future features of COPD may already be present in early asthma. Another important message of this study is that persistent airway obstruction and reduced transfer factor are both signs of COPD, but they are distinct entities in asthma in terms of symptoms and causes. This message may have consequences for treatment approaches in asthma and the overlap phenotypes.

Small airway obstruction has long been recognized as one of the underlying mechanisms of COPD. In the last decades, it has become evident that small airway obstruction also contributes to the clinical presentation of asthma, although it is not clear yet whether this is only present in severe asthma or in mild asthma as well.^{29–31} This gap in knowledge is predominantly caused by the lack of accurate and reproducible measures of small airway function suitable for general use. Signs of small airway dysfunction can already be present even 1 month after birth and they constitute a predictor of subsequent development of asthma.³² However, it remains to be seen whether small airway changes in asthma and COPD originate from similar underlying mechanisms. The difference between inspiratory and expiratory X5, a measure of small airway obstruction, is larger in patients with COPD than in patients with asthma despite similar degrees of large airway obstruction as assessed with FEV₁.³³ Moreover, patients with COPD have greater ventilation heterogeneity than patients with asthma, as measured with slope, acinar component of ventilation heterogeneity (S_{acin}), a measure of the smallest airways where gas exchange takes place. In contrast, people with asthma predominantly have abnormalities in S_{cond} , a measure of the more proximal small conducting airways that are located before the acinus.³⁴ An additional contrast is that treatment

with a bronchodilator induces an improvement in S_{cond} in patients with asthma, whereas it improves S_{acin} in patients with COPD^{35,36} Galban and colleagues³⁷ identified functional small airway disease from computed tomography (CT) imaging across the spectrum of COPD severity and provided suggestive evidence that small airway narrowing and obliteration precede the onset of emphysema in COPD. Together these findings may suggest that the most peripherally located small airway disease contributes to COPD, and that the more proximally located contributes to asthma.

Atopy

Most children with asthma, and a large proportion of adult patients with asthma, are atopic.³⁸ It has long been overlooked that patients with COPD can be atopic as well but it is unclear whether this has clinical implications. A European study on severe asthma identified features of severe asthma that were distinct from milder forms of asthma.³⁹ It showed that patients with severe asthma were less frequently atopic and more frequently lacked a bronchodilator response than patients with milder disease.³⁹ In addition, patients with asthma with atopy respond better to ICS treatment than those without atopy.³⁹ Therefore, recommendations for the treatment of allergy are also included in the treatment guidelines of asthma. Recent studies showed that atopy can be present in patients with COPD as well and that the presence of allergy is a risk factor for future development of COPD.^{40,41} Around 18% of patients with COPD were shown to be atopic in the European Respiratory Society study on Chronic Obstructive Pulmonary Disease (EURO-SCOP) study,²² and logistic regression provided evidence that atopic patients were more likely male, younger, and with a higher body mass index. Of importance, the presence of atopy was not associated with more severe airway obstruction.²² Atopic patients with COPD more frequently develop symptoms of cough and sputum production when not using ICS treatment.²² These symptoms were more likely to improve after ICS treatment of 2 years in atopic than in nonatopic patients with COPD. This finding is compatible with data from 1978 showing that atopic patients with COPD are the ones who benefit most from corticosteroid treatment.⁴²

Airway Hyperresponsiveness

Airway hyperresponsiveness is a risk factor for development both of asthma and of COPD, as well as for a more rapid decline in lung function.⁴³

In general, most patients with asthma express hyperresponsiveness, in contrast with about 60% of patients with COPD, even with mild disease in which the level of FEV₁ does not impinge on the severity of hyperresponsiveness.⁴⁴ However, the drivers of hyperresponsiveness in asthma and COPD, and whether different mechanisms are responsible for this phenomenon, have not been elucidated. There are many physiologic changes that may contribute to hyperresponsiveness: airway luminal diameter, airway wall thickness, smooth muscle mass, vascular engorgement, elastic recoil, airway inflammation, epithelial injury, and neural activity. Short-term treatment with ICS improves hyperresponsiveness in asthma, in conjunction with improvement of eosinophilic inflammation. After long-term ICS treatment, hyperresponsiveness may even disappear in a subset of patients with asthma.^{45,46} In contrast, hyperresponsiveness improves to a smaller extent in COPD, in which it almost never disappears. One study investigating patients with asthma and COPD showed that a higher level of total serum immunoglobulin E predicted improvement in hyperresponsiveness with ICS.⁴⁷ This finding has not been investigated in other studies, but remains an interesting observation because this was present both in asthma and in COPD.⁴⁷ Although a common characteristic, this may be caused by different underlying mechanisms, which have only been studied to a limited extent in COPD. Chanez and colleagues⁴⁸ found that patients with COPD with asthmalike features (ie, eosinophilia and airway hyperresponsiveness) had thicker basement membranes than those without these features. Finkelstein and colleagues⁴⁹ investigated hyperresponsiveness in patients with COPD and showed that the airway wall internal to the smooth muscle layer of the small airways was thickened. A thicker airway wall was associated with more severe hyperresponsiveness. However, smooth muscle mass contributed more to hyperresponsiveness than adventitial or submucosal thickening.^{50,51} This finding is similar with asthma, in which an increase in smooth muscle mass has also been shown to contribute to the presence and severity of hyperresponsiveness.^{52,53} Even within asthma, different mechanisms contribute to severity of hyperresponsiveness. In older patients, this is predicted by air trapping and ventilation heterogeneity in the most distal small airways (S_{acin}), whereas ventilation heterogeneity in the more proximal small airways (S_{cond}) and inflammation predicts the severity of hyperresponsiveness in younger individuals with asthma.⁵⁴ Of interest, exhaled bronchial nitric oxide (NO), a parameter of large airway inflammation (usually related to

eosinophilia) improved by ICS treatment in younger patients with asthma in conjunction with S_{cond} . However, the severity of hyperresponsiveness remaining after 3-month ICS treatment was best predicted by S_{cond} levels only.⁵⁵ It has yet to be established how small airway obstruction affects the severity of hyperresponsiveness in COPD. A recent cross-sectional and longitudinal study in COPD did not assess small airway function directly, but showed that a more severe hyperresponsiveness was associated with higher residual volume, a measure of air trapping related to small airway function, and with airway inflammation reflected by a higher number of neutrophils, macrophages, and lymphocytes in sputum and bronchial biopsies.⁵⁶ Severity of hyperresponsiveness was not associated with eosinophilic inflammation as suggested by Chanez and colleagues,⁴⁸ again suggesting that the mechanisms underlying hyperresponsiveness in asthma and COPD are at least partially different.

The Overlap Phenotype

There is no extensive literature available comparing the overlap phenotype with asthma on one hand and COPD on the other hand.^{6,7,14,57,58} Some reviews have tried to give an overview^{2,59,60} or to develop consensus on how best to define the overlap phenotype.⁶¹ In epidemiologic studies in the United States and United Kingdom, 17% to 19% of patients with obstructive airway disease reported having both asthma and COPD, and these patients accounted for as many as 50% of patients with obstructive airway disease more than 50 years of age.⁷ Thus, patients reporting to have been diagnosed with both asthma and COPD are generally older. However, as indicated earlier, diagnoses in population studies are often not based on lung function testing. When analyzing 175 individuals from a random population sample with objective measures, Weatherall and colleagues⁵⁸ performed a cluster analysis and showed 5 clusters: (1) severe and markedly variable airway obstruction with features of atopic asthma, chronic bronchitis, and emphysema; (2) features of emphysema alone; (3) atopic asthma with eosinophilic airway inflammation; (4) mild airway obstruction without other dominant phenotypic features; and (5) chronic bronchitis in nonsmokers. These findings make the situation even more complex. These investigators identified clusters 2 and 3 as clear emphysema and clear asthma respectively, whereas clusters 1, 4, and 5 represented various other overlapping phenotypes in asthma and COPD. However, Weatherall and colleagues⁵⁸ did not

examine the extent to which patients in these clusters differed with respect to other clinical or physiologic characteristics. In addition, these 5 clusters remain to be confirmed in other studies. Kauppi and colleagues⁶² based an asthma and COPD diagnosis on UK guidelines and American Thoracic Society/European Respiratory Society criteria respectively. In this large group of patients with clinical disease, 1084 had asthma only, 237 COPD only, and 225 the overlap phenotype.⁶² As expected, patients with asthma were younger, more frequently female, and less frequently had a history of smoking.⁶² In addition, 26% of patients with asthma had been smoking for more than 10 years, compared with 72% and 76% of patients with COPD and the overlap phenotype respectively. The overlap group was between the asthma and COPD groups in other characteristics like gender, disease duration, pack-years smoking, lung function parameters, and comorbidities. These findings are compatible with those reported by Gibson and Simpson² in their review (ie, it was present in 64% of patients with the overlap syndrome, intermediate between a prevalence of 100% of patients with asthma and 25% of patients with COPD). Hypertension was highly prevalent as comorbidity with 32% in asthma, 41% in the overlap group, and 45% in patients with COPD, ages being on average 53, 61, and 64 years. However, it is also clear that the prevalence of comorbidities is higher in COPD than in asthma (**Table 1**), either as a result of long-standing smoking in COPD or because of the systemic inflammation present in COPD. In addition, patients with the overlap syndrome are more likely frequent exacerbators (ie, >2 exacerbations per year), have more gas trapping on CT, worse quality of life, more respiratory symptoms, more hospitalizations, and

Table 1
Proportion of patients with comorbidities

| | Asthma (n = 1084) | Overlap (n = 225) | COPD (n = 237) |
|-----------------------------------|----------------------|----------------------|-------------------|
| Hypertension | 32.3 | 41.3 | 44.7 |
| Coronary disease | 7.7 | 19.1 | 25.3 |
| Diabetes | 6.8 | 12.9 | 19.8 |
| Cerebrovascular disease | 3.2 | 7.1 | 10.1 |
| Peripheral vascular disease | 0.6 | 3.6 | 7.2 |

Data from Kauppi P, Kupiainen H, Lindqvist A, et al. Overlap syndrome of asthma and COPD predicts low quality of life. *J Asthma* 2011;48(3):279–85.

consume much more health care resources than pure asthmatics.^{6,7,14,57–62} Moreover, patients with the overlap phenotype are reported to have higher mortalities,⁶³ especially when peripheral blood eosinophilia is present.⁶⁴ Hardin and colleagues¹⁴ additionally found that subjects with both COPD and asthma combined frequently have rhinitis, although it still remains to be established whether or not this reflects underlying atopy. Overall, data show that the overlap syndrome has characteristics between those of asthma and COPD, and is frequently present, irrespective of whether reported by patients or doctors, or objectively characterized.

GENETICS AND ENVIRONMENT

Genetic factors contribute to the development of both asthma and COPD, in conjunction with environmental factors. Many environmental factors contribute to both asthma and COPD and some only to either asthma or COPD alone. **Table 2** shows an overview of these factors as published in a recent review.⁶⁵ More severe airway hyperresponsiveness, lower lung function, maternal smoking during pregnancy, air pollution, and personal cigarette smoking are risk factors for development of both asthma and COPD. One of the features that drive several of these risk factors may be abnormal lung development in utero. It may be that this abnormal lung development, for

instance caused by maternal smoking, drives one of the underlying mechanisms of the abnormal lung response that patients with asthma and COPD express after inhalation of noxious stimuli that all individuals encounter, which then results in abnormal lung function measures, caused by airway inflammation and remodeling superimposed on this abnormal lung development. This mechanism would also explain, at least partially, the overlap syndrome if abnormal lung development in utero is the underlying mechanism of asthma and COPD.

There are additional differences in asthma and COPD caused by differences in the underlying genetic makeup of these two diseases. Genome-wide association studies (GWAS) have shown differential genes to be associated with COPD and asthma.^{65,66} Recent GWAS have identified loci that harbor susceptibility genes for asthma and other pulmonary conditions. Many of the genes at these loci have unknown functions and have not previously been considered biologically plausible candidates for disease pathogenesis. Genes found by GWAS in asthma are *ORMDL3*, *GSMD3*, *IL18R1*, *IL1RL1*, *IL33*, *SMAD3*, *IL2RB*, *DENND1B*, *HLA-Dr/DQ* region, *PDE4D2*, *RAD50-IL13*, *WDR36*, *TLE4*, and *MYB*.⁶⁷ Studies have recently started to investigate the genome for subphenotypes of asthma. Thus, Himes and colleagues⁶⁸ found that the presence of a bronchodilator response is associated with *SPATS2*.

Table 2
Risk factors for asthma and COPD

| | | |
|---------------------|--|------------------------------|
| Host factors | Male sex in childhood, female sex in adulthood | Family history of COPD |
| | (Family) history of asthma | Family history asthma/atopy |
| | Genetic constitution | Genetic constitution |
| | Airway hyperresponsiveness | Airway hyperresponsiveness |
| | Atopy | — |
| | Low lung function | Low lung function |
| | Overweight | — |
| Perinatal factors | Maternal smoking | Maternal smoking |
| | Maternal diet | — |
| | Mode of delivery | — |
| Childhood exposures | Viral respiratory infections | Respiratory tract infections |
| | No breastfeeding | — |
| | Microbial deprivation | Maternal smoking |
| | Environmental tobacco smoke exposure | Indoor air pollution |
| | Air pollution | — |
| Adult exposures | Occupational exposures | Occupational exposures |
| | Cigarette smoking | Cigarette smoking |
| | Outdoor air pollution | Outdoor air pollution |
| | — | Indoor air pollution |
| | — | — |

From Postma DS, Kerkhof M, Boezen HM, et al. Asthma and chronic obstructive pulmonary disease: common genes, common environments? *Am J Respir Crit Care Med* 2011;183(12):1588–94; with permission.

However, this has not been tested in COPD so far. In addition, the level of lung function and its accelerated decline were investigated specifically in asthma.⁶⁹ Unfortunately, the numbers of individuals investigated were too small to find significant genome-wide associations. Nevertheless, this is the way forward to assess whether similar genes are associated with development of a fixed airflow obstruction in asthma and a more severe disease with a higher level of lung function decline in COPD. This research may determine whether similar and/or differential mechanisms are underlying the fixed airflow obstruction in asthma and COPD.

Several genes have been associated with COPD (defined usually by low FEV₁ and FEV₁/forced vital capacity <70%) in GWAS (ie, *CHRNA3*, *CHRNA3/4*, *HHIP*, and *FAM13A*). Furthermore, several genes have been associated with a lower lung function in the general population, like *AGER*, *GPR126*, *GSTCD*, *HTR4*, *THSD4*, and *TSN1*. However, a low lung function, in the general population without further testing, may reflect asthma, COPD, or both, especially at older age, which hampers the interpretation of genetics of COPD to a large extent. Therefore, the genes published so far might not be specific to asthma or COPD, but it could be hypothesized that they reflect abnormal lung development in utero, which by itself has not been tested so far. Moreover, because COPD encompasses several phenotypes such as chronic bronchitis, airway obstruction, and emphysema, and asthma may encompass individuals with persistent airway obstruction, it is not possible to tell which genes are associated with which phenotype of COPD if not tested formally.

Overlap of Asthma and COPD

Many candidate genes and genes found by GWAS have been associated on multiple occasions with asthma, and sometimes with COPD as well.⁶⁵ Bosse⁶⁶ recently published an overview of COPD genes found by GWAS and frequently replicated candidate genes. **Table 3** combines the data on the number of publications with association of genes with asthma and with COPD as reviewed in these two articles.^{65,66} The common genes identified for both asthma and COPD are *ADRB2*, *GSTM1*, *GSTP1*, *IL13*, *TGFB1*, and *TNF*.⁶⁵ We reported that this, so far limited, list of candidate genes underlying both asthma and COPD might be extended in the near future, because some genes identified in COPD have not been studied yet in asthma or too few studies have been performed that have tried to replicate genes associated with asthma in COPD. In

Table 3
Number of reports showing genes that are replicated in asthma more than 10 times, and their positive reports in COPD, and the converse number of reports with more than 10 times replication of association with COPD and their reports in asthma

| | Number of Reports in Asthma | Number of Reports in COPD |
|---|-----------------------------|---------------------------|
| Genes >10 Times in Asthma and also Reported in COPD | | |
| <i>ADAM33</i> | 23 | 6 |
| <i>ADRB2</i> | 46 | 12 |
| <i>CCL5</i> | 12 | 1 |
| <i>CD14</i> | 34 | 2 |
| <i>GSTM1</i> | 6 | 16 |
| <i>GSTP1</i> | 17 | 16 |
| <i>HLA</i> | 15 | 2 |
| <i>IL4</i> | 23 | 3 |
| <i>IL10</i> | 18 | 7 |
| <i>IL13</i> | 38 | 9 |
| <i>IL1B</i> | 12 | 6 |
| <i>IL4R</i> | 43 | 2 |
| <i>LTA4</i> | 12 | 5 |
| <i>STAT6</i> | 15 | 1 |
| <i>TGFB1</i> | 12 | 13 |
| <i>TNF</i> | 28 | 20 |
| Genes >10 Times in Asthma but not in COPD | | |
| <i>HLADRB1</i> | 32 | Not reported |
| <i>FCERB1</i> | 22 | Not reported |
| <i>FLG</i> | 18 | Not reported |
| <i>NPSR1</i> | 12 | Not reported |
| <i>ORMDL3</i> | 12 | 0 |
| Genes >10 Times in COPD, but not in Asthma | | |
| <i>EPHX</i> | Not tested | 25 |
| <i>SERPINA1</i> | 0 | 19 |

From Postma DS, Kerkhof M, Boezen HM, et al. Asthma and chronic obstructive pulmonary disease: common genes, common environments? *Am J Respir Crit Care Med* 2011;183(12):1588–94, with permission; and Bosse Y. Updates on the COPD gene list. *Int J Chron Obstruct Pulmon Dis* 2012;7:607–31, with permission.

addition, it is likely that genes that affect lung development in utero and lung growth in early childhood in interaction with environmental detrimental stimuli, such as smoking and air pollution, are contributing to asthma in childhood, progression of asthma to a phenotype with persistent airway obstruction, as well as development of COPD (**Fig. 1**).⁶⁵ Additional genes and environmental factors drive specific immunologic

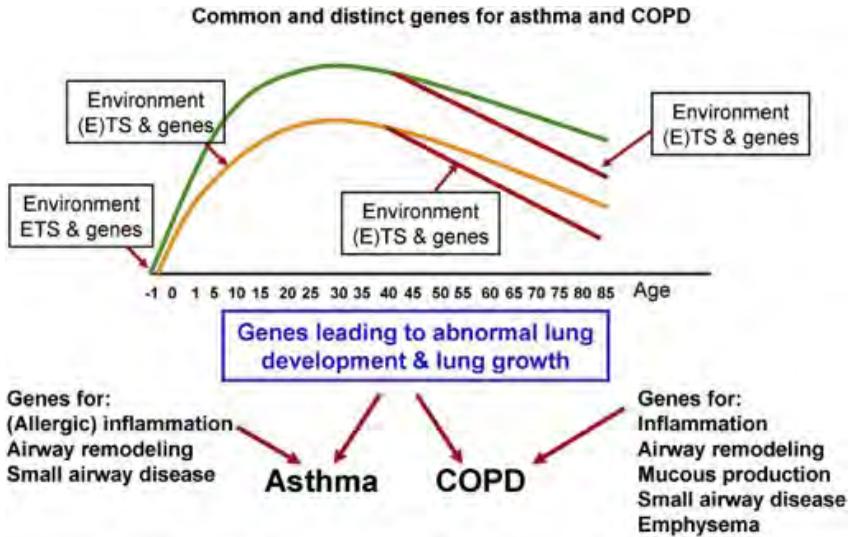


Fig. 1. Lung development, growth, and decline in interaction with genetic and environmental factors. Green line represents normal lung development, growth, and decline. Orange line represents abnormal prenatal lung development and growth. Red line represents abnormal lung decline caused by exposure to tobacco smoke. (E)TS, (environmental) tobacco smoke. (*From* Postma DS, Kerkhof M, Boezen HM, et al. Asthma and chronic obstructive pulmonary disease: common genes, common environments? *Am J Respir Crit Care Med* 2011;183(12):1588–94, copyright © 2011, American Thoracic Society; with permission.)

mechanisms that underlie asthma (like the Th2/Th1 (Thelper2/Thelper1) balance) and these may also contribute to the overlap phenotype of asthma and COPD (Fig. 2).

One approach to studying shared genes may be to compare the top hits of GWAS in distinct asthma and COPD populations. However, to unravel whether there exists an overlap phenotype that is genetically driven, a more fruitful method might be to search for shared genetics of asthma and COPD by performing a GWAS in one cohort including patients across the spectrum of chronic airways disease, and then examining whether the overlap phenotype has shared or distinct genes

with asthma and with COPD. Such a study would require a large number of well-characterized patients, but it seems the way forward.

INFLAMMATION AND REMODELING

Inflammation and remodeling are present in COPD throughout the bronchial tree and lung tissue. There are 3 distinct processes present, and in different combinations in COPD: (1) chronic sputum production and cough, so called chronic bronchitis; (2) small airway disease; and (3) emphysema, which is the loss of elastic tissue in the peripheral lung.⁷⁰ Respiratory bronchioles of young smokers are already inflamed,⁷⁰ likely reflecting early signs of COPD. This inflammation has been shown to predominantly comprise mononuclear cells in the airway wall and macrophages in the small airway lumen. In the peripheral airways of patients with established COPD, there is also an inflammatory infiltrate, in which neutrophils and predominantly CD8-positive lymphocytes as well as mast cells predominate (mast cells particularly in patients with centrilobular emphysema).^{71,72} In addition, squamous cell metaplasia, fibrosis, and increased smooth muscle mass, associated with hypertrophy and hyperplasia of smooth muscle cells, are present.⁷³ Each of these components may contribute to airway narrowing, with consequences for severity of the disease and of respiratory symptoms. Moreover,

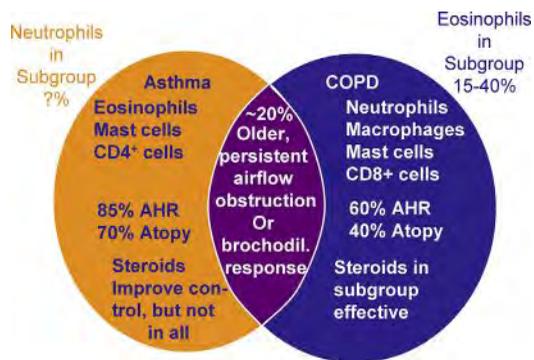


Fig. 2. The characteristics of patients with asthma, COPD, and the overlap phenotype. AHR, airway hyperresponsiveness.

goblet cell hyperplasia is frequently present and may contribute to chronic cough and phlegm in COPD, next to the contribution of increased mucus tenacity resulting from changes in soluble factors in the mucus, components that are different in asthma and COPD.⁵ These types of inflammation and remodeling processes are also present in asthma (ie, increased numbers of eosinophils, CD4-positive lymphocytes and mast cells have been shown in both diseases).⁵ Fabbri and colleagues⁷⁴ showed that patients with a history of asthma or a history of COPD with a similar level of airway obstruction and hyperresponsiveness have different inflammatory patterns (eosinophils in asthma and neutrophils in COPD), suggesting that there is no overlap in inflammatory pattern between asthma and COPD. However, in this case patients with COPD were all ex-smokers and current smokers and, as mentioned earlier, this may have skewed findings in the inflammatory pattern toward neutrophils, particularly because inflammation persists after smoking cessation in COPD.^{75,76} Furthermore, although there was a significant difference in airway inflammation at a group level, there was also considerable overlap between asthma and COPD. Thus, these findings do not exclude an overlap phenotype of asthma and COPD.

Smoking induces inflammation in the lung with increased numbers of CD8 cells, neutrophils, mast cells, and macrophages in COPD.⁷⁷ It is not surprising that smoking in asthma induces comparable changes in inflammation (ie, more mast cells and fewer eosinophils in airway wall biopsies).⁹ In addition, there is more remodeling in smokers with asthma, as reflected by more goblet cells and mucus-positive epithelium, increased epithelial thickness, and a higher proliferation rate of intact and basal epithelium in smokers with asthma.^{9,22} Although asthma outside the context of smoking does not generally lead to neutrophilia, severe asthma is accompanied by a more neutrophilic inflammation compared with milder forms of asthma,^{5,78} and some investigators have reported neutrophilic inflammation in patients with milder disease.⁷⁹ In contrast, severe asthma has a distinctive inflammatory phenotype as well: Benayoun and colleagues⁸⁰ showed that particularly high numbers of fibroblasts and airway smooth muscle hypertrophy in the proximal airways differentiates severe persistent asthma from milder asthma and COPD. Whether this is also the case in the smaller airways remains to be established. Next to neutrophilic asthma, there also exists a subset of patients with COPD with eosinophilia. The prevalence of eosinophilic COPD has been reported to range between 12% and 25% or even

higher (up to 50% of stable patients with COPD).⁸¹ This type of inflammatory cell in particular increases during exacerbations of COPD.⁸² Bafadhel and colleagues⁸³ showed that the presence of blood eosinophilia (>2%) during an exacerbation of COPD may be a useful biomarker to direct corticosteroid therapy. In addition, it has been shown that stable patients with COPD and sputum eosinophilia can be effectively treated with inhaled steroids.⁸⁴

Next to inflammation, remodeling plays a role in the clinical expression of asthma and COPD. It has been postulated that airway remodeling underlies the phenotypic overlap in asthma and COPD.²² Airways are thickened in both asthma and COPD. However, Kuwano and colleagues⁸⁵ showed that the small airways in asthma are thicker than in COPD and healthy controls. Moreover, despite thickening of the airway wall in asthma, the airway lumen is larger⁸⁶ than in COPD, suggesting differential effects of airway wall thickening in asthma and COPD, possibly reflecting different underlying remodeling processes. This finding is underscored by the observation that patients with asthma generally do not develop emphysema. Parenchymal changes occur in asthma, in the sense of abnormal alveolar attachments and reduced numbers and changed geometry of elastic fibers.^{87,88} These changes occur in the peribronchial region, whereas in emphysema there are widespread changes in lung tissue, not only in the peribronchiolar region, which differentiates people with asthma from patients with COPD with emphysema. However, there are also similarities with respect to remodeling in asthma and COPD, as recently pointed out in a review by Mauad and colleagues,⁵ namely that structural changes occur in both diseases because of chronic inflammatory tissue injury, especially in the most severe cases. Because there are limited patterns of repair in the lungs, similar structural abnormalities may exist in some patients, possibly contributing to the clinical overlap. The latter review by Mauad and colleagues⁵ and the studies discussed earlier show that some changes are characteristic of each disease (emphysema in COPD, epithelial desquamation and prominent increases in airway smooth muscle mass in the central airways in asthma), but in the overlap phenotype changes of both asthma and COPD may be present.

PHARMACOLOGIC RESPONSES

One of the difficulties in discussing treatment response in asthma and COPD is that patients with overlap phenotypes of asthma and COPD

have been systematically excluded from drug trials, which are designed to include patients with pure COPD and pure asthma. This exclusion represents a problem for evidence-based guidelines on obstructive airway disease. Travers and colleagues⁸⁹ showed that only 5 of 100 individuals identified with COPD in a general population survey would fulfill inclusion criteria for major randomized controlled trials and reported comparable findings for asthma.⁹⁰ Thus, it is difficult to predict in an evidence-based way what the response to antiinflammatory and/or bronchodilator treatment would be in the full spectrum of COPD and the full spectrum of asthma.

Treatment of asthma and COPD is based on targeting inflammation and remodeling as well as counteracting contraction of the smooth muscles around the airways. Treatment is driven by the manifestations of disease both in asthma and COPD and aims to reduce symptoms, exacerbation frequency, and to improve health status, and, with severe disease, to improve exercise tolerance.¹¹ A proportion of patients with asthma or COPD does not achieve an acceptable level of control despite combination treatment with ICSs and long-acting bronchodilators, and has a more rapid loss of FEV₁ over time. This finding has been attributed to unresponsiveness of the underlying inflammatory and remodeling processes in the airways in the case of COPD. However, as mentioned earlier, it may also represent an overlap syndrome with neutrophilia in severe or persistent asthma, or clinicians may be treating patients with large-particle drugs, so the small airways are not being reached and inflammation and remodeling are not being adequately treated in either asthma or COPD.³⁰

In general, lung function does not improve to a large extent in COPD and randomized studies have shown that the accelerated lung function decline, a major clinical characteristic of COPD, is not affected to a large extent by pharmacotherapy. However, 2 recent studies suggested that the decline in lung function can be significantly attenuated with ICS treatment, at least in a subset of patients with COPD, irrespective whether long acting beta agonists (LABAs) were added.^{91,92} A recent meta-analysis showed that ICSs have immune-modulating effects in COPD,⁹³ hence this may be plausible. However, most studies do not show effects on lung function decline and the parameters that can predict a favorable ICS response in COPD remain to be determined.⁹⁴ Siva and colleagues⁹⁴ recently showed that patients with COPD with sputum eosinophilia (>3%) may respond better to ICS with respect to reduction in exacerbations, whereas the Groningen Leiden Universities Corticosteroids in

Obstructive Lung Disease (GLUCOLD) study suggested that the presence of hyperinflation (a sign of small airway involvement) may predict a better response to ICS with respect to lung function decline, whereas disturbed diffusion capacity, a marker of emphysema, predicts a worse response.⁹⁵ Here, eosinophilia in sputum did not predict a better or worse response, suggesting that some markers associate with exacerbation frequency and others with lung function loss. The observation that signs of emphysema predict worse ICS response is plausible because regeneration of destroyed alveoli has never been shown in COPD, or in any other lung disease.

In eosinophilic asthma, ICS doses can be down-titrated based on sputum eosinophilia. Whether this is also the case in COPD, in which ICS doses have typically been much higher than in asthma, needs to be firmly established in future studies, but a pilot study suggested that this may be a good approach,⁸⁴ particularly given the concern about pneumonia with ICS in COPD (although not in asthma). However, in clinical practice it is difficult to perform sputum induction on regular basis, and, at least in asthma, the inflammatory profile can vary from visit to visit⁹⁶; thus new inflammatory markers have to be found for optimal initiation and down-titration of ICS.

If a diagnosis of asthma or COPD is not reached, it could be worth establishing in all patients with airway obstruction, either asthma or COPD or overlap phenotypes, whether sputum eosinophilia is present, and, if so, initiating ICS treatment.⁶¹ In addition, it could be worth starting long-acting bronchodilators if symptoms persist, because this improves clinical stability further. Welte and colleagues⁹⁷ showed that triple therapy (ICS with LABA and long-acting muscarinic anticholinergic) has great benefit in COPD, with many patients showing considerable bronchodilator responses (up to 50%). From this, it could be inferred that the overlap phenotype, in more severe disease, could benefit from triple therapy as well, which is also consistent with the observations of Magnusson and colleagues⁹⁸ showing that patients with COPD and concomitant asthma improve considerably with tiotropium bromide with respect to lung function and need for rescue medication.

SUMMARY

It is easy to differentiate pure asthma from pure COPD, because they reflect the extremes of a spectrum. However, in many, especially older, patients, features of both asthma and COPD can be present, leading to an overlap phenotype. There is no extensive literature available on the overlap

phenotype, and interpretation of studies thus far has been hampered by differential age and smoking status in asthma and COPD. The balance of evidence so far suggests that the severity of airway obstruction and hyperresponsiveness in asthma, COPD, and the overlap phenotypes is driven by some similar and some different mechanisms. In addition, there is an unmet need to assess treatment effects in individuals with the overlap phenotype of asthma and COPD, because they have been consistently excluded from pharmacologic studies.

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