

# Asthma–COPD overlap 2015: now we are six

Peter G Gibson,<sup>1,2</sup> Vanessa M McDonald<sup>1,2</sup>

<sup>1</sup>Priority Research Centre for Asthma and Respiratory Diseases, University of Newcastle, Newcastle, New South Wales, Australia

<sup>2</sup>Department of Respiratory and Sleep Medicine, John Hunter Hospital, New Lambton Heights, New South Wales, Australia

## Correspondence to

Professor Peter G Gibson, Department of Respiratory and Sleep Medicine, John Hunter Hospital, Level 2, Hunter Medical Research Institute, Kookaburra Circuit, New Lambton Heights, NSW 2305, Australia; Peter.Gibson@hnehealth.nsw.gov.au

Received 5 January 2015

Revised 9 April 2015

Accepted 17 April 2015

Published Online First

6 May 2015

## ABSTRACT

**Background** The overlap between asthma and COPD is increasingly recognised. This review examines the new insights, treatment and remaining knowledge gaps for asthma–COPD overlap.

**Method** A systematic literature review of cluster analyses of asthma and COPD was performed. Articles from 2009 to the present dealing with prevalence, morbidity and treatment of asthma–COPD overlap were identified and reviewed.

**Results** Asthma–COPD overlap was consistently recognised in studies using a variety of different study designs and sampling. The prevalence was approximately 20% in patients with obstructive airway diseases. Asthma–COPD overlap was associated with increased morbidity and possibly an increased mortality and comorbidity. There was evidence of a heterogeneous pattern of airway inflammation that included eosinophilic (in adult asthma), neutrophilic or mixed patterns (in severe asthma and COPD). Systemic inflammation was present in asthma–COPD overlap and resembled that of COPD. Within asthma–COPD overlap, there is evidence of different subgroups, and recognition using bronchodilator responsiveness has not been successful. Guidelines generally recommend a serial approach to assessment, with treatment recommendations dominated by an asthma paradigm. Research is needed into key clinical features that impact outcome, mechanisms and treatment approaches in asthma–COPD overlap. Identifying and treating disease components by multidimensional assessment shows promise.

**Conclusions** Asthma–COPD overlap has drawn attention to the significant heterogeneity that exists within obstructive airway diseases. It should be replaced by novel approaches that identify and manage the components of this heterogeneity, such as multidimensional assessment and treatment. Future research is needed to test these novel and personalised approaches.

## INTRODUCTION

Since *Thorax* reviewed this topic in 2009,<sup>1</sup> there have been many publications addressing the heterogeneity within asthma and COPD and the problem of the overlap between asthma and COPD. What progress has been made? What new insights have been gained? How can we treat this problem? What knowledge gaps remain? This review will address these issues (box 1).

## DEFINITION

This review adopts a nominalist approach to disease definition.<sup>2</sup> The overlap of asthma and COPD is diagnosed when a patient has the defining characteristic of COPD, namely incompletely reversible airflow limitation<sup>3</sup> as well as features of asthma.<sup>2</sup> This is consistent with the description of the

asthma–COPD overlap syndrome (ACOS) recommended by the Global Initiative for Asthma (GINA) and Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines committees, which is “Asthma–COPD overlap syndrome (ACOS) is characterized by persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD. ACOS is therefore identified by the features it shares with both asthma and COPD”.<sup>4</sup>

## PREVALENCE AND IMPACT

Articles from 2009 to the present dealing with prevalence, morbidity and treatment of asthma–COPD overlap were identified and reviewed. We searched MEDLINE (2009–2014) using the search terms (overlap AND asthma [MeSH Terms] OR COPD [MeSH Terms] OR (chronic obstructive pulmonary disease [MeSH Terms]) OR (chronic obstructive airway disease [MeSH Terms])). The prevalence of asthma–COPD overlap, and the impact of comorbid disease have been described in cohort and population-based studies<sup>5–9</sup> (box 1 and figure 1). A variety of sampling methods and case definitions have been used to assess asthma–COPD overlap. The prevalence was found to be approximately 20% of participants with obstructive airway disease (figure 1) and 2% of adult population samples.<sup>8–10</sup> Patients with coexisting asthma and COPD have an increased illness burden compared with asthma or COPD alone. They suffer greater health status impairment and more frequent acute exacerbations resulting in increased hospitalisation<sup>5–7</sup> (box 1). Mortality may also be increased.<sup>10</sup> Diaz-Guzman<sup>10</sup> reported a population sample of 15 203 participants and found that 2.7% had coexisting asthma and COPD. This group had the highest risk of mortality (HR 1.45, 95% CI 1.06 to 1.98), followed by COPD alone (HR 1.28, 95% CI 1.13 to 1.45) and asthma alone (HR 1.04, 95% CI 0.85 to 1.27).

## COMORBIDITIES

Comorbidities are common and contribute to a significant disease burden in COPD.<sup>11</sup> In asthma, comorbidities are generally not a recognised problem, except in severe asthma<sup>12</sup> and asthma in the elderly.<sup>13</sup> The comorbidity spectrum in asthma–COPD overlap is an area of increasing research interest. The Charlson Co-morbidity Index has been reported and compared with asthma and COPD alone in a number of recent studies (table 1). Some studies identify increased comorbidity in asthma–COPD overlap,<sup>5 8 14–16</sup> whereas others do not<sup>7 17</sup> (table 1). One study reported excess diabetes, stroke and arthritis in asthma–COPD overlap.<sup>8</sup> There is a need to investigate comorbidities in asthma–COPD



► <http://dx.doi.org/10.1136/thoraxjnl-2015-207228>



CrossMark

**To cite:** Gibson PG, McDonald VM. *Thorax* 2015;**70**:683–691.

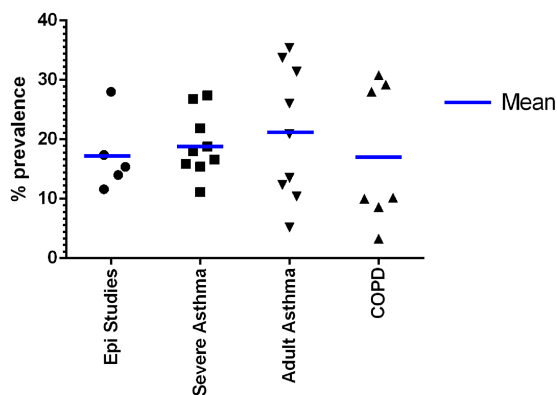
### Box 1 Why is asthma–COPD overlap important?

- Prevalence:** Asthma–COPD overlap has a prevalence of approximately 20% of patients with obstructive airway disease (asthma or COPD) and 2% in the general population. This is consistent across study designs and varying definitions.
- Increased illness burden:** Asthma–COPD overlap leads to significant health status impairment, increased exacerbations and increased hospitalisations.
- Treatment implications:**
  - ▶ When asthma is not recognised, there is potential for increased adverse events and drug toxicity from long-acting  $\beta_2$  agonists use.
  - ▶ There is an increased response to inhaled corticosteroids and long-acting  $\beta_2$  agonists in COPD patients with asthma.
  - ▶ There is limited evidence for treatment recommendations because asthma–COPD overlap patients are excluded from randomised controlled trials.
- Childhood onset:** There may be opportunities to prevent the development of asthma–COPD overlap by studying early-life origins.

overlap in terms of their frequency, severity, impact on outcomes and mechanisms.

### CLUSTER ANALYSIS: ASTHMA–COPD OVERLAP AS AN AIRWAY DISEASE PHENOTYPE

Is asthma–COPD overlap a phenotype of airway disease?<sup>18</sup> Cluster analyses of asthma and COPD can be used to answer this question.<sup>19</sup> In asthma, a MEDLINE search was conducted up to 1 September 2014 using the terms (asthma[MeSH Terms] AND cluster, n=621 hits), and reference lists of relevant articles were assessed. Eligible articles included adult patients with asthma, used clustering statistical methodology and included post-bronchodilator FEV<sub>1</sub> among the cluster variables (since this is the defining characteristic of COPD). The asthma–COPD overlap phenotype was identified by inclusion of ‘overlap’ or ‘airflow obstruction’ in the label of the phenotype, or in the textual description of the phenotypic characteristics. The tables of phenotype characteristics were also required to demonstrate significant differences in post-bronchodilator FEV<sub>1</sub> in the asthma–COPD overlap phenotype. Relevant articles were



**Figure 1** Prevalence of asthma–COPD overlap in studies of varying designs.

**Table 1** Charlson comorbidity index in asthma–COPD overlap studies

	Asthma	COPD	Overlap	p Value
Fu <i>et al</i> <sup>17</sup>	3.1±1.2	3.8±0.9	3.8±1.1	>0.05
Miravittles <i>et al</i> <sup>5</sup>	–	0.89±1.07	1.44±0.78	<0.001
Menezes <i>et al</i> <sup>7</sup>	1.2±1.1	0.9±0.9	0.9±1.0	0.079
McDonald <i>et al</i> <sup>16</sup>	3.6±1.2	4.2±0.8	3.6±1.1*	<0.04
Blanchette <i>et al</i> <sup>14</sup>	–	2.3±2.3	2.6±2.1	<0.001
Rhee <i>et al</i> <sup>15</sup>	–	–	Comorbidities increased compared with COPD	<0.02

\*COPD vs overlap.

identified and assessed and included 11 in severe asthma, and 12 in adult asthma. If an asthma–COPD overlap cluster was reported, it was assessed for generalisability (was it reported by other studies?), characteristics (are they similar between studies?), temporal stability, independent validation, prognostic relevance and association with treatment responsiveness.

### Asthma–COPD overlap in severe asthma

Asthma–COPD overlap was identified as a distinct phenotype of severe asthma in nine studies, whereas two studies failed to find it as a separate phenotype (table 2).<sup>20–29</sup> These results establish that asthma–COPD overlap is a distinct phenotype that can be identified across different severe asthma populations. Independent validation of asthma–COPD overlap as a phenotype was confirmed in four studies,<sup>21 23 24 26</sup> and two studies reported that the asthma–COPD overlap phenotype was stable over time.<sup>23 26</sup> Two studies evaluated the prognostic impact of asthma–COPD overlap.<sup>23 26</sup> One study found similar 1-year outcomes in asthma–COPD overlap compared with other phenotypes,<sup>26</sup> whereas Newby *et al*<sup>23</sup> observed an improvement in lung function when asthma–COPD overlap patients had systematic treatment over a 1-year period. Ortega *et al*<sup>27</sup> identified that the asthma–COPD overlap sub-phenotype of severe eosinophilic asthma with frequent exacerbations had the best response to mepolizumab, with a 68% reduction in severe exacerbations.

The overlap phenotype in severe asthma had a mean prevalence of 17.9%, ranging from 11% to 27% (figure 1 and table 2). There was no specific gender dominance (45% were men). The severe asthma–COPD overlap phenotype had severe airflow limitation with post-bronchodilator FEV<sub>1</sub> of 56.5% predicted, ranging from 50% to 66% predicted. Asthma duration was a mean of 25 years, ranging between 9 and 34 years, with asthma onset in the twenties. There were high rates of maintenance oral corticosteroid (OCS) treatment (mean 45%, range 26–62) and high rates of severe exacerbations (3/year). Atopy was variable, occurring in 33–91% of patients. A neutrophil-dominant inflammation was reported in four studies where it was measured.<sup>21 24 29 30</sup>

There were two studies that failed to identify asthma–COPD overlap.<sup>20 22</sup> The reasons for this are unclear. Gupta *et al*<sup>20</sup> conducted a cluster analysis of patients with severe asthma and related quantitative CT thorax findings. While the unsupervised cluster analysis did not identify a specific asthma–COPD overlap subgroup, the supervised a priori analysis did identify a group with severe asthma and persistent airflow limitation. Haldar *et al*<sup>22</sup> performed cluster analysis on asthma groups derived from primary care and secondary care/refractory asthma. Asthma–COPD overlap was not identified as a specific phenotype in either analysis.

**Table 2** Overlap phenotype in severe asthma

Author (year)	n (%)	% male	FEV <sub>1</sub> , predicted, post bronchodilator	Duration	Age of onset	OCS maintenance, %	Airway inflammatory phenotype
Moore (2010) <sup>24</sup>	116 (15.9)	37	58	–	–	47	E N
Jang (2013) <sup>28</sup>	21 (21.9)	38	49	24	24	–	N
Ghebre <i>et al.</i> (2015) <sup>21</sup>	47 (27.4)	55	60	9	–	40	N
Newby (2014) <sup>23</sup>	54 (15.4)	43	53	–	25	57	–
Bourdin (2014) (A) <sup>26</sup>	21 (18.8)	57	50	34	–	62	–
Bourdin (2014) (B) <sup>26</sup>	30 (26.8)	57	52	32	–	57	–
Moore (2014) <sup>29</sup>	47 (11.1)	57	61	28	22	26	N
Ortega (2014) <sup>27</sup>	102 (16.6)	20.5	66	19	–	33	E

E, eosinophilic; N, neutrophilic; OCS, oral corticosteroid.

### Asthma–COPD overlap in adult asthma

Relevant cluster analyses of adult asthma were reported in 12 papers.<sup>23 31–40</sup> Asthma–COPD overlap was identified as a distinct phenotype in nine studies. There were three studies that failed to identify an asthma–COPD overlap phenotype.<sup>31–33</sup> The study participants were sampled from respiratory clinics (n=6), population surveys (n=4), clinical trial populations (n=2) and an asthma register (n=1). Independent validation of asthma–COPD overlap as a phenotype was confirmed in two of three studies.<sup>32 34</sup> Temporal stability and treatment responses were not evaluated. One study evaluated the prognostic impact of asthma–COPD overlap and reported it to be associated with more OCS use and worse asthma control.<sup>35</sup>

In adult asthma, the asthma–COPD overlap phenotype had a prevalence of 20.9% (range 5.2–35.4%) (figure 1). While there was not an overall gender dominance (54% men), in some populations the overlap phenotype were predominantly men.<sup>36–38</sup> The adult asthma–COPD overlap phenotype had more severe airflow limitation with post-bronchodilator FEV<sub>1</sub> of 59.5% predicted (range from 47% to 84%), a mean asthma duration of 19 years (range 10–32) and a mean age of onset of 33 years old. The rates of maintenance OCS treatment were low. Atopy was present in 62%. An eosinophil-dominant inflammation was reported in six studies. Treatment optimisation was found to improve FEV<sub>1</sub> in three studies.<sup>23 39 40</sup>

### Asthma–COPD overlap and cluster analyses of COPD

In order to address whether an asthma–COPD phenotype was identified by unbiased analysis of patients with COPD, a MEDLINE search was conducted up to 1 September 2014 using the terms (COPD[MeSH Terms] OR (chronic obstructive pulmonary disease [MeSH Terms]) OR (chronic obstructive airway disease [MeSH Terms] AND cluster, n=293 hits) and reference

lists of relevant articles were assessed. Eligible articles included patients with COPD, used clustering statistical methodology and included asthma (as an inclusion criteria or comorbidity), bronchodilator responsiveness (BDR), airway hyper-responsiveness, atopy or eosinophilia among the cluster variables. Articles were excluded if they were reviews, not cluster analyses (eg, cluster sampling, cluster randomised controlled trials (RCTs)) or not in English. We identified 20 cluster analysis studies of COPD. There were 11 relevant studies that included asthma or asthma-related variables in the population selection or in the variables selected for clustering. Of these 11 studies, 7 identified an overlap phenotype<sup>21 41–46</sup> and 4 did not.<sup>47–50</sup>

The prevalence of the asthma–COPD overlap phenotype in COPD was 21.4%, and ranged between 8.6% and 33% (figure 1 and table 3). Most (69%) asthma–COPD overlap patients were men (range 54–86%), and aged between 60 and 68 years (mean age 64.6) with a smoking exposure of 38.7 (range 11–68.6) pack-years. Post-bronchodilator FEV<sub>1</sub>% predicted was 49.3%, and mean BDR was 23.9%. Bafadhel *et al.*<sup>45</sup> reported the overlap phenotype to be associated with eosinophilic bronchitis, whereas Ghebre *et al.*<sup>21</sup> reported a neutrophilic pattern of inflammation associated with elevated interleukin (IL)-1β levels and bacterial colonisation. Two studies showed that asthma–COPD overlap had a better response to inhaled corticosteroid (ICS).<sup>41 51</sup> In a cluster analysis of two RCTs involving patients with COPD, the overlap cluster had a significant reduction in COPD exacerbations with Salmeterol/Fluticasone proportionate.<sup>41</sup>

### ASTHMA–COPD OVERLAP AND INFLAMMATORY BIOMARKERS

#### Systemic inflammation

Low-grade systemic inflammation is hypothesised as a unifying mechanism in COPD.<sup>11 52</sup> Its role in asthma is less defined but

**Table 3** The prevalence of the asthma–COPD overlap phenotype in COPD

Author (year)	n (%)	% male	FEV <sub>1</sub> , predicted, post bronchodilator	Age, years	Smoking % (pack years)
Wardlaw (2005) <sup>46</sup>	5 (10.2)	80	46.8	59.8	–(18.4)
Weatherall (2010) <sup>42</sup>	15 (8.6)	73	58	65	–(36)
Cho (2010) <sup>43</sup>	102 (33)	64	34	68	–(68)
Jo (2010) <sup>44</sup>	59 (30.8)	86	59.6	67	81 (36.6)
Bafadhel (2011) <sup>45</sup>	19 (25)	74	51	68	42 (50)
Disantostefano (2013) <sup>41</sup>	156 (10)	54	31.3	64	100 (50)
Ghebre (2014) <sup>21</sup>	47 (27.4)	55	63.9	60	62 (11)

is likely to be significant particularly in the presence of comorbidity and severe disease. Little is known about the role of systemic inflammation in asthma–COPD overlap. In several studies, evidence of systemic inflammation was identified in asthma–COPD overlap, and it was similar to COPD,<sup>5 53 54</sup> with elevated IL-6, C-reactive protein, tumour necrosis factor- $\alpha$ , surfactant protein A and a reduction in plasma levels of soluble receptor for advanced glycation end-products. These data suggest that systemic inflammation in asthma–COPD overlap is common and that the inflammatory systemic profile resembles that of COPD.

### Airway inflammation

While asthma has traditionally been considered a disease associated with eosinophilic airway inflammation and COPD one of neutrophilic inflammation, it is now evident that eosinophilia, neutrophilia and a mixed inflammatory phenotype can exist in both asthma<sup>55</sup> and in COPD.<sup>56 57</sup> The pattern of airway inflammation in asthma–COPD overlap was reported in a large cross-sectional study of >4000 patients with airway disease,<sup>58</sup> where approximately 9% of participants had asthma–COPD overlap. Their airway inflammatory profile demonstrated eosinophilic bronchitis (35%), neutrophilic bronchitis (19%) and a mixed inflammatory pattern in 10%. These data support the concept that asthma–COPD overlap is a heterogeneous inflammatory disorder of the airways.

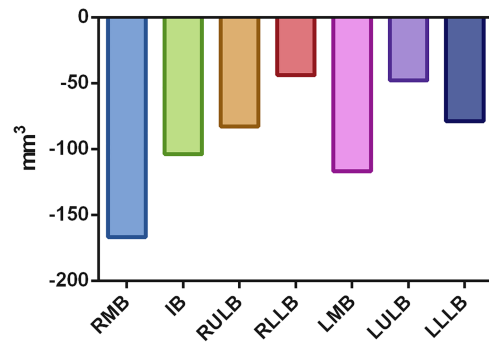
Iwamoto<sup>54</sup> reported increased induced sputum levels of myeloperoxidase in overlap and in COPD, and that neutrophil gelatinase-associated lipocalin was significantly elevated in the overlap group compared with COPD. An analysis of the Severe Asthma Research Programme (SARP) cohort (n=378) for 112 variables in a cluster analysis reported that in the reduced lung function group (ie, overlap) the majority of these subjects (>83%) had sputum neutrophilia either alone or with concurrent sputum eosinophilia.<sup>25</sup>

### CHILDHOOD ORIGIN OF ASTHMA–COPD OVERLAP

Since the last review,<sup>1</sup> there is now evidence that asthma–COPD overlap can have its origins in childhood. Incompletely reversible airflow limitation that results from long-standing asthma was recognised by clinical observation in the 1980s<sup>59</sup> and later confirmed by population-based studies in adults. This indicates that long-term adult asthma could lead to incompletely reversible airflow limitation or asthma–COPD overlap.<sup>1</sup> When this fixed airflow limitation begins and whether childhood asthma is also a risk for asthma–COPD overlap have recently been investigated. Longitudinal studies of children with asthma who have now reached adulthood show that long-standing childhood asthma can lead to the development of incompletely reversible airflow obstruction in adults.<sup>60 61</sup> The effect is greatest in asthmatics who smoke<sup>60</sup> and in children with severe asthma.<sup>61</sup> In children with milder asthma, only approximately 2% develop overlap,<sup>60</sup> whereas severe asthma in childhood massively increases the risk for adult COPD.<sup>61</sup>

These epidemiological associations have now been supported by CT measurements of airway dimensions. Adult smokers with a history of childhood onset asthma have smaller airways than smokers without a history of childhood asthma.<sup>62</sup> These smaller airway dimensions extended throughout the entire bronchial path that was examined (figure 2).

Whether fixed airflow limitation is present in childhood or develops during adulthood is not yet resolved. There is certainly evidence that fixed airflow limitation is present to some degree very early on in childhood asthma.<sup>63 64</sup> Studies also indicate a



**Figure 2** Effect of childhood asthma on airway volume loss in smokers.<sup>62</sup> RMB, right main bronchus; IB, Intermediate bronchus; RULB, right upper lobe bronchus; RLLB, right lower lobe bronchus; LMB, left main bronchus; LULB, left upper lobe bronchus; LLLB, left lower lobe bronchus.

likely interaction between adverse maternal factors that act during pregnancy (such as smoking, atopy and infection), and childhood factors (such as candidate genes, asthma, infections, premature birth), which then can influence lung growth. Superimposed on this are environmental exposures such as air pollution and smoking that also predispose towards the development of COPD.<sup>65</sup>

The specific mechanisms of asthma–COPD overlap resulting from childhood asthma are not clear. Both airway inflammation and airway remodelling have been proposed. These do occur in childhood asthma<sup>66</sup> and in adults have been linked to accelerated decline in lung function.<sup>67</sup> However, whether they can also lead to incomplete lung growth is unclear. It is likely that there are other relevant issues that determine optimal lung growth. The role of severe childhood asthma has been evaluated in the SARP cohort<sup>30</sup> where a cluster with ‘early-onset atopic asthma with advanced airflow limitation’ was identified. The prevalence of this cluster was 18% and children in this cluster had the highest exhaled nitric oxide values, the highest extent of health-care use, highest daily doses of ICS, and most were receiving at least three asthma controller medications. This suggests that severe eosinophilic asthma in childhood leads to incomplete reversibility of airflow obstruction. This cluster has been replicated,<sup>68</sup> and it was found that they had the best treatment response to ICSs and long-acting  $\beta_2$  agonist (LABA) therapy.

Since childhood asthma is a risk factor for asthma–COPD overlap, and severe childhood asthma with airflow limitation is eosinophilic in nature, the question arises as to whether ICS use for childhood asthma can protect against overlap? This issue is not yet settled but seems unlikely based on the CAMP studies and the observations of the Dunedin cohort, where adults with the lowest lung function were using ICS.<sup>69</sup> Addressing these issues in childhood asthma may offer opportunities for prevention of asthma–COPD overlap (box 1).

### ASTHMA–COPD OVERLAP AND CLINICAL PRACTICE GUIDELINES

The evidence base to inform diagnosis, treatment decisions and management approaches in asthma–COPD overlap is limited. This is largely because RCTs recruit highly selected populations and exclude patients with a dual diagnosis.<sup>70–73</sup> Recently, however, a number of key bodies have attempted to include assessment and management guidance for asthma–COPD overlap (table 4). These recommendations have been derived from consensus of expert opinion. They predominantly focus

**Table 4** Summary of consensus documents for asthma–COPD overlap

GINA/GOLD <i>Diagnosis of Diseases of Chronic Airflow Limitation: Asthma, COPD and Asthma-COPD Overlap Syndrome (ACOS)</i> <sup>4</sup>	In 2014, representatives of the scientific committees of GOLD and GINA joined to produce the 'Diagnosis of Diseases of Chronic Airflow Limitation: Asthma, COPD and Asthma-COPD Overlap Syndrome (ACOS)' consensus document. A stepwise approach was recommended whereby the chronic airways disease is recognised through clinical history, physical examination, radiology and potentially screening questionnaires. Next a syndromic approach is recommended where the features of airways disease are assembled and the features that favour asthma and COPD are compared. Three or more features of one disease gives a high likelihood of the correct diagnosis; if there are a similar number of asthma and COPD features, then the overlap of asthma–COPD overlap is more likely. Spirometry is then recommended for confirmation of the diagnosis. If asthma–COPD overlap is confirmed, the initiation of asthma therapy is advised; that is, combination ICS/LABA. Recommendation for specialised referral is the final step
Australian Asthma Management Handbook 2014 <sup>78</sup>	The Australian Asthma Management Handbook recommends pooling of features corresponding to asthma and COPD in order to make a diagnosis, followed by a trial of ICS and then the addition of LABA for symptom control
Guidelines for the Diagnosis and Treatment of COPD <sup>75</sup>	The Japanese Respiratory Society's COPD guidelines suggest the following indices for diagnosis of an asthma component: paroxysmal dyspnoea, cough and wheeze that is worse at night and in the early morning, atopy and the presence of peripheral blood and or sputum eosinophilia. These guidelines also recommend the initiation of ICS irrespective of the severity of COPD, together with a LABA or LAMA
Consensus document on the overlap phenotype COPD–asthma in COPD <sup>74</sup>	The Spanish COPD consensus document <sup>74</sup> for asthma–COPD overlap agreed upon six major and minor criteria required for a diagnosis of asthma–COPD overlap. They suggest that two major criteria (increase in FEV <sub>1</sub> ≥15% and ≥400 mL, eosinophilia in sputum and a history of asthma) or one major and two minor (elevated total IgE, history of atopy and positive bronchodilator response of ≥12% and ≥200 mL) on two or more occasions) are strongly suggestive of the overlap phenotype. Treatment recommendations include ICS with adjustment according to symptoms, lung function and sputum eosinophilia in conjunction with a LABA, and as disease severity increases triple therapy with a LAMA is recommended
Consensus guidelines for the Czech Pneumological and Physiological Society <sup>79</sup>	The Czech guideline defined major and minor criteria for the diagnosis of asthma–COPD overlap: Major criteria included (a) strong bronchodilator test (BDT) positivity (FEV <sub>1</sub> >15% and >400 mL), (b) bronchoconstrictor test (BCT) positivity, (c) FeNO ≥45–50 ppb and/or ↑eosinophils (sputum) ≥3%, (d) history of asthma. Minor criteria included (a) mild BDT positivity (FEV <sub>1</sub> > 12% and > 200 mL), (b) ↑ total IgE, (c) history of atopy and definite COPD diagnosis. The COPD+asthma phenotype can be confirmed by the presence of two major criteria or one major plus two minor criteria

FeNO, fractional exhaled nitric oxide; GINA, Global Initiative for Asthma; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroid; LABA, long-acting β<sub>2</sub> agonist; LAMA, long-acting muscarinic antagonist.

on COPD as a starting point and suggest identifying features typically associated with asthma, then assign an arbitrary weight to these in order to determine whether a person has asthma–COPD overlap. Some proposed asthma features include bronchodilator reversibility,<sup>74</sup> peripheral blood<sup>57</sup> and sputum eosinophilia,<sup>56 58 74</sup> atopy,<sup>74 75</sup> early onset of airways disease,<sup>6</sup> childhood asthma and adult smoking, asthma with neutrophilic bronchitis and a score of several asthma characteristics.<sup>4</sup>

### BDR AS PHENOTYPE MIMICRY

It is likely that certain phenotypic features will be more useful than others. For example, in 2009, it was proposed that asthma–COPD overlap be identified using the combined physiological criteria of COPD (incompletely reversible airflow limitation, post-bronchodilator FEV<sub>1</sub> <80% predicted and FEV<sub>1</sub>/FVC% <0.7), and of asthma (variability of airflow limitation, increased BDR). The 'COPD' component of this definition remains valid and useful in the settings of asthma and COPD. However, BDR has not been found to be a useful way to recognise asthma in patients with COPD. It has been found that BDR is not reproducible, is not related to other typical asthma features<sup>76</sup>, does not predict ICS responsiveness, and is not specific for the asthma–COPD phenotype.<sup>51</sup> This means that in asthma–COPD overlap BDR is an example of phenotype mimicry since, while it is an accepted phenotypic feature of asthma, it does not usefully recognise asthma in the setting of COPD, meaning it is a phenotypic feature that mimics asthma in COPD. This has been an important advance since 2009.

Future work should determine the clinical utility of specific phenotypic features based around their ability to predict risk,

treatment responsiveness or health utility. This requirement for clinically useful criteria aligns with recommendations for phenotype recognition in COPD.<sup>18</sup> Some attempts have been made to do this using health utility assessment for asthma–COPD overlap defined according to the Spanish guidelines.<sup>74</sup> When compared to COPD non-exacerbators, asthma–COPD overlap had significantly lower scores on the health utility assessment.<sup>77</sup>

In response to these limitations, a problem-based individualised approach has been developed where each of the pathological processes are identified and treatment is targeted to these.<sup>13 56 79 80</sup>

### THE FUTURE OF ACOS?

Studies of asthma–COPD overlap have reinforced the heterogeneity of asthma and COPD. It was initially proposed that asthma–COPD overlap could be diagnosed by the coexistence of airflow variability (asthma) and incompletely reversible airflow limitation (COPD). However, this definition has not been useful. Furthermore, it is now recognised that there are several phenotypes that might fall under the asthma–COPD overlap banner but appear to have very different features. These include severe asthma with incomplete airflow reversibility, childhood asthma and adult smoking, and eosinophilic COPD. These phenotypes appear to have such different mechanisms and treatment approaches, and it does not seem useful to assign them the same diagnostic label of asthma–COPD overlap. Coincident with this there have been calls to develop a new taxonomy for asthma and COPD,<sup>19</sup> and to develop management approaches for obstructive airway disease that address the specific components of the illness.<sup>13 80 81</sup> These developments

question the utility of asthma–COPD overlap as a distinct phenotype. We therefore recommend that ACOS be abandoned as a specific phenotype in favour of multidimensional assessment and management of complex obstructive airway diseases. This approach is described below and involves assessment in several domains followed by a personalised management plan. The COPD control panel<sup>80</sup> recommends assessment of disease severity, disease activity and disease impact. While it has not specifically been proposed for asthma–COPD overlap, several domains could be adapted to this purpose. Multidimensional assessment and treatment starts with recognition of obstructive airway disease (similar to the GINA–GOLD recommendations), assesses clinical problems in four domains (airway, comorbidity, risk factors, behavioural management (figure 3) and uses this assessment to design an individualised management plan. Preliminary data from a controlled clinical trial show that this approach leads to major improvements in health status.<sup>56</sup>

### FUTURE RESEARCH

Given the paucity of evidence available to guide treatment decisions in asthma–COPD overlap, it is no surprise that there are many areas of research that require investigation. The areas of research enquiry can be considered in four domains: questions related to the airways, comorbidity, risk factors and self-management (figure 3).

#### Airways

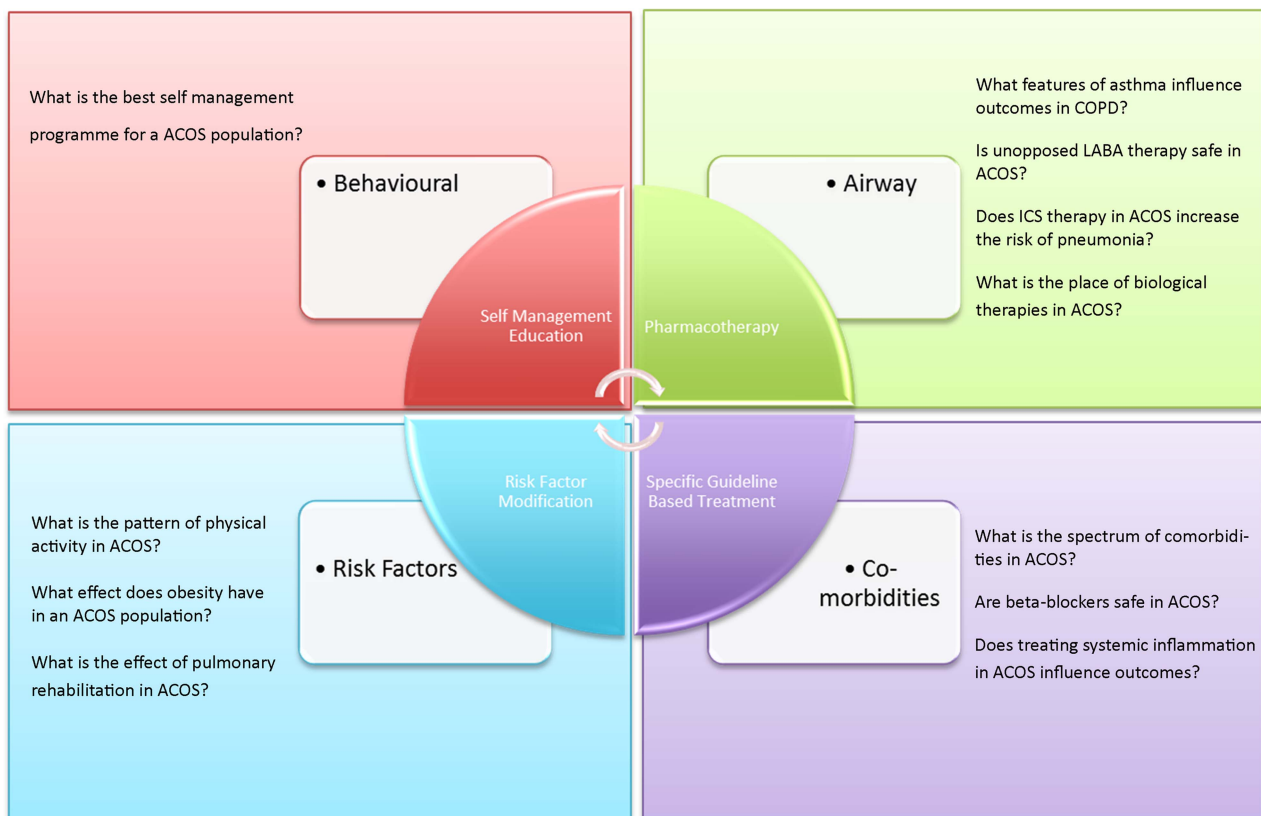
There is a need to improve the characterisation of asthma–COPD overlap. It is likely that a risk-based approach will be most useful, as has occurred in other diseases. For example, which features of asthma, such as BDR, eosinophilia and atopy, confer an increased risk to a patient with COPD? Alternatively,

in a patient with asthma, what is the increased risk associated with coexisting incomplete reversibility of airflow limitation? Some forms of asthma–COPD overlap seem so different that combining them into a single phenotype is unlikely to be useful. For example, the phenotype of long-standing asthma with the development of incomplete reversibility seems very different to asthma in a current smoker, or COPD with eosinophilia.

The treatment recommendations for managing COPD are to initiate long-acting bronchodilator therapy to control symptoms and add ICS once the FEV<sub>1</sub> falls below 50% predicted or patients experience frequent exacerbations.<sup>3</sup> In asthma, one would first initiate ICS and continue to step up the ICS dose and add on LABA to achieve good control. The risk profiles of ICS and LABA may be different in asthma and COPD. In COPD, ICS use can increase the risk of pneumonia. In asthma, the use of LABA without ICS, as recommended in COPD, is associated with deteriorating asthma control, increased severity and mortality. A person with asthma–COPD overlap, where the coexisting asthma is not recognised, could be treated with LABA alone.

Is there an increased risk of unopposed LABA therapy in asthma–COPD overlap? In a population-based longitudinal cohort study,<sup>82</sup> new users of LABA and ICS/LABA were followed for a median of 2.5 years. The asthma–COPD overlap group comprised 28% of the population and had an increased relative risk of hospitalisation or death by approximately 8% when they received LABA monotherapy. These data suggest that the unopposed use of LABA in asthma–COPD overlap may be associated with increased risk compared with a COPD population without asthma.

Does ICS therapy in asthma–COPD overlap cause the same toxicity and pneumonia risk as in COPD alone? This may not be



**Figure 3** Asthma–COPD overlap syndrome (ACOS) research directions. ICS, inhaled corticosteroid; LABA, long-acting  $\beta_2$  agonist. Adapted with permission from 'The Lancet'.

the case, as Gershon *et al*<sup>82</sup> reported no difference in pneumonia risk compared with LABA alone. This requires further investigation. ICS back titration is now a focus of both asthma and COPD management following studies published in 2014 showing that ICS dose reduction in COPD was possible without an increase in exacerbations.<sup>83–84</sup> Whether this is safe in asthma–COPD overlap remains to be determined. Inflammation-guided therapy is recommended in severe asthma,<sup>85</sup> but is it effective in asthma–COPD overlap? The place of pathway-specific biologicals in asthma–COPD overlap should also be investigated based on promising results from targeted therapy studies.<sup>27–86</sup>

## COMORBIDITY

Comorbidities are common in COPD and have a significant impact on patient outcomes. The spectrum and prevalence of asthma–COPD overlap comorbidities is not well established, nor is the impact. Very little is also known about the mechanisms that link comorbidities with asthma–COPD overlap. Studies investigating comorbidities in asthma–COPD overlap will provide much needed insight.

β-Blockers are effective in chronic heart disease where they reduce mortality. They are safe in COPD but underused.<sup>87</sup> In asthma, β-blockers can induce serious bronchoconstriction. Their risk–benefit profile in patients with asthma–COPD overlap and comorbid cardiac disease is unclear.

## RISK FACTORS

The importance of physical activity is well established in COPD,<sup>88</sup> and patients with COPD are less active and more sedentary than their healthy aged match counterparts.<sup>89</sup> Far less research has characterised physical activity in an asthma population. Investigating physical inactivity and sedentary behaviour characteristics, impact and treatment interventions in an asthma–COPD overlap population is an evolving area of research.

In COPD, mild-to-moderate obesity has been associated with improved survival<sup>90</sup> and reduced lung function decline.<sup>91</sup> Conversely in asthma obesity is detrimental and associated with increased disease severity, poor symptom control and increased airway inflammation.<sup>92</sup> The effect of obesity in asthma–COPD overlap is unknown.

Pulmonary rehabilitation, a fundamental treatment recommendation for patients with symptomatic COPD, has not been rigorously evaluated in asthma–COPD overlap. One RCT demonstrated improved health status compared with usual care following an exercise programme.<sup>93</sup> The most appropriate pulmonary rehabilitation approach in an asthma–COPD overlap population warrants further investigation.

## SELF-MANAGEMENT

What self-management approaches work in asthma–COPD overlap? Self-management programmes for both asthma and COPD have proven effective; however, asthma self-management programmes are not directly transferrable to patients with COPD,<sup>94</sup> and careful selection of patients with COPD is required to avoid harm.<sup>95</sup> It is therefore reasonable to assume that patients with asthma–COPD overlap may require a different approach; this needs to be tested in an overlap population.

## CONCLUSIONS

Highlighting the overlap between asthma and COPD has increased recognition of the heterogeneity in obstructive airway diseases. Asthma–COPD overlap is consistently identified with a prevalence of around 20% of patients with asthma or COPD (box 1 and figure 1). People with features of asthma and COPD

have increased morbidity, mortality and possibly more comorbidities. The underlying airway inflammatory pattern can be eosinophilic (adult asthma and childhood asthma), neutrophilic (severe asthma, COPD) or both. Whereas airway inflammation is heterogeneous, the systemic inflammation that occurs in asthma–COPD overlap resembles that of COPD. A precise and useful definition of asthma–COPD overlap has not been possible, and the condition itself appears to compromise several different sub-phenotypes. It is proposed that addressing disease components via a multidimensional approach to assessment and management of obstructive airway diseases will be useful to manage the heterogeneity of these conditions.

**Contributors** PGG developed the concepts, wrote and critically reviewed the manuscript. VMM developed the concepts, wrote and critically reviewed the manuscript.

**Competing interests** None declared.

**Provenance and peer review** Not commissioned; externally peer reviewed.

## REFERENCES

- Gibson PG, Simpson JS. The overlap syndrome of asthma and COPD: what are its features and how important is it? *Thorax* 2009;64:728–35.
- Campbell EJM, Scadding JG, Roberts RS. The concept of disease. *BMJ* 1979;2:757–62.
- Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease. 2014.
- Global Initiative for Asthma (GINA). Diagnosis of Diseases of Chronic Airflow Limitation: Asthma, COPD and Asthma–COPD Overlap Syndrome (ACOS): Global Strategy for Asthma Management and Prevention. 2014.
- Miravittles M, Soriano JB, Ancochea J, *et al*. Characterisation of the overlap COPD–asthma phenotype. Focus on physical activity and health status. *Respir Med* 2013;107:1053–60.
- Hardin M, Cho M, McDonald M, *et al*. The clinical and genetic features of the COPD asthma overlap syndrome. *Eur Respir J* 2014;44:341–50.
- Menezes AM, Montes de Oca M, Perez-Padilla R, *et al*. Increased risk of exacerbation and hospitalization in subjects with an overlap phenotype: COPD–asthma. *Chest* 2014;145:297–304.
- Pleasant RA, Ohar JA, Croft JB, *et al*. Chronic obstructive pulmonary disease and asthma–patient characteristics and health impairment. *COPD* 2014;11:256–66.
- de Marco R, Pesce G, Marcon A, *et al*. The coexistence of asthma and chronic obstructive pulmonary disease (COPD): prevalence and risk factors in young, middle-aged and elderly people from the general population. *PLoS ONE* 2013;8:e62985.
- Diaz-Guzman E, Khosravi M, Mannino DM. Asthma, chronic obstructive pulmonary disease, and mortality in the U.S. population. *COPD* 2011;8:400–7.
- McDonald VM, Higgins I, Gibson PG. Managing older patients with coexistent asthma and COPD: diagnostic and therapeutic challenges. *Drugs Aging* 2013;30:1–17.
- McDonald VM, Gibson PG. Exacerbations of severe asthma. *Clin Exp Allergy* 2012;42:670–7.
- Gibson PG, McDonald VM, Marks GB. Asthma in the Older Adult. *Lancet* 2010;374:803–13.
- Blanchette CM, Gutierrez B, Ory C, *et al*. Economic burden in direct costs of concomitant chronic obstructive pulmonary disease and asthma in a Medicare Advantage population. *J Manag Care Pharm* 2008;14:176–85.
- Rhee CK, Yoon HK, Yoo KH, *et al*. Medical utilization and cost in patients with overlap syndrome of chronic obstructive pulmonary disease and asthma. *COPD* 2014;11:163–70.
- McDonald VM, Simpson JL, Higgins I, *et al*. Multidimensional assessment of older people with asthma & COPD: clinical management and health status. *Age Ageing* 2011;40:42–9.
- Fu JJ, Gibson PG, Simpson JL, *et al*. Longitudinal changes in clinical outcomes in older patients with asthma, COPD and asthma–COPD overlap syndrome. *Respiration* 2014;87:63–74.
- Han MK, Agusti A, Calverley PM, *et al*. Chronic obstructive pulmonary disease phenotypes: the future of COPD. *Am J Respir Crit Care Med* 2010;182:598–604.
- Vanfleteren LE, Kocks JW, Stone IS, *et al*. Moving from the Oslerian paradigm to the post-genomic era: are asthma and COPD outdated terms? *Thorax* 2014;69:72–9.
- Gupta S, Siddiqui S, Haldar P, *et al*. Quantitative analysis of high-resolution computed tomography scans in severe asthma subphenotypes. *Thorax* 2010;65:775–81.

- 21 Ghebre MA, Bafadhel M, Desai D, *et al.* Biological clustering supports both "Dutch" and "British" hypotheses of asthma and chronic obstructive pulmonary disease. *J Allergy Clin Immunol* 2015;135:63–72.
- 22 Haldar P, Pavord ID, Shaw DE, *et al.* Cluster analysis and clinical asthma phenotypes. *Am J Respir Crit Care Med* 2008;178:218–24.
- 23 Newby C, Heaney LG, Menzies-Gow A, *et al.* Statistical cluster analysis of the British Thoracic Society Severe refractory Asthma Registry: clinical outcomes and phenotype stability. *PLoS ONE* 2014;9:e102987.
- 24 Moore WC, Meyers DA, Wenzel SE, *et al.* Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. *Am J Respir Crit Care Med* 2010;181:315–23.
- 25 Wu W, Bleecker E, Moore W, *et al.* Unsupervised phenotyping of Severe Asthma Research Program participants using expanded lung data. *J Allergy Clin Immunol* 2014;133:1280–8.
- 26 Bourdin A, Molinari N, Vachier I, *et al.* Prognostic value of cluster analysis of severe asthma phenotypes. *J Allergy Clin Immunol* 2014;134:1043–50.
- 27 Ortega H, Li H, Suruki R, *et al.* Cluster analysis and characterization of response to mepolizumab. A step closer to personalized medicine for patients with severe asthma. *Ann Am Thorac Soc* 2014;11:1011–7.
- 28 Jang AS, Kwon HS, Cho YS, *et al.* Identification of subtypes of refractory asthma in Korean patients by cluster analysis. *Lung* 2013;191:87–93.
- 29 Moore WC, Hastie AT, Li X, *et al.* Sputum neutrophil counts are associated with more severe asthma phenotypes using cluster analysis. *J Allergy Clin Immunol* 2014;133:1557–63 e5.
- 30 Fitzpatrick AM, Teague WG, Meyers DA, *et al.* Heterogeneity of severe asthma in childhood: confirmation by cluster analysis of children in the National Institutes of Health/National Heart, Lung, and Blood Institute Severe Asthma Research Program. *J Allergy Clin Immunol* 2011;127:382–9 e1–13.
- 31 Siroux V, Basagana X, Boudier A, *et al.* Identifying adult asthma phenotypes using a clustering approach. *Eur Respir J* 2011;38:310–17.
- 32 Boudier A, Curjurić I, Basagana X, *et al.* Ten-year follow-up of cluster-based asthma phenotypes in adults. A pooled analysis of three cohorts. *Am J Respir Crit Care Med* 2013;188:550–60.
- 33 Sutherland ER, Goleva E, King TS, *et al.* Cluster analysis of obesity and asthma phenotypes. *PLoS ONE* 2012;7:e36631.
- 34 Patrawalla P, Kazeros A, Rogers L, *et al.* Application of the asthma phenotype algorithm from the Severe Asthma Research Program to an urban population. *PLoS ONE* 2012;7:e44540.
- 35 Kim TB, Jang AS, Kwon HS, *et al.* Identification of asthma clusters in two independent Korean adult asthma cohorts. *Eur Respir J* 2013;41:1308–14.
- 36 Weatherall M, Travers J, Shirlcliffe PM, *et al.* Distinct clinical phenotypes of airways disease defined by cluster analysis. *Eur Respir J* 2009;34:812–8.
- 37 Musk AW, Knuiam M, Hunter M, *et al.* Patterns of airway disease and the clinical diagnosis of asthma in the Busselton population. *Eur Respir J* 2011;38:1053–9.
- 38 Sakagami T, Hasegawa T, Koya T, *et al.* Cluster analysis identifies characteristic phenotypes of asthma with accelerated lung function decline. *J Asthma* 2014;51:113–8.
- 39 Meyer N, Nuss SJ, Rothe T, *et al.* Differential serum protein markers and the clinical severity of asthma. *J Asthma Allergy* 2014;7:67–75.
- 40 Park SY, Baek S, Kim S, *et al.* Clinical significance of asthma clusters by longitudinal analysis in Korean asthma cohort. *PLoS ONE* 2013;8:e83540.
- 41 Disantostefano RL, Li H, Rubin DB, *et al.* Which patients with chronic obstructive pulmonary disease benefit from the addition of an inhaled corticosteroid to their bronchodilator? A cluster analysis. *BMJ Open* 2013;3.
- 42 Weatherall M, Shirlcliffe P, Travers J, *et al.* Use of cluster analysis to define COPD phenotypes. *Eur Respir J* 2010;36:472–4.
- 43 Cho MH, Washko GR, Hoffmann TJ, *et al.* Cluster analysis in severe emphysema subjects using phenotype and genotype data: an exploratory investigation. *Respir Res* 2010;11:30.
- 44 Jo KW, Ra SW, Chae EJ, *et al.* Three phenotypes of obstructive lung disease in the elderly. *Int J Tuberc Lung Dis* 2010;14:1481–8.
- 45 Bafadhel M, McKenna S, Terry S, *et al.* Acute exacerbations of chronic obstructive pulmonary disease: identification of biologic clusters and their biomarkers. *Am J Respir Crit Care Med* 2011;184:662–71.
- 46 Wardlaw AJ, Silverman M, Siva R, *et al.* Multi-dimensional phenotyping: towards a new taxonomy for airway disease. *Clin Exp Allergy* 2005;35:1254–62.
- 47 Fens N, van Rossum AG, Zanen P, *et al.* Subphenotypes of mild-to-moderate COPD by factor and cluster analysis of pulmonary function, CT imaging and breathomics in a population-based survey. *COPD* 2013;10:277–85.
- 48 DiSantostefano RL, Li H, Hinds D, *et al.* Risk of pneumonia with inhaled corticosteroid/long-acting beta2 agonist therapy in chronic obstructive pulmonary disease: a cluster analysis. *Int J Chron Obstruct Pulmon Dis* 2014;9:457–68.
- 49 Garcia-Aymerich J, Gomez FP, Benet M, *et al.* Identification and prospective validation of clinically relevant chronic obstructive pulmonary disease (COPD) subtypes. *Thorax* 2011;66:430–7.
- 50 Castaldi PJ, Dy J, Ross J, *et al.* Cluster analysis in the COPDGene study identifies subtypes of smokers with distinct patterns of airway disease and emphysema. *Thorax* 2014;69:415–22.
- 51 Fingleton J, Travers J, Williams M, *et al.* Treatment responsiveness of phenotypes of symptomatic airways obstruction in adults. *J Allergy Clin Immunol*. Published Online First: 4 Mar 2015. doi:10.1016/j.jaci.2015.01.013.
- 52 Barnes PJ, Celli BR. Systemic manifestations and comorbidities of COPD. *Eur Respir J* 2009;33:1165–85.
- 53 Fu JJ, McDonald VM, Gibson PG, *et al.* Systemic Inflammation in Older Adults With Asthma-COPD Overlap Syndrome. *Allergy Asthma Immunol Res* 2014;6:316–24.
- 54 Iwamoto H, Gao J, Koskela J, *et al.* Differences in plasma and sputum biomarkers between COPD and COPD-asthma overlap. *Eur Respir J* 2014;43:421–9.
- 55 Simpson JL, Scott R, Boyle M, *et al.* Inflammatory subtypes in asthma: Assessment and identification using induced sputum. *Respirology* 2006;11:54–61.
- 56 McDonald VM, Higgins I, Wood LG, *et al.* Multidimensional assessment and tailored interventions for COPD: respiratory utopia or common sense? *Thorax* 2013;68:691–4.
- 57 Singh D, Kolsum U, Brightling CE, *et al.* Eosinophilic inflammation in COPD: prevalence and clinical characteristics. *Eur Respir J* 2014;44:1697–700.
- 58 D'Silva L, Hassan N, Wang HY, *et al.* Heterogeneity of bronchitis in airway diseases in tertiary care clinical practice. *Can Respir J* 2011;18:144–8.
- 59 Brown PJ, Greville HW, Finucane KE. Asthma and irreversible airflow obstruction. *Thorax* 1984;39:131–6.
- 60 Perret JL, Dharmage SC, Matheson MC, *et al.* 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;187:42–8.
- 61 Tai A, Tran H, Roberts M, *et al.* The association between childhood asthma and adult chronic obstructive pulmonary disease. *Thorax* 2014;69:805–10.
- 62 Diaz AA, Hardin ME, Come CE, *et al.* Childhood-onset asthma in smokers. Association between CT measures of airway size, lung function, and chronic airflow obstruction. *Ann Am Thorac Soc* 2014;11:1371–8.
- 63 Reed CE. The natural history of asthma. *J Allergy Clin Immunol* 2006;118:543–8; quiz 49–50.
- 64 Stern DA, Morgan WJ, Wright AL, *et al.* Poor airway function in early infancy and lung function by age 22 years: a non-selective longitudinal cohort study. *Lancet* 2007;370:758–64.
- 65 Narang I, Bush A. Early origins of chronic obstructive pulmonary disease. *Semin Fetal Neonatal Med* 2012;17:112–8.
- 66 Svanes C, Sunyer J, Plana E, *et al.* Early life origins of chronic obstructive pulmonary disease. *Thorax* 2010;65:14–20.
- 67 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.
- 68 Chang TS, Lemanske RF Jr, Mauger DT, *et al.* Childhood asthma clusters and response to therapy in clinical trials. *J Allergy Clin Immunol* 2014;133:363–9.
- 69 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;349:1414–22.
- 70 Travers J, Marsh S, Caldwell B, *et al.* External validity of randomized controlled trials in COPD. *Respir Med* 2007;101:1313–20.
- 71 Travers J, Marsh S, Williams M, *et al.* External validity of randomised controlled trials in asthma: to whom do the results of the trials apply? *Thorax* 2007;62:219–23.
- 72 Scichilone N, Basile M, Battaglia S, *et al.* What proportion of chronic obstructive pulmonary disease outpatients is eligible for inclusion in randomized clinical trials? *Respiration* 2014;87:11–7.
- 73 Gibson PG, McDonald VM. Why is COPD phenotyping like sorting diamonds? *Eur Respir J* 2014;44:277–9.
- 74 Soler-Cataluna JJ, Cosio B, Izquierdo JL, *et al.* Consensus document on the overlap phenotype COPD-asthma in COPD. *Arch Bronconeumol* 2012;48:331–7.
- 75 Committee for the Third Edition of the COPD Guidelines of The Japanese Respiratory Society. Guidelines for the Diagnosis and Treatment of COPD (Chronic Obstructive Pulmonary Disease). 3rd ed, 2010.
- 76 Albert P, Agusti A, Edwards L, *et al.* Bronchodilator responsiveness as a phenotypic characteristic of established chronic obstructive pulmonary disease. *Thorax* 2012;67:701–8.
- 77 Miravittles M, Huerta A, Fernandez-Villar JA, *et al.* Generic utilities in chronic obstructive pulmonary disease patients stratified according to different staging systems. *Health Qual Life Outcomes* 2014;12:120.
- 78 National Asthma Council. Australian Asthma Management Handbook. 2014.
- 79 Koblicek V, Chlumsky J, Zindr V, *et al.* Chronic Obstructive Pulmonary Disease: official diagnosis and treatment guidelines of the Czech Pneumological and Phthysiological Society; a novel phenotypic approach to COPD with patient-oriented care. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub* 2013;157:189–201.
- 80 Agusti A, MacNee W. The COPD control panel: towards personalised medicine in COPD. *Thorax* 2013;68:687–90.
- 81 Hargreave FE, Nair P. The definition and diagnosis of asthma. *Clinical & Experimental Allergy* 2009;39:1652–8.
- 82 Gershon AS, Campitelli MA, Croxford R, *et al.* Combination long-acting beta-agonists and inhaled corticosteroids compared with long-acting beta-agonists alone in older adults with chronic obstructive pulmonary disease. *JAMA* 2014;312:1114–21.
- 83 Magnussen H, Watz H, Kirsten A, *et al.* Stepwise withdrawal of inhaled corticosteroids in COPD patients receiving dual bronchodilation: WISDOM study design and rationale. *Respir Med* 2014;108:593–9.



- 84 Rossi A, Guerriero M, Corrado A. Withdrawal of inhaled corticosteroids can be safe in COPD patients at low risk of exacerbation: a real-life study on the appropriateness of treatment in moderate COPD patients (OPTIMO). *Respir Res* 2014;15:77.
- 85 Chung KF, Wenzel SE, Brozek JL, *et al.* International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J* 2014;43:343–73.
- 86 Brightling CE, Bleecker ER, Panettieri RA Jr, *et al.* Benralizumab for chronic obstructive pulmonary disease and sputum eosinophilia: a randomised, double-blind, placebo-controlled, phase 2a study. *Lancet Respir Med* 2014;2:891–901.
- 87 Minor DS, Meyer AM, Long RC, *et al.* beta-Blockers and chronic obstructive pulmonary disease: inappropriate avoidance? *J Clin Hypertens (Greenwich)* 2013;15:925–30.
- 88 Waschki B, Kirsten A, Holz O, *et al.* Physical activity is the strongest predictor of all-cause mortality in patients with COPD: a prospective cohort study. *Chest* 2011;140:331–42.
- 89 Pitta F, Troosters T, Spruit MA, *et al.* Characteristics of physical activities in daily life in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2005;171:972–7.
- 90 Schols AM, Slangen J, Volovics L, *et al.* Weight loss is a reversible factor in the prognosis of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998;157:1791–7.
- 91 Celli BR, Thomas NE, Anderson JA, *et al.* Effect of pharmacotherapy on rate of decline of lung function in chronic obstructive pulmonary disease: results from the TORCH study. *Am J Respir Crit Care Med* 2008;178:322–3.
- 92 Scott HA, Gibson PG, Garg ML, *et al.* Dietary restriction and exercise improve airway inflammation and clinical outcomes in overweight and obese asthma: a randomized trial. *Clin Exp Allergy* 2013;43:36–49.
- 93 Turner S, Eastwood P, Cook A, *et al.* Improvements in symptoms and quality of life following exercise training in older adults with moderate/severe persistent asthma. *Respiration* 2011;81:302–10.
- 94 Zwerink M, Brusse-Keizer M, van der Valk PD, *et al.* Self management for patients with chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2014;3:CD002990.
- 95 Bourbeau J, Saad N. Integrated care model with self-management in chronic obstructive pulmonary disease: from family physicians to specialists. *Chron Respir Dis* 2013;10:99–105.