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Controversies in Allergy: Is Asthma COPD Overlap (ACO) a distinct syndrome that changes treatment and patient outcomes?

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SUMMARY

While asthma/COPD overlap (ACO), like both asthma and COPD alone, is not a distinct syndrome, nonetheless it does have features that distinguish it from asthma and COPD only. Similar to the latter obstructive pulmonary disorders, it most likely represents a complex spectrum of diseases comprising several different phenotypes and underlying pathophysiologies. It also not yet clear how ACO is best defined, i.e., by clinical features (age, physiology, bronchodilator responsiveness, symptom variability, history of asthma), biomarkers or a combination of these features. The lack of generally agreed-on diagnostic criteria probably accounts for the marked heterogeneity of the results of published surveys of its prevalence. Until a true consensus is achieved regarding the definition of ACO, it will not be possible to determine with confidence not only its prevalence, but also its natural history (outcomes), its underlying biology or its optimal treatment based on findings from randomized controlled clinical trials focused specifically on patients with well-defined ACO.

Keywords

asthma; COPD; overlap; guidelines

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INTRODUCTION

It has long been recognized that some patients with persistent airflow obstruction have overlapping features of both asthma and COPD, referred to as asthma/COPD overlap. However, there is a notable lack of consensus as to how to define asthma/COPD overlap (ACO). Moreover, uncertainty remains as to whether or not ACO represents a disorder that is distinctly different from both asthma and COPD alone (a distinct syndrome, if you will), whether a diagnosis of ACO alters treatment options and whether disease-related outcomes in patients with ACO differ from those of patients with either asthma or COPD only. These issues are the focus of a debate, the PRO and CON sides of which are the subject of this article.

THE PRO POSITION (DR. DONALD TASHKIN)

There is little doubt that asthma and chronic obstructive pulmonary disease (COPD) sometimes co-exist,(1, 2) although the prevalence of the overlap between these two obstructive pulmonary disorders has been shown to vary considerably.(3–5) According to an extensive literature search that included 21 studies examining the prevalence of ACO in patients with COPD and 17 studies of the prevalence of the asthma/COPD overlap (ACO) in patients with asthma, the proportion of patients with ACO varied from 12.1% to 56.2% of patients with COPD and from 13.3% to 61.0% among patients with asthma.(5) The reasons for this marked heterogeneity in the prevalence of ACO is likely due to a number of factors, including the lack of consensus regarding the definition of ACO,(6–9) differences in the methods used for ascertaining the diagnosis of asthma and COPD and variability in the characteristics of the patients included in the prevalence surveys, such as gender, age, race/ethnicity and smoking history. However, the questions being addressed in this debate concern whether ACO is a *distinct* syndrome and whether its presence affects treatment and outcomes. These issues will be discussed separately.

Characterization of ACO as a *syndrome* (by using the designation *ACOS*) has been discouraged because of the belief that ACO, like asthma and COPD alone, represents a complex spectrum of varying phenotypes/endotypes and underlying pathophysiologies, rather than a homogeneous disorder.(10) On the other hand, the *distinctness* of ACO derives from observations that it can be distinguished from asthma alone and from COPD alone, as reflected in variously proposed diagnostic criteria (Figures 1–4). While these criteria are not completely aligned, they do share similarities in some important respects, namely the presence of persistent airflow obstruction consistent with COPD, a previous history of asthma (further characterized in two of the proposed sets of criteria as having been diagnosed before the age of 40 years to avoid diagnostic confusion with COPD, which is rarely diagnosed prior to 40 years of age) and an especially marked degree of bronchodilator responsiveness, namely an improvement in forced expired volume in 1 sec (FEV_1) by at least 15% and 400 ml over the pre-bronchodilator value. Whereas most patients with COPD at one time or another exhibit a significant response to a bronchodilator (i.e., ≥12% and ≥200 ml above the pre-bronchodilator value),(11, 12) improvement by ≥15% and ≥400 ml is distinctly uncommon.(12) An additional feature of ACO distinguishing it from COPD alone that is shared among the different proposed sets of criteria is a biomarker indicating a high

Th-2 signature, namely a high sputum or blood eosinophil count with or without an elevated fraction of expired nitric oxide levels (FeNO) or IgE level.(4, 6–9, 13) Additional biomarkers have also been found to distinguish ACO from COPD or asthma alone. For example, Shirai et al. demonstrated that high serum periostin levels were more characteristic of ACO and asthma alone compared with COPD, while high serum levels of chitinase-3-like protein 1 (YKL-40), a glycoprotein secreted by inflammatory and airway epithelial cells and thought to be involved in COPD pathogenesis, were more characteristic of COPD and ACO than asthma.(14) Consequently, combined assessment of both serum periostin and YKL-40 might be used to identify ACO. In addition, Iwamoto et al. found that sputum levels of neutrophil gelatinase-associated lipocalin (NGAL), a neutrophil-derived inflammatory molecule, was significantly elevated in ACO in comparison with both asthma and COPD alone, suggesting the potential utility of sputum NGAL in distinguishing ACO as a distinct entity.(15)

Regarding the question whether the presence of ACO affects treatment choices, one could argue that no controlled clinical trials have been conducted in patients with ACO to determine the efficacy and safety of different pharmacotherapeutic options. This state of affairs exists since there is no agreed-on definition of ACO, clinical trials in COPD exclude patients with asthma, and trials in asthma similarly exclude patients with COPD or patients with asthma who smoke. Thus, it is imperative that consensus is achieved regarding a uniform definition of ACO that will allow controlled clinical trials of different treatments to be conducted in patients with overlapping asthma and COPD. On the other hand, current COPD guidelines do recommend an inhaled corticosteroid (ICS)-containing regimen in patients with COPD who have an asthma component (namely patients with ACO), whereas long-acting inhaled bronchodilators without ICS are recommended as a preferred treatment option for most symptomatic patients with COPD alone, even including patients with frequent exacerbations.(16)

The final question is whether ACO affects clinical outcomes. Despite the current lack of consensus regarding criteria for diagnosing ACO, several different groups have found that ACO is associated with worse outcomes than either COPD or asthma alone. Hardin et al. conducted a cross-sectional study to compare subjects with ACO to those with COPD alone in the COPDGene study using linear and logistic regression models that adjusted for potentially confounding variables.(17) Compared with COPD-only, subjects with ACO exhibited worse disease-related quality of life (St. George’s Respiratory Questionnaire [SGRQ] score 36.6 vs. 44.1, respectively; $p=0.0075$), and a significantly higher proportion of subjects with ACO than those with COPD alone had severe exacerbations (32.8 vs. 17.6%, respectively; $p=0.0001$) as well as frequent exacerbations (42.7% and 18%, respectively; $p<0.0001$), despite similarities in gender, body mass index, current smoking, spirometry, BODE index and measures of extent of emphysema and air-trapping on high resolution computed tomography (HRCT) images. While this study was not prospective, severe and frequent exacerbations have been shown to be associated with a markedly increased risk of subsequent exacerbations, including hospitalized exacerbations,(18) worse quality of life,(19) a greater rate of disease progression (reflected in a steeper annual rate of decline in FEV_1),(20) and higher mortality as a consequence of severe exacerbations.(21)

Using the multi-center, population-based Latin American Project for the Investigation of Obstructive Lung Disease (PLATINO) to compare subjects with ACO to those with COPD-only with respect to clinical outcomes, Menezes et al. found, in multivariate analyses, that those with ACO had significantly more respiratory symptoms, worse lung function, more respiratory medication utilization, more hospitalizations and exacerbations and a worse perception of general health than those with COPD only.(22)

Using the 2009 Korean National Health Insurance database, Rhee et al. identified patients with COPD-only and ACO.(23) They found that the percentages of emergency room visits, hospital admissions, intensive care unit admissions and the cost of medical utilization for both outpatient and inpatient services were significantly higher in patients with ACO than those with COPD-only.

Kauppi and associates identified all outpatients aged 18–75 years of age who had been discharged from the Helsinki University Central Hospital with a diagnosis of asthma, COPD or both and found that those with ACO had a significantly higher independent risk for poor health-related quality of life than those with asthma or COPD-only in multivariate analyses that controlled for confounding variables.(24)

Based on data from a population-based study in Spain among 40–80 year-old subjects, Miravitlles and colleagues found that those with ACO were significantly more likely than subjects with COPD-only to have dyspnea and wheezing, frequent exacerbations, reduced physical activity and worse respiratory-specific quality of life, as well as more co-morbidities, in adjusted multivariate models, despite considerably less lifetime exposure to smoking and comparable FEV_1 values.(25)

Using data from the Majorca Real-Life Investigation in COPD cohort study, van Bowen et al. reported that gastro-esophageal reflux disease in ACO was more commonly associated with an increased risk of a hospitalized exacerbations than in COPD-only patients. On the other hand, anxiety and sleep apnea in COPD only were more commonly associated with an increased risk of severe exacerbations than in ACO, and cardiovascular and metabolic comorbidities were similarly common in both ACO and COPD-only and associated with comparable risks for severe exacerbations.(26)

In contrast to some of the findings from other investigators noted above, Izuierdao-Alonso et al. did not find any significant differences in exacerbations or emergency room visits between patients with ACO and those with COPD-only.(27) While differences in the manner in which patients with ACO were identified in the aforementioned studies could account for some of the differences in outcomes noted, most studies, on balance, suggest that ACO is associated with worse outcomes than COPD alone after adjusting for potential confounders. Clearly, however, additional cohort studies of the natural history of ACO are required, but these will need to await the development of generally agreed-on criteria for the diagnosis of ACO.

THE CON POSITION (DR. STOKES PEEBLES)

The focus of this debate is that the diagnosis of ACO changes treatment and patient outcomes. The debate is not that asthma and COPD overlap. The concept that patients may have features of asthma and COPD has been known since at least the mid-18th century. In his Lumleian Lecture on "Bronchitis, Pulmonary Emphysema, and Asthma," delivered before the Royal College of Physicians in London in 1899, Dr. Samuel Gee recounted that in 1764 Dr. William Watson read before the Royal Society "an account of what appeared on opening the body of an asthmatic person…an emphysematous state of the lung."(28) Thus, Dr. Watson gave us one of the earliest descriptions of a person diagnosed with asthma who instead had the pathologic of emphysema at autopsy.

As mentioned above, the topic of this debate is not whether ACO exists, but instead whether a diagnosis of ACO changes treatment and patient outcomes. My argument is that we do not have the scientific information necessary to make specific treatment recommendations based on this diagnosis, mainly because the necessary studies in clearly defined patient populations of ACO have not yet been performed. Further, while we have some information as to the natural history of asthma in people who smoke compared to those who do not, there is little data describing the natural history of people with ACO compared to those with either asthma or COPD by themselves, or to persons without respiratory disease. The dearth of studies is not a function of a lack of patients who have ACO. Using data from the Medical Expenditure Panel Survey, of patients with asthma or COPD in the United States, 45% had asthma alone, 37% had COPD alone, and 17% had ACO.(29) Therefore, by simple math, approximately 27% of all persons with asthma also have ACO. With the current estimate of 25 million Americans having a diagnosis of asthma,(30) this would mean that there are approximately 6.85 million people living in our country with ACO, roughly the population of the state of Tennessee.(31) Instead, the paucity of prospectively performed studies in ACO subjects is more a function of three main factors: 1) the lack of clearly defined, widely accepted diagnostic criteria, and 2) the systematic elimination of persons with ACO from clinical studies of asthma or COPD, and 3) little knowledge of the endotypes leading to ACO. We will review each of these shortcomings separately.

The definition of ACO varies substantially between organizations that have issued diagnostic criteria. In 2015, the monograph "Diagnosis of Diseases of Chronic Airflow Limitation: Asthma COPD and Asthma-COPD Overlap Syndrome" was published as a joint project of Global Initiative for Asthma (GINA) and Global Initiative for Chronic Obstructive Lung Disease (GOLD).(32) This document provided a description of ACO for clinical use: "persistent airflow obstruction with several features usually associated with asthma and several features usually associated with COPD. ACO is therefore identified in clinical practice by the features it shares with both asthma and COPD. A specific definition for ACO cannot be developed until more evidence is available about its clinical phenotypes and underlying mechanisms." This was a very honest appraisal of the state of the knowledge of ACO and in the monograph, the authors were careful to provide comprehensive tables describing the usual features of asthma and COPD, and which features would favor a clinical scenario of ACO. However, as the authors stated, a significant limitation of this monograph was the absence of a clear definition. Several countries' pulmonary specialty organizations

have now published diagnostic criteria for ACO and each vary somewhat. For instance, the Czech Pneumological and Physiological Society has published ACO guidelines (Figure 2).(7) The major criteria include a vigorous bronchodilator therapy (BDT) response (such as short acting beta-agonist), bronchoconstrictor response (such as methacholine or histamine responsiveness), high FeNO, and a history of asthma. The minor criteria include the total serum IgE level.

Other groups have also developed their own criteria for ACOS. A panel of respiratory medicine experts from North America, Western Europe and Asia published the definition shown in Figure 4.(8) They defined three major criteria, all of which must be present for a diagnosis of ACO. These criteria include persistent airflow obstruction, again with a post bronchodilator FEV_1/FVC ratio less than 70%, but in patients greater than 40 years of age. Another major criteria is at least 10 pack/years of smoking or exposure to biomass, which is organic matter used as fuel. The third criteria is a documented history of asthma before 40 years or bronchodilator responsiveness in FEV_1 greater than 400 ml. The minor criteria, of which only one is necessary, include a documented history of atopy or allergic rhinitis, bronchial responsiveness, and peripheral blood eosinophil count of at least 300 cells/μL. While some elements of this definition are similar to those by the Czech Pneumological and Physiological Society, there are significant differences such as smoking history, quantifying peripheral blood versus sputum eosinophils, and serum IgE. Other national pulmonary organizations that have published recommendations regarding ACO include Australia,(33) Japan,(34) and Spain.(9) A consensus definition that includes input and agreement from all pulmonary specialty organizations would be a major step forward.

While the lack of a standardized definition has been a challenge for investigators who are interested in ACO and for clinicians who care for patients with ACO, the major obstacle for research in this field is that patients with ACO have largely been eliminated from clinical trials. This is a consequence of pharmaceutical companies having focused on enrolling what are considered pure populations of either asthma or COPD, without any overlap, largely because of guidelines set forth by regulatory agencies to evaluate treatment for specific patient populations.(35) For asthma studies, inclusion criteria have comprised subjects a) with allergic disease, b) who have a very limited or no smoking history, c) with significant bronchodilator reversibility, and d) who are early middle age or younger. In COPD trials, the emphasis has been on enrolling subjects a) who are current or ex-smokers, b) with fixed airway obstruction, and c) who are middle age or older. Therefore, asthma studies have excluded those with significant smoking history and who do not have bronchial responsiveness, while studies in COPD have excluded those who are nonsmokers. Therefore, the result of these exclusionary tactics is few prospective treatment trials of: a) patients with asthma who smoke, b) smokers who may have features of allergic disease such as eosinophilic inflammation, c) or asthma patients who have never smoked, but who have fixed airway obstruction secondary to airway wall remodeling. Inclusion of these types of patients is critical to understand optimal therapeutic strategy for patients with ACO. It is of interest, however, that despite the lack of randomized controlled trials to assess the relative benefits and risks of different treatment options, a recent observational study from Taiwan that included over 250,000 patients with ACO and over 500,000 patients with COPD alone found that the same medications (i.e., a LAMA or an ICS/LABA combination) that were

effective in lowering the risk of acute exacerbations in patients with COPD alone were also found to be effective in patients with asthma-COPD overlap.(36)

The lack of studies in patients with ACOS has not prevented medical journals from publishing papers on this topic. A PubMed search in March 2018 using the search terms “asthma”, “COPD, and “overlap”, returned interesting results (Figure 5). In the decades of the 1970s, 1980s, and 1990s, I could only find one article in each decade using this search approach, while there were five such papers from 2000–2009. In 2011 and 2012, I found less than five papers for each year, but there has been a marked increase starting in 2013, almost as if a light in a closet had been turned on, implying that we should now be aware of the possibility that patients with asthma might have COPD, and vice-versa. This light became a beacon when it was further recognized that physicians were not sure how these patients should be treated. While there were 90 papers written on the topic in 2016, there were 159 written in 2017 and early 2018. Therefore, since 2013, over 96% of the entirety of medical papers on ACO have been written; however, a close examination of these papers shows that almost 60% of these are review articles (Figure 5). The other concern is that the original research articles are predominantly retrospective (Figure 6). When the number of review articles exceeds research articles, and the research articles are not prospective, we are then left with “expert opinion” as a guiding principle for therapy. These experts are certainly very knowledgeable and no doubt have the best intentions, but we have fallen victim to relying on expert opinion in the past with resultant dire consequences. For example, for over 2 decades, the expert opinion was that early life peanut exposure should be avoided in those at risk for peanut allergy.(37) The LEAP study taught us that the expert opinion and recommendation about early life peanut avoidance was largely incorrect and instead likely caused more peanut allergy than it prevented.(38) While it is doubtful that the current expert recommendations about ACOS therapy would be as detrimental as early life peanut avoidance, we should have evidence on which to base our therapeutic recommendations.

The solution to defining a strategy that will truly optimize ACO treatment and patient outcomes is multipronged. First, we need to encourage funding, whether it be from foundations, government, or the pharmaceutical industry, for randomized, double-blind, placebo-controlled trials that will enroll persons who have, or who are at risk for having, asthma and COPD. In addition, it is important to encourage the design of innovative studies that may include discovery of biomarkers specific for ACO, in addition to novel therapies. Thirdly, we have more than enough review articles, including the one that our group wrote.(35) Instead of more review articles, our intellectual energy should instead be redirected to generate high quality data that will help us make informed decisions that will guide optimal treatment for real patients with a serious condition. The final frontier is determining the endotypes that lead to the ACO phenotype. By defining the mechanisms that lead to ACO, we will have the opportunity to define more rationale treatment strategies. Elucidating these mechanisms will be laborious, painstaking, and expensive, mainly because of the interactions related to the inflammation caused by tobacco smoke and other environmental exposures that are involved in COPD pathogenesis, with the immune response that leads to asthma. However, there has been substantial recent success in defining asthma endotypes that has translated into strategic biologic therapies that have clearly improved outcomes for

patients with severe disease. Since we have not been able to eliminate smoking, hopefully, novel insights into ACO endotypes will also lead to improved therapies and outcomes.

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Abbreviations:

(COPD)	chronic obstructive pulmonary disease
(ACO)	asthma/COPD overlap
(FEV_1)	forced expired volume in 1 sec
(FeNO)	fraction of expired nitric oxide levels
(ICS)	inhaled corticosteroid
(HRCT)	high resolution computed tomography
(PLATINO)	Project for the Investigation of Obstructive Lung Disease
(GINA)	Global Initiative for Asthma
(GOLD)	Global Initiative for Chronic Obstructive Lung Disease
(BDT)	bronchodilator therapy

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Spanish Proposed Diagnostic Criteria

- Major criteria
  - Marked reversibility with bronchodilators (>15% and >400 ml in FEV_1)
  - History of asthma (<40 yrs of age)
  - Sputum eosinophilia
- Minor criteria
  - Reversibility on 2 separate occasions (≥12% and ≥ 200 mil in FEV_1)
  - History of atopy
  - Increased total serum IgE
- Diagnosis of ACO by 2 major criteria *or* 1 major + 2 minor criteria;

Figure 1.
Proposed Spanish Diagnostic Criteria for ACO. Adapted from Soler-Cataluna et al. (Arch Bronconeumol. 2012;48(9):331–337.)

Czech Pneumological and Physiological Society ACOS Guidelines

- Major criteria
  - Strong BDT positivity (FEV_1>15% and >400 ml)
  - Bronchoconstrictor test positivity
  - FeNO ≥ 45-50 ppb and/or ↑ eos in sputum (>3%)
  - History of asthma
- Minor criteria
  - Mild BDT (FEV_1>12% and >200 ml)
  - ↑ total IgE
  - History of atopy and definite COPD diagnosis
- Diagnosis of ACOS by 2 major, or 1 major + 2 minor criteria

Figure 2.
Czech Pnumological and Physiological Society ACOS Guidelines. Adapted from Koblizek et al. (Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2013;157(2):189–201)

Updated Spanish Proposed Diagnostic Criteria

- Major criteria
  - Previous history of asthma
  - Marked reversibility with bronchodilators (>15% and >40 ml in FEV_1)
- Minor criteria
  - IgE >100 IU
  - History of atopy
  - Reversibility on 2 separate occasions (≥12% and ≥ 200 mil in FEV_1)
  - Blood eosinophils >5%
- Diagnosis of ACO requires ≥1 major criteria *or* 2 minor criteria
  - *Also*, requires fulfilling ≥3 of the usual features of COPD: age >40; post-bronchodilator FEV1/FVC <0.70 and smoking history

Figure 3.
Updated Spanish Proposed Diagnostic Criteria. Adapted from Cosio et al. (Chest. 2016;149(1):45–52)

Global Expert Panel Criteria for Diagnosis of ACOS

- Major criteria (all 3 must be present)
  - Persistent airflow limitation (post-BD FEV_1/FVC <0.70) in patients ≥40 yr
  - At least 10 pack/years of tobacco smoking or equivalent biomass
  - Documented history of asthma before 40 or BDR>400 ml FEV_1
- Minor criteria (1 must be present)
  - Documented history of atopy or allergic rhinitis
  - BDR of FEV_1 ≥200ml and 12% from baseline values on 2 or more visits
  - Peripheral blood eosinophil count of ≥300 cells/μL

Figure 4.
Global Expert Panel Criteria for Diagnosis of ACOS. Adapted from Sin et al. (Eur Respir J. 2016;48(3):664–673)

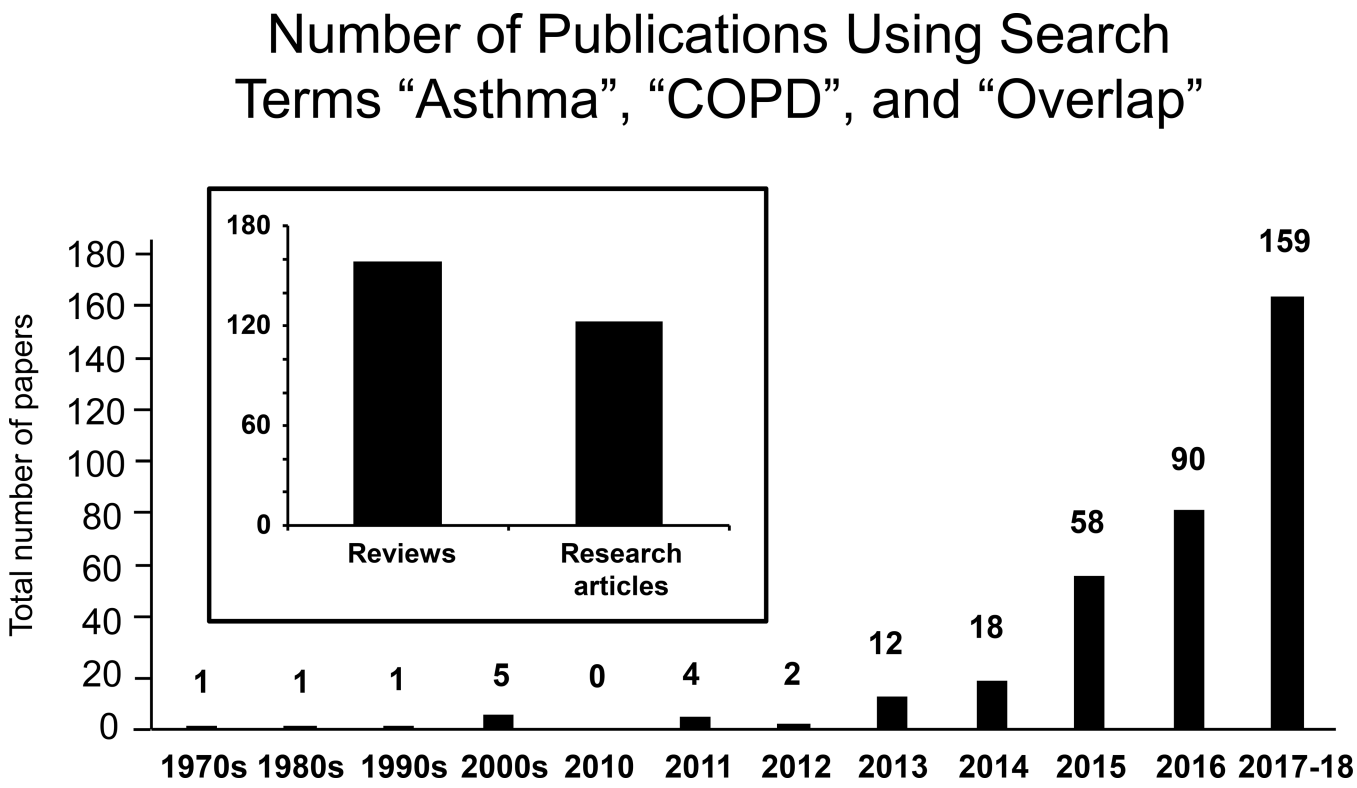

Figure 5.
Number of Publications Using Search Terms “Asthma”, “COPD” and “Overlap”

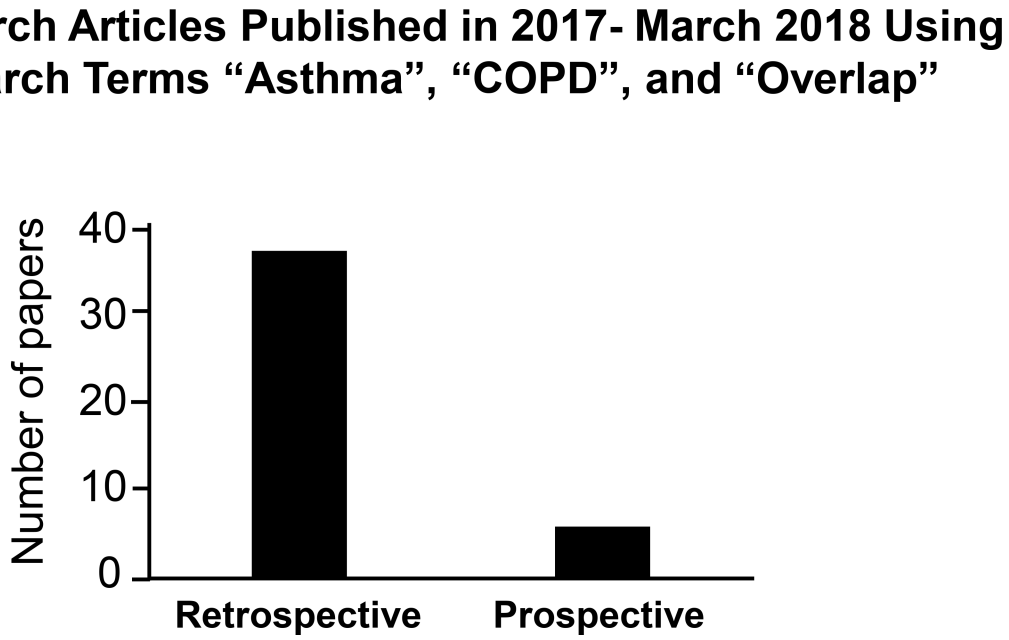

Figure 6.
Research Articles Published in 2017-March 2018 Using Search Terms “Asthma”, “COPD”, and “Overlap”