

Overlap of asthma and chronic obstructive pulmonary disease

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Purpose of review

Asthma and chronic obstructive pulmonary disease (COPD) are both defined by the presence of airflow obstruction, but they present distinguishing differences in terms of both risk factors and clinical phenotypes. Yet it is quite common in the clinical setting to observe patients with asthma showing COPD-like phenotypes, and *vice versa*, making it a priority to search for optimal prevention, treatment, and management strategies for these cases of coexisting lung obstructive diseases.

Recent findings

Recent studies have provided further evidence of strong epidemiologic and clinical links between asthma and COPD. Adult subjects with active asthma are as much as 12 times more likely to acquire COPD over time than subjects with no active asthma. Signs identifying patients with asthma predisposed to developing COPD may already be present at the early stages of the disease, a finding with potential implications for prevention of COPD. In addition to spirometry and other pulmonary function tests (such as measurements of residual volume and diffusing capacity of the lung for carbon monoxide), recent evidence suggests that the assessment of type and degree of airway remodeling and the evaluation of inflammatory markers might prove useful in the future to characterize phenotypically patients with coexisting asthma and COPD.

Summary

The nature of the association between asthma and COPD remains unclear and open to discussion. Further research is required to develop effective management algorithms for patients with multiple obstructive lung diseases, determine to what extent early treatment and optimal management of asthma may protect against progression into COPD, and identify genetic markers of individual susceptibility to specific lung disease phenotypes and pharmacologic treatments.

Keywords

asthma, chronic bronchitis, emphysema, COPD

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Supported in part by a grant award from the American Thoracic Society/Alpha One Foundation.

Current Opinion in Pulmonary Medicine 2005, 11:7–13

Abbreviations

COPD	chronic obstructive pulmonary disease
DLCO	diffusing capacity of the lung for carbon monoxide
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HRCT	high-resolution CT

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1070-5287

Introduction

In the last decades, the overlap among asthma, chronic bronchitis, and emphysema has received much attention, and evidence has been accumulating on the similarities but also on the distinguishing differences among these three diseases. One of the most significant driving forces behind this intense research activity has been the so-called Dutch hypothesis [1]. In the early 1960s, Orie *et al.* [2] proposed that asthma, chronic bronchitis, and emphysema should be considered different expressions of one disease entity in which both host factors (such as genetic predisposition to atopy and bronchial hyperresponsiveness) and environmental factors (such as smoking) play major roles. Although this hypothesis has never been completely abandoned by the scientific community, asthma and chronic obstructive pulmonary disease (COPD) have been increasingly differentiated over time in terms of risk factors, clinical presentations, prognosis, and management. Current guidelines for their management are to a large extent different [3–5]. Yet there is no consensus on whether asthma and COPD represent distinct diseases that share some common characteristics or whether they represent a single disease with multiple phenotypes. The answer to this question is likely to have a major impact on the way we will prevent and treat these diseases in the years to come. This review discusses some of the most significant advances in the understanding of the overlap between asthma and COPD published between October 2002 and June 2004.

Definition and comorbidity

Much of the difficulty in distinguishing asthma, chronic bronchitis, and emphysema comes from the fact that

Table 1. Definitions of asthma, chronic bronchitis, emphysema, and chronic obstructive pulmonary disease (COPD)

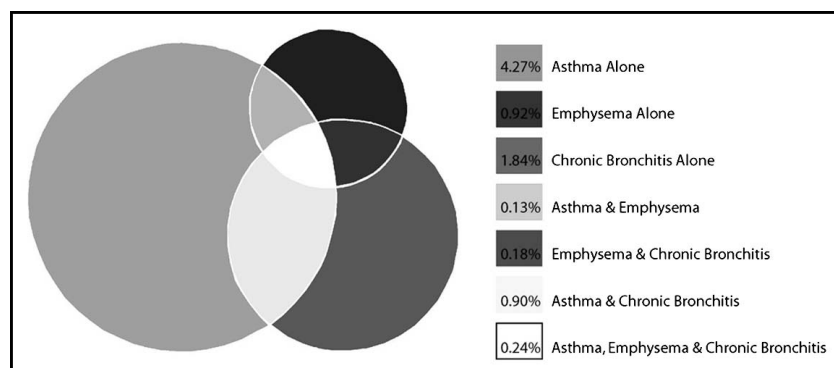
	Definition
Asthma [3]	Chronic inflammatory disorder of the airways in which many cells and cellular elements play a role, in particular, mast cells, eosinophils, T lymphocytes, neutrophils, and epithelial cells. In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and cough, particularly at night and in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment. The inflammation also causes an associated increase in the existing bronchial hyperresponsiveness to a variety of stimuli. (Clinical and functional definition)
Chronic bronchitis [6]	Chronic productive cough for 3 months in each of 2 successive years in a patient in whom other causes of productive chronic cough have been excluded. (Clinical definition)
Emphysema [6]	Permanent enlargement of the airspaces distal to the terminal bronchioles, accompanied by destruction of their walls and without obvious fibrosis. (Anatomic definition)
COPD [4,5]	Disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response to the lungs to noxious particles or gases. The chronic airflow limitation characteristic of COPD is caused by a mixture of small airway disease (obstructive bronchiolitis) and parenchymal destruction (emphysema). (Functional definition)

their definitions are not mutually exclusive and are differentially based on clinical, anatomic, or functional conditions (Table 1) [3–6]. To complicate things even more, the working definition of COPD developed within the Global Initiative for Chronic Obstructive Lung Disease (GOLD) [4,5] is mostly based on the presence of a nonfully reversible airflow limitation, independent of the presence of chronic cough and phlegm (*ie*, chronic

bronchitis) and of the existence of emphysematous structural changes in the lungs. Of note, a nonfully reversible airway obstruction is also a common feature in subjects with long-term asthma. The GOLD definition of COPD does not include the terms *emphysema* and *chronic bronchitis* [4], which are often used incorrectly and capture only some of the complex structural abnormalities and clinical symptoms associated with the disease. In this review, the GOLD working definition of COPD will be used mainly, but evidence will also be discussed from epidemiologic studies using the diagnostic categories of emphysema and chronic bronchitis. In fact, these terms may represent useful disease indicators for COPD in large population studies, particularly when data on lung function after bronchodilator are not available.

The overlap in terminology of the definitions of asthma, chronic bronchitis, emphysema, and COPD represents a major source of confusion, because it affects the ability not only to distinguish these diseases from each other but also to estimate consistently the prevalence of airway obstruction in the general population itself. Celli *et al.* [7•] found that rates of airway obstruction in adults varied dramatically (by more than 200%) in the general population according to the definition used (either self-reported diagnosis of chronic bronchitis/emphysema or the finding of a ratio forced expiratory volume in 1s (FEV₁)/forced vital capacity (FVC) < .70 at spirometry).

The fact that individual patients can have different combinations of asthma, chronic bronchitis, and emphysema has been effectively illustrated using the Venn diagram [6]. Recently, Soriano *et al.* [8•] used data from two large databases from the United States and the United Kingdom to estimate a proportional Venn diagram of obstructive lung disease. As shown in Figure 1, in the US population, 8.5% of the participants reported asthma, chronic bronchitis, or emphysema. Of these subjects, approximately 17% reported more than one condition. Subjects with more than one condition accounted for as many as 50% of patients with obstructive lung disease older than

Figure 1. Proportional Venn diagram of obstructive lung disease (asthma, chronic bronchitis, and emphysema) in the United States [National Health and Nutrition Examination Survey (NHANES) III surveys 1988–1994] for all ages

The circle areas are a proportional representation of the prevalence of asthma, chronic bronchitis, and emphysema in the US NHANES III population. The areas of intersection represent subjects with more than one condition. Prevalence rates are listed for each of the seven possible combinations. In the US NHANES III population, the prevalence of asthma was 5.5%, the prevalence of chronic bronchitis 3.2%, and the prevalence of emphysema 1.5%. Subjects with more than one condition accounted for approximately 17% of patients with lung obstructive disease. Adapted with permission [8•].

50 years in the United Kingdom [8•]. This proportion was 25% in an Australian study on subjects age 45 to 69 years [9]. A report from the Italian Study on Asthma in Young Adults (20–44 years) showed that approximately 20% of the subjects reporting chronic cough and phlegm (*ie*, the clinical definition of chronic bronchitis) had coexisting asthma [10]. Subjects reporting the coexistence of two or three obstructive lung diseases are on average older and have higher prevalence of airway obstruction on spirometry [8•]. In addition, the coexistence of COPD and asthma has been associated with increased mortality in several studies, including a recent report from a nationally representative sample of US deaths [11]. One striking finding in the study by Soriano *et al.* [8•] was that as many as 58% of subjects with airway obstruction confirmed by spirometry reported no diagnosis, suggesting that obstructive lung diseases are severely underdiagnosed in the general population.

The common messages emerging from these epidemiologic studies are that (1) the prevalence of obstructive lung diseases, although strictly definition-dependent, represents a major social and economic burden; (2) the coexistence of asthma, chronic bronchitis, and/or emphysema in the same patient is associated with increased severity of disease and risk of mortality; and (3) as many as half of the cases of airflow obstruction remain undiagnosed in the general population. Screening programs using spirometry [12•] or even the simple measurement of peak flow rate [13] might help to detect a significant proportion of these undiagnosed cases.

Relation between the natural history of asthma and chronic obstructive pulmonary disease

In the vast majority of cases, the coexistence of asthma and COPD is restricted to adult and, particularly, elderly patients. However, asthma most frequently has its onset in childhood. In the 1970s, Burrows *et al.* [14] reported that adults with COPD were more likely to recall respiratory troubles during childhood than those without COPD, suggesting the existence of a possible progression of the natural history of childhood asthma into adult COPD. This hypothesis has not yet been tested conclusively. However, longitudinal cohort studies are providing growing evidence that childhood asthma does frequently persist into adulthood, and the likelihood of persistence is directly correlated with the severity of the disease [15–17]. Are these cases of long-term persistent asthma destined to develop into a nonfully reversible airflow obstruction, *ie*, COPD? In a recent report from the large longitudinal cohort of the Tucson Epidemiological Study of Airway Obstructive Disease [18••], adult subjects with active asthma were found to have a 12 times higher risk of acquiring COPD over time than subjects with no asthma after adjusting for smoking. One of the strengths of this report was that, unlike most other

epidemiologic studies, COPD was defined by the presence of both a physician-confirmed diagnosis and objective measurements (FEV_1 or diffusing capacity of the lung for carbon monoxide [DLCO] < 80% predicted). However, this study did not have information on response to bronchodilator, leaving unanswered the question of whether this progression of asthma into COPD was indeed marked by the major hallmark of COPD, *ie*, the development of nonreversible airflow obstruction.

This question has been addressed in an interesting study from The Netherlands [19••] in which a group of 228 asthmatics admitted to an asthma clinic in the 1960s were extensively re-evaluated 26 years later. At the follow-up visit, 16% of the patients had nonreversible airflow obstruction, 23% reduced carbon monoxide transfer coefficient, and 5% both. Interestingly, lower FEV_1 values, less reversibility of airway obstruction, and less severe bronchial hyperresponsiveness at enrollment predicted the presence of nonreversible obstruction at follow-up. Similarly, the presence of functional emphysematous signs at enrollment, such as high residual volume and total lung capacity, predicted the presence of a reduced carbon monoxide transfer coefficient at follow-up. These findings suggest that subtle signs identifying patients with asthma predisposed to develop COPD are already present at the early stages of the disease.

In interpreting the findings of these long-term longitudinal studies, a word of caution should be said regarding the possible presence of a cohort effect [20]. In the past, childhood asthma was more strongly associated with recurrent infections, and its treatment was less effective than today. This means that, if a link between childhood asthma and adult COPD exists among the patients with COPD we see today, this may change in the future when children with asthma who have benefited from the new modern asthma treatments and management strategies will enter their late adulthood. However, to date, to what extent (if any) an early anti-inflammatory treatment of asthma is beneficial against the development of nonreversible airway obstruction remains a vital, but still open, question.

Lung function testing in asthma and chronic obstructive pulmonary disease

There is probably no phenotype that illustrates the complexity of the overlap between asthma and COPD better than lung function. Both diseases are characterized by airflow obstruction. Yet although the involvement of small airways and lung parenchyma appears to be predominant in COPD [21••,22•,23], more so than in asthma, a real distinction between the two diseases based simply on baseline spirometry is very difficult.

One major discriminatory factor is represented by the presence of a significant response to bronchodilator in

asthma, whereas airflow obstruction in COPD is not fully reversible by definition [4]. However, a partial response to bronchodilator is a common feature in patients with COPD [24•,25–27] who appear to benefit frequently from the use of short-acting and long-acting β_2 -agonists [28•,29]. Several studies have shown that almost 50% of patients with COPD may have significant improvement in FEV₁ after bronchodilator [25,27], and this appears true even among subjects with severe α_1 -antitrypsin deficiency [24•]. Interestingly, among patients with COPD, reversibility to β_2 -agonists appears to be associated with other asthma-related phenotypes, such as blood eosinophilia [27], IgE levels, and bronchial hyperresponsiveness [30•].

If patients with COPD frequently show asthma-related phenotypes such as partial bronchoreversibility and bronchial hyperresponsiveness [31], patients with asthma may develop airflow function signs that are characteristic of COPD. In addition to the aforementioned development of irreversible lung obstruction, long-term asthma has been associated with an accelerated decline of FEV₁ [32]. There has been much debate on whether this accelerated decline is present only among those patients with asthma who eventually progress into COPD [33•,34,35] and on what factors might help identify these subgroups of patients with asthma susceptible to accelerated decline of lung function [33•,35–40]. There is not yet conclusive evidence to answer these two questions, which are likely to have essential clinical implications, because FEV₁ decline is one of the strongest predictors of mortality among patients with obstructive lung diseases.

Taken together, these studies confirm the difficulty of distinguishing asthma and COPD based simply on spirometric parameters and reinforce the need of more discriminatory tests, such as DLCO measurement [41•]. Most importantly, they suggest that basing the definition of asthma and COPD on functional parameters emphasizes similarities rather than differences between these diseases.

Overlap of asthma and chronic obstructive pulmonary disease: is airway remodeling the link?

Some researchers believe that a significant part of the phenotypic overlap between asthma and COPD can be ascribed to the airway remodeling that takes place in these diseases. This area is being extensively investigated, and it was identified as one of the six priority areas for research in asthma in a recent National Heart, Lung, and Blood Institute Working Group report [42••]. Airway remodeling is characterized by functionally relevant changes of the cellular and molecular constituents of the airway wall [43•,44] that are linked to the surrounding inflammatory process. Airway remodeling occurs in both

asthma and COPD, but it presents important differences in the structures, anatomic sites, and cell types involved in the two diseases [45].

Airway remodeling has been postulated to be linked among patients with asthma to the development of COPD-like pulmonary signs, such as nonreversible airflow obstruction and accelerated FEV₁ decline [46–48]. However, to date, this association is far from being fully elucidated. Indirect evidence is provided by a recent study by Benayoun *et al.* [49••] in which fibroblast accumulation and airway smooth muscle hypertrophy in proximal airways were found to characterize severe persistent asthma and to correlate negatively with both pre-bronchodilator and postbronchodilator FEV₁ values among patients with asthma.

The availability of new technologic tools less invasive than the histologic examination of lung biopsies will make it easier to assess the functional impact of airway remodeling in asthma and COPD. Nakano *et al.* [43•] have reviewed the use of high-resolution CT (HRCT) to assess airway remodeling and concluded that, although further technologic advances are hoped for, asthma and COPD do show different patterns of remodeling with the current HRCT quantitative methods. However, in both diseases, it appears possible to identify HRCT parameters derived from the airway wall area, the airway luminal area, and the lung tissue density that correlate with lung function and disease severity [50–55]. Most importantly, among patients with asthma, the degree of airway wall thickness and low attenuation areas in the lungs, as assessed by HRCT scan, was found to correlate with COPD-like functional signs, such as irreversible airflow obstruction and reduced diffusing capacity for carbon monoxide [56•,57]. These findings suggest that the histologic or HRCT-derived assessment of the type and degree of airway remodeling may help to characterize phenotypically patients with coexisting lung obstructive diseases.

Inflammation in asthma and chronic obstructive pulmonary disease

Important contributions to the differentiation of asthma and COPD come from studies comparing the type and degree of airway inflammation in these diseases. Both asthma and COPD are airway inflammatory diseases, but with distinct characteristics [58••]. In asthma, eosinophils, mast cells, and CD4⁺ T lymphocytes represent the most prominent inflammatory cell types, whereas neutrophils, macrophages, and CD8⁺ T cells are prominent in COPD [21••,58••].

Can the inflammatory phenotype help distinguish patients with asthma from those with COPD in the presence of an irreversible airflow obstruction? To address this question, Fabbri *et al.* [59••] studied 27 subjects

with a history of COPD and 19 subjects with a history of asthma with comparable degrees of fixed airflow obstruction. The two groups differed according to a large number of factors related to lung function (residual volume, diffusing capacity), imaging (HRCT scan emphysema score), bronchial biopsy (thickening of the epithelial basement membrane), and inflammatory cells (eosinophils, neutrophils, and CD4⁺/CD8⁺ ratio of T cells) in collected specimens. Interestingly, the percentages of sputum and bronchoalveolar lavage eosinophils were the best predictors of a history of asthma.

The immunologic differentiation of asthma and COPD may also have important prognostic and therapeutic implications. Sputum eosinophilia is associated with poorly controlled asthma [60], and normalization of eosinophil count in induced sputum has been linked to reduction in asthma exacerbations and hospital admissions [61•]. Neutrophilic inflammation is less sensitive to treatment with steroids than eosinophilic inflammation [21••,62], and the percentage of neutrophils in induced sputum has been shown to correlate with accelerated FEV₁ decline among patients with asthma [33•]. However, the use of immunologic markers to differentiate asthma and COPD can prove challenging in the clinical setting, even with invasive procedures such as bronchial biopsies [63]. Further research is needed to determine whether minimally invasive methodologies, such as inflammatory cell count in induced sputum or measurements of stimulated production of cytokines from peripheral blood mononuclear cells [64], can improve the ability to diagnose and treat patients with coexisting lung obstructive diseases.

Risk factors and susceptibility for asthma and chronic obstructive pulmonary disease: a dynamic relation

The presented evidence illustrates the complexity of the phenotypic overlap between asthma and COPD. Yet there is another equally important overlap between the risk factors associated with these diseases. Smoking, the long-recognized major risk factor for COPD [65], is also associated with asthma-related intermediate phenotypes, such as elevated IgE [66•], eosinophilia [67•], and bronchial hyperresponsiveness [31,66•,67•]. Conversely, bronchial hyperresponsiveness and IgE levels are significant predictors of the rate of FEV₁ decline among patients with COPD [68] and late-onset airway obstruction among adults [69]. The interrelationship between risk factors for lung obstructive diseases is also evident in the occupational setting. Recently, approximately 15% of both asthma and COPD were estimated to be work-related in a statement by the American Thoracic Society [70••]. Although the relative importance of the underlying mechanisms (IgE-mediated versus irritant-induced) is likely to be different in occupational asthma and

COPD, subjects with asthma and COPD can be susceptible to the same noxious occupational agents.

This overlap of phenotypes and risk factors suggests that a rigid model cannot describe the complexity of the relation between asthma and COPD, and factors such as individual genetic susceptibility and interaction between different risk factors and/or clinical phenotypes must also be taken into account.

Conclusion

In the last few years, intense research efforts have been devoted to expand understanding of the overlap between asthma and COPD. It is increasingly evident that a distinction between these diseases cannot be based simply on spirometry testing, with or without bronchodilator response. Supplemental pulmonary function tests, such as measurements of residual volume and DLCO, remain useful tools in patients with coexisting obstructive lung diseases. Assessment of type and degree of airway remodeling and evaluation of inflammatory markers might also prove useful in the future to characterize phenotypically patients with asthma and COPD. The ultimate goal of differentiating patients with asthma and COPD is to provide better prevention, treatment, and management of these diseases. Future research is required to determine whether patients with coexisting signs of asthma and COPD may benefit from management strategies that are based on multiple functional, morphologic, and immunologic assessments rather than on a categorization into rigid diagnostic labels of either asthma or COPD. Another essential research question will be whether early treatment and optimal management of asthma may reduce the proportion of asthma cases that ultimately develop COPD-like signs. In this framework, the completion of the sequencing of the human genome is providing a new extraordinary opportunity to identify genetic markers of individual susceptibility to specific risk factors, to specific disease phenotypes, and to specific pharmacologic treatments. This is probably the most promising research area for the years to come.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- Of special interest
 - Of outstanding interest
- 1 Sluiter HJ, Koeter GH, de Monchy JG, et al.: The Dutch hypothesis (chronic non-specific lung disease) revisited. *Eur Respir J* 1991, 4:479–489.
 - 2 Orie NGM, Sluiter HJ, de Vries K, et al.: The host factor in bronchitis. In: Orie NGM, Sluiter HJ, editors. *Bronchitis an International Symposium*. Assen, Netherlands: Royal vanGorcum; 1961.
 - 3 The National Asthma Education and Prevention Program: Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma, Bethesda, MD. NIH Publication No. 02-5074. June 2003.
 - 4 Pauwels RA, Buist AS, Calverley PM, et al.: Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease.

- NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. *Am J Respir Crit Care Med* 2001, 163:1256–1276.
- 5 Global Initiative for Chronic Obstructive Lung Disease: Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Workshop report. 2004. Available at: <http://www.goldcopd.com>. Accessed August 30, 2004.
 - 6 Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. American Thoracic Society. *Am J Respir Crit Care Med* 1995, 152:S77–S121.
 - 7 Celli BR, Halbert RJ, Isonaka S, et al.: Population impact of different definitions of airway obstruction. *Eur Respir J* 2003, 22:268–273.
An interesting report showing that rates of obstructive airway disease among adults in the general population can vary dramatically according to the case definition used.
 - 8 Soriano JB, Davis KJ, Coleman B, et al.: The proportional Venn diagram of obstructive lung disease: two approximations from the United States and the United Kingdom. *Chest* 2003, 124:474–481.
In this study, two large data sets were used to estimate a proportional Venn diagram of obstructive lung disease and to examine the relationship between self-reported diagnosis of lung obstructive disease and spirometry findings.
 - 9 Abramson M, Matheson M, Wharton C, et al.: Prevalence of respiratory symptoms related to chronic obstructive pulmonary disease and asthma among middle aged and older adults. *Respirology* 2002, 7:325–331.
 - 10 Cerveri I, Accordini S, Corsico A, et al.: Chronic cough and phlegm in young adults. *Eur Respir J* 2003, 22:413–417.
 - 11 Meyer PA, Mannino DM, Redd SC, et al.: Characteristics of adults dying with COPD. *Chest* 2002, 122:2003–2008.
 - 12 Buffels J, Degryse J, Heyrman J, et al.: Office spirometry significantly improves early detection of COPD in general practice: the DIDASCO Study. *Chest* 2004, 125:1394–1399.
This study demonstrates that routine use of spirometry by trained general practitioners may help detecting a substantial number of undiagnosed cases of obstructive lung disease.
 - 13 Jackson H, Hubbard R: Detecting chronic obstructive pulmonary disease using peak flow rate: cross sectional survey. *BMJ* 2003, 327:653–654.
 - 14 Burrows B, Knudson RJ, Lebowitz MD: The relationship of childhood respiratory illness to adult obstructive airway disease. *Am Rev Respir Dis* 1977, 115:751–760.
 - 15 Horak E, Lanigan A, Roberts M, et al.: Longitudinal study of childhood wheezy bronchitis and asthma: outcome at age 42. *BMJ* 2003, 326:422–423.
 - 16 Sears MR, Greene JM, Willan AR, et al.: A longitudinal, population-based, cohort study of childhood asthma followed to adulthood. *N Engl J Med* 2003, 349:1414–1422.
 - 17 Guerra S, Wright AL, Morgan WJ, et al.: Persistence of asthma symptoms during adolescence: role of obesity and age at the onset of puberty. *Am J Respir Crit Care Med* 2004, 170:78–85.
 - 18 Silva GE, Sherrill DL, Guerra S, et al.: Asthma as a risk factor for COPD in a longitudinal study. *Chest* 2004, 126:59–65.
In this study, findings are reported from a large longitudinal population-based cohort on more than 3000 subjects followed for more than 20 years. Findings on the risk associated with active asthma for acquiring chronic bronchitis, emphysema, and COPD are striking, although no information was available on response to bronchodilator to corroborate the asthma and COPD diagnoses.
 - 19 Vonk JM, Jongepier H, Panhuysen CI, et al.: 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, 58:322–327.
This is an excellent study suggesting that irreversible airflow obstruction and reduced transfer coefficient represent two distinct clinical phenotypes in adult patients with asthma. Most interestingly, findings suggest that signs identifying patients with asthma predisposed to develop COPD might already be present at the early stages of the disease.
 - 20 Orie NG: The Dutch hypothesis. *Chest* 2000, 117(suppl 1):299S.
 - 21 Buist AS: Similarities and differences between asthma and chronic obstructive pulmonary disease: treatment and early outcomes. *Eur Respir J Suppl* 2003, 39:30s–35s.
An excellent review addressing similarities and differences between asthma and COPD. Particular attention is devoted to the differences in staging, management, and assessment of outcomes between these two diseases.
 - 22 Hogg JC, Chu F, Utokaparch S, et al.: The nature of small-airway obstruction in chronic obstructive pulmonary disease. *N Engl J Med* 2004, 350:2645–2653.
This study investigates the nature of small airway obstruction in COPD and emphasizes the importance of its inflammatory response.
 - 23 Barnes PJ, Shapiro SD, Pauwels RA: Chronic obstructive pulmonary disease: molecular and cellular mechanisms. *Eur Respir J* 2003, 22:672–688.
 - 24 Eden E, Hammel J, Rouhani FN, et al.: Asthma features in severe alpha1-antitrypsin deficiency: experience of the National Heart, Lung, and Blood Institute Registry. *Chest* 2003, 123:765–771.
Using data from a prospective National Heart, Lung, and Blood Institute Registry, this study provides surprising evidence on the frequency of asthma and bronchodilator response among subjects with severe $\alpha 1$ -antitrypsin deficiency.
 - 25 Reid DW, Soltani A, Johns DP, et al.: Bronchodilator reversibility in Australian adults with chronic obstructive pulmonary disease. *Intern Med J* 2003, 33:572–577.
 - 26 Calverley PM, Burge PS, Spencer S, et al.: Bronchodilator reversibility testing in chronic obstructive pulmonary disease. *Thorax* 2003, 58:659–664.
 - 27 Sitkauskienė B, Sakalauskas R, Malakauskas K, et al.: Reversibility to a beta2-agonist in COPD: relationship to atopy and neutrophil activation. *Respir Med* 2003, 97:591–598.
 - 28 Ram FS, Sestini P: Regular inhaled short acting beta2 agonists for the management of stable chronic obstructive pulmonary disease: Cochrane systematic review and meta-analysis. *Thorax* 2003, 58:580–584.
A comprehensive Cochrane systematic review and meta-analysis supporting the effectiveness of short-acting β_2 -agonists for the management of stable COPD.
 - 29 Mahler DA: The effect of inhaled beta2-agonists on clinical outcomes in chronic obstructive pulmonary disease. *J Allergy Clin Immunol* 2002, 110(suppl):S298–S303.
 - 30 Lapperre TS, Snoeck-Stroband JB, Gosman MM, et al.: Dissociation of lung function and airway inflammation in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2004, 170:499–504.
In this study, an original approach (factor analysis) is used to differentiate the phenotypic components of COPD. Findings support the hypothesis that asthma-related features represent distinct factors in the pathophysiology of COPD.
 - 31 Willemse BW, Postma DS, Timens W, et al.: The impact of smoking cessation on respiratory symptoms, lung function, airway hyperresponsiveness and inflammation. *Eur Respir J* 2004, 23:464–476.
 - 32 Lange P, Parner J, Vestbo J, et al.: A 15-year follow-up study of ventilatory function in adults with asthma. *N Engl J Med* 1998, 339:1194–1200.
 - 33 Boulet LP, Turcotte H, Turcot O, et al.: Airway inflammation in asthma with incomplete reversibility of airflow obstruction. *Respir Med* 2003, 97:739–744.
Despite the reduced sample size, this study provides evidence for a possible involvement of neutrophilic inflammation in FEV₁ decline among patients with asthma.
 - 34 Sherrill D, Guerra S, Bobadilla A, et al.: The role of concomitant respiratory diseases on the rate of decline in FEV1 among adult asthmatics. *Eur Respir J* 2003, 21:95–100.
 - 35 Oga T, Nishimura K, Tsukino M, et al.: Longitudinal changes in airflow limitation and airway hyperresponsiveness in patients with stable asthma. *Ann Allergy Asthma Immunol* 2002, 89:619–625.
 - 36 Litonjua AA, Sparrow D, Guevarra L, et al.: Serum interferon-gamma is associated with longitudinal decline in lung function among asthmatic patients: the Normative Aging Study. *Ann Allergy Asthma Immunol* 2003, 90:422–428.
 - 37 Kanazawa H, Yoshikawa J: Accelerated decline in lung function and impaired reversibility with salbutamol in asthmatic patients with chronic hepatitis C virus infection: a 6-year follow-up study. *Am J Med* 2004, 116:749–752.
 - 38 Kupczyk M, Kuprys I, Gorski P, et al.: Long-term deterioration of lung function in asthmatic outpatients. *Respiration (Herrlisheim)* 2004, 71:233–240.
 - 39 Cibella F, Cuttitta G, Bellia V, et al.: Lung function decline in bronchial asthma. *Chest* 2002, 122:1944–1948.
 - 40 Jongepier H, Boezen HM, Dijkstra A, et al.: Polymorphisms of the ADAM33 gene are associated with accelerated lung function decline in asthma. *Clin Exp Allergy* 2004, 34:757–760.
 - 41 Saydain G, Beck KC, Decker PA, et al.: Clinical significance of elevated diffusing capacity. *Chest* 2004, 125:446–452.
By using a large laboratory database, the authors investigate the clinical significance of elevated DLCO and show a strong association with asthma and obesity.
 - 42 Busse W, Banks-Schlegel S, Noel P, et al.: Future research directions in asthma: an NHLBI Working Group report. *Am J Respir Crit Care Med* 2004, 170:683–690.
This article reports results from a National Heart, Lung, and Blood Institute Working Group of extramural experts on the most promising future research areas in asthma. The six priority areas are discussed in detail, and for each of them, the scientific background is provided in concise and focused sections.
 - 43 Nakano Y, Muller NL, King GG, et al.: Quantitative assessment of airway remodeling using high-resolution CT. *Chest* 2002, 122(suppl):271S–275S.

This is a nice and clear review on the use of HRCT to assess airway remodeling in obstructive lung diseases. Particular attention is devoted to the relationship between HRCT findings and lung function testing.

- 44 McParland BE, Macklem PT, Pare PD: Airway wall remodeling: friend or foe? *J Appl Physiol* 2003, 95:426–434.
- 45 Jeffery PK: Remodeling in asthma and chronic obstructive lung disease. *Am J Respir Crit Care Med* 2001, 164:S28–S38.
- 46 Elias JA: Airway remodeling in asthma: unanswered questions. *Am J Respir Crit Care Med* 2000, 161:S168–S171.
- 47 Davies DE, Wicks J, Powell RM, et al.: Airway remodeling in asthma: new insights. *J Allergy Clin Immunol* 2003, 111:215–225; quiz 226.
- 48 Ten Hacken NH, Postma DS, Timens W: Airway remodeling and long-term decline in lung function in asthma. *Curr Opin Pulm Med* 2003, 9:9–14.
- 49 Benayoun L, Druille A, Dombret MC, et al.: Airway structural alterations selectively associated with severe asthma. *Am J Respir Crit Care Med* 2003, 167:1360–1368.
- A very interesting study comparing bronchial biopsies from patients with severe persistent asthma with those from patients with milder asthma and patients with COPD. This is an important contribution to the characterization of the structural alterations that occur in severe asthma and their functional consequences.
- 50 Niimi A, Matsumoto H, Amitani R, et al.: Airway wall thickness in asthma assessed by computed tomography: relation to clinical indices. *Am J Respir Crit Care Med* 2000, 162:1518–1523.
- 51 Nakano Y, Muro S, Sakai H, et al.: Computed tomographic measurements of airway dimensions and emphysema in smokers: correlation with lung function. *Am J Respir Crit Care Med* 2000, 162:1102–1108.
- 52 Spiropoulos K, Trakada G, Kalamboka D, et al.: Can high resolution computed tomography predict lung function in patients with chronic obstructive pulmonary disease? *Lung* 2003, 181:169–181.
- 53 Little SA, Sproule MW, Cowan MD, et al.: High resolution computed tomographic assessment of airway wall thickness in chronic asthma: reproducibility and relationship with lung function and severity. *Thorax* 2002, 57:247–253.
- 54 Cerveri I, Dore R, Corsico A, et al.: Assessment of emphysema in COPD: a functional and radiologic study. *Chest* 2004, 125:1714–1718.
- 55 Boschetto P, Miniati M, Miotto D, et al.: Predominant emphysema phenotype in chronic obstructive pulmonary. *Eur Respir J* 2003, 21:450–454.
- 56 Gono H, Fujimoto K, Kawakami S, et al.: Evaluation of airway wall thickness and air trapping by HRCT in asymptomatic asthma. *Eur Respir J* 2003, 22:965–971.
- A significant contribution to understanding of the structural changes (assessed by HRCT) that occur in airways of patients with asthma and how these changes may affect development of irreversible airflow obstruction.
- 57 Mitsunobu F, Ashida K, Hosaki Y, et al.: Complexity of terminal airspace geometry assessed by computed tomography in asthma. *Am J Respir Crit Care Med* 2003, 167:411–417.
- 58 Sutherland ER, Martin RJ: Airway inflammation in chronic obstructive pulmonary disease: comparisons with asthma. *J Allergy Clin Immunol* 2003, 112:819–827; quiz 828.
- An excellent overview of airway inflammation in asthma and COPD. Involvement of inflammatory cells and mediators is contrasted between asthma and COPD. The link between inflammation and clinical outcomes in these diseases is also discussed.

- 59 Fabbri LM, Romagnoli M, Corbetta L, et al.: Differences in airway inflammation in patients with fixed airflow obstruction due to asthma or chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2003, 167:418–424.

One of the most significant recent contributions to understanding of the overlap between asthma and COPD. This study demonstrates that even in the presence of fixed airflow obstruction, asthma and COPD can be differentiated based on a large number of distinct characteristics.

- 60 Romagnoli M, Vachier I, Tarodo de la Fuente P, et al.: Eosinophilic inflammation in sputum of poorly controlled asthmatics. *Eur Respir J* 2002, 20:1370–1377.
- 61 Green RH, Brightling CE, McKenna S, et al.: Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. *Lancet* 2002, 360:1715–1721.

This study investigates a treatment strategy in moderate-severe asthma directed at normalization of eosinophil count and compares its effectiveness with that of standard asthma guidelines.

- 62 Keatings VM, Jatakanon A, Worsdell YM, et al.: Effects of inhaled and oral glucocorticoids on inflammatory indices in asthma and COPD. *Am J Respir Crit Care Med* 1997, 155:542–548.
- 63 Bourdin A, Serre I, Flamme H, et al.: Can endobronchial biopsy analysis be recommended to discriminate between asthma and COPD in routine practice? *Thorax* 2004, 59:488–493.
- 64 Stankiewicz W, Dabrowski MP, Chcialowski A, et al.: Cellular and cytokine immunoregulation in patients with chronic obstructive pulmonary disease and bronchial asthma. *Mediat Inflamm* 2002, 11:307–312.
- 65 Burrows B, Knudson RJ, Cline MG, et al.: Quantitative relationships between cigarette smoking and ventilatory function. *Am Rev Respir Dis* 1977, 115:195–205.
- 66 Mitsunobu F, Ashida K, Hosaki Y, et al.: Influence of long-term cigarette smoking on immunoglobulin E-mediated allergy, pulmonary function, and high-resolution computed tomography lung densitometry in elderly patients with asthma. *Clin Exp Allergy* 2004, 34:59–64.

The authors investigate the influence of cigarette smoking on clinical features in elderly patients with asthma. This study provides new evidence on the effects of smoking on generation of leukotrienes and other asthma-related phenotypes, such as IgE and bronchial hyperresponsiveness.

- 67 Petays T, von Hertzen L, Metso T, et al.: Smoking and atopy as determinants of sputum eosinophilia and bronchial hyper-responsiveness in adults with normal lung function. *Respir Med* 2003, 97:947–954.

An interesting report on adults with normal lung function living in Finland and Russia. This study investigates determinants of sputum eosinophilia and bronchial hyperresponsiveness and provides evidence for a major effect of cigarette smoking on these phenotypes in populations from both countries.

- 68 Tashkin DP, Altose MD, Connett JE, et al.: Methacholine reactivity predicts changes in lung function over time in smokers with early chronic obstructive pulmonary disease. The Lung Health Study Research Group. *Am J Respir Crit Care Med* 1996, 153:1802–1811.
- 69 Ruse CE, Hill MC, Burton PR, et al.: Associations between polymorphisms of the high-affinity immunoglobulin E receptor and late-onset airflow obstruction in older populations. *J Am Geriatr Soc* 2003, 51:1265–1269.
- 70 Balmes J, Becklake M, Blanc P, et al.: American Thoracic Society statement: occupational contribution to the burden of airway disease. *Am J Respir Crit Care Med* 2003, 167:787–797.

In this important statement from the American Thoracic Society, epidemiologic and experimental evidence for the occupational contribution to asthma and COPD is nicely reviewed. The importance of considering potential occupational etiologies when assessing patients with obstructive lung disease is outlined.