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Prevalence and features of asthma–chronic obstructive pulmonary disease overlap in Northern Italy general population

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ABSTRACT

Objective: There is controversy about the diagnostic criteria, prevalence, symptoms, and spirometry characteristics of asthma–chronic obstructive pulmonary disease (COPD) overlap (ACO). Recent data indicate that the fixed method for diagnosing airway obstruction (AO) may overestimate ACO prevalence in the elderly, and a variable method may be more accurate. We aimed at estimating ACO prevalence in a general population sample and comparing patient and clinical features in subjects with ACO, COPD, and asthma. **Methods:** We analyzed data from a cross-sectional study estimating COPD prevalence in randomly selected adults aged 20–79 years in Verona, Italy, and estimated prevalence and analyzed characteristics of asthma, COPD, and ACO. ACO was defined as AO (Forced Expiratory Volume in one second–FEV₁/ Forced Vital Capacity–FVC < Lower Limit of Normal–LLN), highly positive bronchodilator test ($\geq 15\%$ increase in FEV₁ and FVC ≥ 400 mL), and personal self-reported history of physician diagnosed asthma and atopy. **Results:** One thousand two hundred and thirty-six patients were included; 207 (16.7%) had asthma, COPD, or ACO (mean ages: 61.2, 59.7, and 57.2 years, respectively). The 3 groups had similar clinical and demographic variables; however, spirometry revealed differences between ACO and COPD patients, particularly post-bronchodilator FEV₁ reversibility, which was detected in ACO and asthma patients but not in those with COPD. **Conclusion:** ACO prevalence in Northern Italy was estimated at 2.1%, in the range of values reported by previous studies. Marked differences between ACO and COPD revealed by spirometry may have important clinical implications in terms of treatment for patients with ACO.

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Introduction

Asthma and chronic obstructive pulmonary disease (COPD) are different diseases which share many pathologic features. Some patients, particularly the elderly (1), show components of both COPD and asthma. Although controversial, co-existence of the 2 conditions has been termed asthma–chronic obstructive pulmonary disease overlap (ACO) (2,3). Indeed, the presence of a range of overlapping phenotypes including aspects of chronic bronchitis (CB), emphysema, or asthma within the umbrella term of COPD has long been recognized in the literature (4–7).

ACO is a newly identified condition, thus the precise nature and characteristics of the syndrome are not yet established and there is intense ongoing controversy surrounding its nature (8,9). ACO may be associated with more frequent and more severe respiratory exacerbations and hospitalizations than COPD despite the younger age and reduced lifetime smoking history in ACO patients versus the average patient with COPD (10,11). Other data

indicate worse perceived general health status (10,12,13) and worse quality of life (QoL) (14,15) versus asthma or COPD alone. Furthermore, ACO is associated with less emphysema than COPD, as well as with elevated reversibility and enhanced response to inhaled corticosteroids (ICS) due to the predominance of bronchial inflammation (1,16–19).

There is no standardized definition of ACO, therefore reported prevalence rates widely vary (8,9). The 2011 Spanish guidelines for COPD (EPOC GesEPOC) (20,21) recognized a mixed COPD–asthma phenotype and the need for individualized treatment based on clinical phenotype and severity. Consensus criteria were drawn up for the diagnosis of ACOS (currently defined as ACO) (3) in patients with existing COPD (13). For a diagnosis of ACO, patients should have an underlying condition of obstructive airways disease or COPD (diagnostic method not defined) and should meet 2 of the following major criteria—a highly positive bronchodilator (BD) test (increase in forced expiratory volume in 1 second

[FEV₁] ≥ 15% and ≥ 400 mL), sputum eosinophilia, and a personal history of asthma – and 2 of the following minor criteria – high total plasma immunoglobulin E (IgE) concentration, personal history of atopy, and positive BD test (increase in FEV₁ ≥ 12% and ≥ 200 mL) on 2 or more occasions ((13)).

New information on diagnosis of ACO were included in the 2015 and 2017 reports published by the Global Initiative for Asthma (GINA) and the Global Initiative of Chronic Obstructive Lung Disease (GOLD) on the management of asthma and COPD (22–24), and in a consensus guideline on asthma, COPD, and ACO arising from a joint GINA and GOLD project (25).

In Italy, co-existence of asthma and COPD has been reported in epidemiological studies based on questionnaire and spirometry (26) or on questionnaire only (27) with both studies showing an age-related trend in ACO prevalence rate.

Our aim was to estimate ACO prevalence as a sub-analysis of a recently published general population study (26) by applying a precise definition of ACO using both spirometry and questionnaire response data. We also compared patient and clinical features in subjects with ACO, COPD, and asthma.

Methods

Study design

A cross-sectional study on a general population sample living in Verona, Italy was performed between 2011 and 2012. Full details of the study design have been published elsewhere (26). In brief, 1236 randomly selected subjects completed a questionnaire and underwent medical assessment and spirometry. Local and regional ethical approvals were obtained.

Study endpoints

The endpoint of this analysis was ACO prevalence according to the following definition: airway obstruction (FEV₁/forced vital capacity [FVC] below the lower limit of normal [LLN]); a highly positive BD test (increase in FEV₁ ≥ 15% and FVC ≥ 400 mL); and a personal self-reported history of physician diagnosed asthma and atopy.

Statistical analysis

Statistical methodology for the general population study is fully reported elsewhere (26). Results of this sub-analysis are expressed as mean and standard deviation (SD) or median and interquartile range (IQR) if variables

are continuous or ordinal, or as percentage if variables are categorical.

The following tests were used: Shapiro–Wilk test, to test normality of distribution for continuous variables; one-sample test of proportion, to compare categorical data; *t*-test, to compare the mean values between 2 groups, ACO versus asthma and ACO versus COPD; and the Chi-square test, to assess the association between categorical variables. A *p*-value < 0.05 was considered statistically significant. Analyses were performed using STATA version 12.0 (Stata Corp, College Station, TX, USA).

Results

Overall, 1236 individuals were included; 69 (5.6%) had asthma only, 112 (9.1%) had COPD only, and 26 (2.1%) had ACO. In a comparison of adult/elderly patients with asthma, COPD, and ACO (mean age 57.2–61.2 years), the statistical analyses showed that patients with ACO were very similar to those with asthma and COPD in terms of symptoms and other clinical and demographic variables (Table 1).

ACO patients were more likely to be male (*p* = 0.045) or smokers (*p* = 0.0376) compared to asthma patients. There were no significant differences in symptoms and other clinical and demographic variables between ACO and COPD groups. Compared to the asthma group, ACO patients reported less wheezing and a lower rate of family history of pulmonary diseases, although without statistical significance. More subjects in the ACO group declared to have performed a prior spirometry test in comparison with asthmatic patients (Table 2).

Compared to the COPD group, patients with ACO showed significantly lower values in terms of: pre- and post-BD % predicted FEV₁; pre- and post-BD % predicted FVC; pre-BD FEV₁/FVC ratio. Conversely, the following parameters were significantly larger in ACO than in COPD patients: absolute and relative FEV₁; absolute and relative changes in FVC; relative change in FEV₁/FVC. In comparison with asthmatic patients, those with ACO were characterized by lower values of pre- and post-BD % predicted FEV₁, absolute change in FEV₁, and pre- and post-BD FEV₁/FVC ratio. A larger pre- and post-BD FVC was observed in ACO group when compared to asthmatic population (Table 3).

The pre- and post-BD % predicted FEV₁ values are also shown in Figure 1. Patients with asthma and ACO had an increase in % predicted post-BD FEV₁ but COPD patients did not. Patients with asthma and ACO also had similar relative increases in FEV₁ values whereas the increase in FEV₁ in patients with COPD was minimal (Figure 2).

Table 1. Demographics of patients with asthma, COPD, and ACO ($n = 207$).

	Asthma only	COPD only	ACO	p-value	
				ACO vs Asthma	ACO vs COPD
N (%)	69 (33.3%)	112 (54.1%)	26 (12.6%)		
Age, years	61.2 (12.8)	59.7 (14.1)	57.2 (14.8)	0.3403	0.3986
Male, n (%)	29 (42.0)	67 (59.8)	13 (50.0)	0.045	0.867
BMI, kg/m ²	26.3 (4.7)	25.8 (3.7)	25.8 (3.6)	0.3836	0.1767
Smoking, pack-years	18.3 (23.1)	27.8 (34)	34.5 (31.2)	0.0376	0.1547
Smoking status, n (%)					0.323
Never	22 (31.9)	31 (27.7)	12 (46.2)		
Former	15 (21.7)	31 (27.7)	8 (30.8)		
Current	8 (11.6)	26 (23.2)	4 (15.4)		
Environmental exposure, n (%)					
Traffic	19 (27.5)	32 (28.6)	8 (30.8)	0.471	0.784
Pollution	21 (30.4)	42 (37.5)	12 (46.2)	0.792	0.843

Note. Values are mean (standard deviation) or number of patients (%).

ACO, asthma–chronic obstructive pulmonary disease overlap; BMI, body mass index; COPD, chronic obstructive pulmonary disease.

Table 2. Clinical characteristics of patients with asthma, COPD, and ACO ($n = 207$).

	Asthma only	COPD only	ACO	p-value	
				ACO vs Asthma	ACO vs COPD
Respiratory symptoms, n (%)					
Cough	18 (26.1)	31 (27.7)	7 (26.9)	0.373	0.555
Phlegm	15 (21.7)	28 (25.0)	7 (26.9)	0.724	0.778
Dyspnoea	12 (17.4)	23 (20.5)	5 (19.2)	0.592	0.538
Wheezing	18 (26.1)	33 (29.5)	5 (19.2)	0.118	0.249
Respiratory drug, n (%)	7 (10.1)	15 (13.4)	5 (19.2)	0.582	0.668
Childhood PD, n (%)	8 (11.6)	23 (20.5)	4 (15.4)	0.594	0.323
Family history of PD, n (%)	18 (26.1)	29 (25.9)	5 (19.2)	0.108	0.24
Prior spirometry, n (%)	11 (15.9)	33 (29.5)	10 (38.5)	0.139	0.739
Clinically diagnosed CB, n (%)	6 (8.7)	17 (15.2)	1 (3.8)	0.409	0.113
Self-reported COPD, n (%)	0 (0.0)	5 (4.5)	1 (3.8)	0.348	0.863
Self-reported asthma, n (%)	5 (7.2)	23 (20.5)	5 (19.2)	0.275	0.523
Self-reported CB, n (%)	1 (1.4)	13 (11.6)	2 (7.7)	0.236	0.685
Antibiotics in the past year, n (%)	10 (14.5)	21 (18.8)	4 (15.4)	0.585	0.438
mMRC > 1, n (%)	7 (10.1)	9 (8.0)	3 (11.5)	0.904	0.707

Note. Data are number of patients (%).

ACO, asthma–chronic obstructive pulmonary disease overlap; CB, chronic bronchitis; COPD, chronic obstructive pulmonary disease; IQR, inter-quartile range; mMRC, modified Medical Research Council Dyspnoea scale; na, not available; PD, pulmonary disease.

Table 3. Spirometry data of patients with asthma, COPD, and ACO.

	Asthma only ($n = 69$)	COPD only ($n = 112$)	ACO ($n = 26$)	p-value	
				ACO vs Asthma	ACO vs COPD
Pre-BD FEV ₁ , L	2.0 (0.5)	2.4 (0.8)	2.1 (0.8)	0.2886	0.1150
Pre-BD FEV ₁ , % predicted	80.9 (12.9)	81.6 (18.7)	69.9 (14.2)	0.0014	0.0008
Post-BD FEV ₁ , L	2.4 (0.6)	2.5 (0.7)	2.5 (0.9)	0.4385	0.4781
Post-BD FEV ₁ , % predicted	95.0 (13.1)	82.2 (18.5)	78.6 (14.1)	0.0014	0.0008
FEV ₁ change, absolute, mL	410.7 (196.0)	120.9 (127.2)	345.8 (133.4)	0.035	0.0001
FEV ₁ change, relative, %	21.2 (11.3)	4.9 (5.8)	18.7 (11.6)	0.1754	0.0001
Pre-BD FVC, L	3.1 (0.8)	3.9 (1.2)	3.7 (1.0)	0.0054	0.2941
Pre-BD FVC, % predicted	98.5 (16.0)	105.1 (19.7)	98.1 (13.2)	0.4553	0.0227
Post-BD FVC, L	3.3 (0.8)	3.8 (1.1)	3.9 (1.0)	0.0081	0.4006
Post-BD FVC, % predicted	95.8 (12.2)	104.6 (17.9)	96.1 (12.8)	0.4553	0.0227
FVC change, absolute, mL	164.9 (241.2)	− 52.9 (232.7)	137.9 (233.2)	0.3103	0.0003
FVC change, relative, %	6.4 (7.9)	− 1.5 (6.1)	4.7 (6.9)	0.1544	0.0001
Pre-BD FEV ₁ /FVC	73.8 (4.5)	63.8 (8.1)	62.2 (8.3)	0.0002	0.0256
Post-BD FEV ₁ /FVC	74.3 (6.5)	64.5 (6.6)	62.8 (8.7)	0.0001	0.2037
FEV ₁ /FVC change	14.4 (9.3)	6.8 (6.9)	14.1 (10.4)	0.4389	0.0019

Note. Values are mean (standard deviation).

ACO, asthma–chronic obstructive pulmonary disease overlap; BD, bronchodilator; CB, chronic bronchitis; COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; mMRC, modified Medical Research Council Dyspnoea scale.

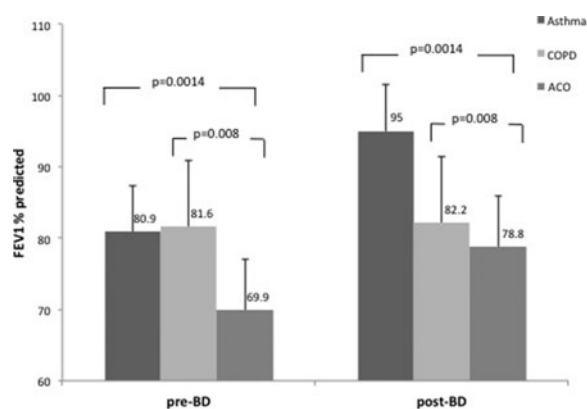


Figure 1. % predicted forced expiratory volume in 1 second (FEV₁) values in patients with asthma, chronic obstructive pulmonary disease (COPD), or asthma-COPD overlap (ACO) pre- and post-bronchodilator (BD) therapy. *P* values were calculated for differences between groups using the Wilks' lambda test.

Discussion

In this analysis, which defined ACO as bronchial obstruction or FEV₁/FVC <LLN, highly positive BD test, and personal history of asthma and atopy, patients with ACO comprised 18.8% of the COPD population of Northern Italy. In terms of overall prevalence, the population with ACO was estimated as 2.1%. The cross-sectional study by Guerriero et al. providing the data for our analyses investigated the prevalence of COPD in a representative sample of adult and elderly individuals in the general population in Northern Italy using both clinical symptoms and spirometry data and reported an estimated COPD prevalence of 9.1% (95% confidence interval [CI] 7.1–11.1%) (26).

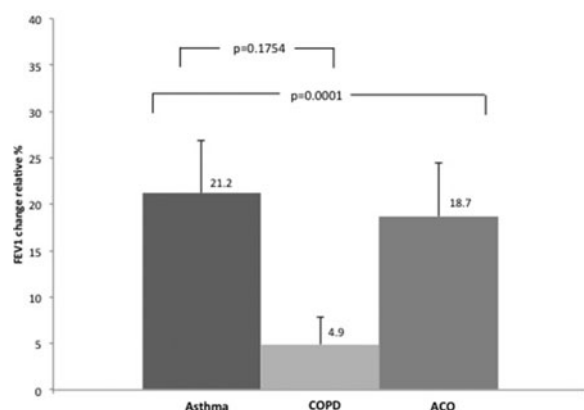


Figure 2. Relative change in forced expiratory volume in 1 second (FEV₁) values (% [standard deviation]) in patients with asthma, chronic obstructive pulmonary disease (COPD), or asthma-COPD overlap (ACO) from pre- to post-bronchodilator (BD). *P* values were calculated for differences between groups using the Wilks' lambda test.

These prevalence rates are in the range of those reported by others (28–30). Studies differ in the definition of ACOS, the precise method used for determining AO (either the LLN criterion as used in our analysis, or the fixed method [FEV₁/FVC <70] used in many other studies), the thresholds used to define a positive BD test (a highly positive test [increase in FEV₁ ≥15% and FVC ≥400 mL] as used in our study or a positive BD test [increase in FEV₁ ≥12% and FVC ≥200 mL] used in many other studies), and the age of studied subjects (31). These differences could explain the slight variations in reported prevalence rates. For example, in our COPD prevalence estimation, using the fixed method gives a prevalence of 11.7%, higher than with the LLN criterion (9.1%).

The ECLIPSE cohort (32) was recently analyzed by focusing on ACO prevalence and features (33). COPD patients answering “yes” to the question “Have you ever had asthma?” were considered to have ACO. According to this definition 25% of COPD patients had ACO.

In a recently published study of COPD, asthma, and ACO prevalence in Italy based on questionnaire data only, ACO prevalence (defined as a physician diagnosis of asthma and COPD) was estimated as 1.6% in members of the general population aged 20–44 years and was shown to increase with age (2.1% in 45–64 year-olds and 4.5% in 65–84 year-olds) (27).

According to a large telephone survey conducted in the United States and involving 12,594 adult respondents, ACO prevalence was 4.0% in female and 2.2% in male (34). The survey relied on patient-reported diagnosis, as well as another recent American study, involving 90,851 adults older than 35 years of age, which estimated ACO prevalence as 3.2% (35). As highlighted by other reports (6,36), the lack of lung function assessment may lead to misdiagnosis and consequent inadequate prevalence rates estimation.

Other studies in Latin America (12) and Spain (28), using the fixed method for defining COPD, estimated the prevalence of ACO as 1.7%. However, it has been demonstrated that the fixed method increases the risk of bronchial obstruction over-estimation, due to the physiological age-related decline of FEV₁/FVC (26,37).

Obstructive airways diseases are relatively common in Italy, with data from 2 population samples reporting that approximately 18% of patients had signs of airway obstruction or at least one of three obstructive lung conditions (asthma, chronic bronchitis, or emphysema) (6). These conditions tended to overlap, as described in our study, particularly in elderly patients (6).

In our sample, patients with ACO, COPD, and asthma do not significantly differ in terms of clinical features and symptoms. This finding is in contrast with previously

published data. The PLATINO study in Latin America for example, showed that patients with ACO were older than those with asthma, but younger than those with COPD. In the same study, ACO group included more males than asthma group (the same as in our study); patients with ACO were more likely to take respiratory medications than patients with COPD or asthma. Furthermore within the ACO group, a higher number of patients underwent prior spirometry and reported to have medically-diagnosed asthma in respect of COPD or asthma patients.

Patterns of symptoms in the 3 groups were also different. In the PLATINO study, the rates of wheezing and dyspnoea were higher in those with ACO than with COPD, but similar to asthma, and rates of cough and phlegm were higher in those with ACO compared to asthma or COPD (12). It should be noted, however, that the overall populations in the PLATINO differed markedly from that in our study, with higher proportions of men in our study (although the proportion of smokers was similar).

Also, the EPI-SCAN study in Spain (28) showed that patients with ACO had more dyspnoea, wheezing, exacerbations, worse respiratory-specific QoL, and reduced levels of physical activity versus those with COPD alone. As with PLATINO, there were significant differences between populations from the EPI-SCAN study and our population (EPI-SCAN included only COPD patients who were more likely to be male and were older, and less likely to have never smoked).

The study published by de Marco et al. also showed that patients with asthma and COPD diagnoses were more likely to experience respiratory symptoms, had larger reported physical impairment, and more likely required hospital admissions compared to those with asthma or COPD alone (27), although variations in study design may partly explain such differences. However, the diagnoses in this study were only made using a questionnaire, without spirometry validation.

The aforementioned ECLIPSE sub-analysis (33) highlighted that, compared to COPD group, patients with ACO were younger and more often female. The disease duration was longer in the ACO group, which was characterized by less cumulative smoking exposure, although the proportion of former smokers was similar between groups. The proportions of co-morbidities were higher in ACO patients, as confirmed by another large retrospective cohort study, which described a strong association between cardiovascular comorbidities and the overall hospitalization risk of patients with ACOS (38).

Other data have also indicated that ACO is associated with more frequent and more severe respiratory exacerbations and hospitalizations than COPD (10,11,32), worse perceived general health status (10,12,13) and worse QoL (14) versus asthma or COPD alone.

Similarly, in the PLATINO study, after adjusting for confounders, ACO was shown to be associated with increased risks of exacerbations (prevalence ratio [PR], 2.11; 95% CI, 1.08–4.12), hospitalizations (PR, 4.11; 95% CI, 1.45–11.67), and worsening general health status (GHS) (PR, 1.47; 95% CI, 1.18–1.85) compared with COPD (12).

In our study, although patients with ACO, COPD, and asthma were similar in terms of symptoms, and clinical and demographic characteristics, there were significant differences in spirometry parameters between ACO and COPD, and between ACO and asthma. ACO patients had significantly lower pre-BD % predicted FEV₁% versus COPD and asthma patients. Furthermore, ACO patients were very similar to asthma patients in terms of response to BD, as seen by similar increases in FEV₁ and FVC values, both significantly higher in patients with ACO or asthma compared to COPD.

Data from a Spanish analysis comparing patients with ACO or different phenotypes of COPD showed that % predicted FEV₁ in ACO patients was not significantly different from that in patients with chronic bronchitis or COPD, and that the proportion of ACO patients with mild dyspnoea was significantly lower compared to COPD patients (29).

Conversely, in our study, % predicted post-BD FEV₁ was significantly lower in ACOS versus COPD patients but there was no significant difference between the patient groups in the proportion of patients with dyspnoea.

Overall, bivariate analysis of our data suggests a slight similarity between COPD and ACO in terms of demographic characteristics, while a peculiar clinical profile specifically identifying ACO is difficult to draw. On the opposite, the evaluation of lung function parameters in ACO patients shows a mixed pattern, sharing characteristics of both asthma and COPD.

Current guidelines, while stating that spirometry is essential for the assessment of patients with suspected chronic airway disease, do not include reversibility as a criterion for ACO (3,22). However no agreement was achieved on the relevance of reversibility test. In fact the Soler-Cataluna guidelines on the management of ACO reached consensus on the use of a very positive BD test as one of the diagnostic criteria for ACO (13). In the 2017 GINA ACO recommendations, one of the features of ACO is “airflow limitation not fully reversible, but often with current or historical variability” (3).

On the other hand, our data, which show that patients with ACO had a reversible FEV₁ response slightly lower than patients with asthma, support those published by Albert et al. who performed a post-hoc analysis of data from randomized trials of COPD treatment and discussed the possibility of a subgroup of COPD patients who were

responsive to BD therapy and had a reversible FEV₁ (30). Nevertheless, spirometry is an important assessment tool and should be more widely used in clinical practice (6).

The main limitation of our study is that it is a sub-analysis of data from a population study aimed at assessing COPD prevalence, i.e., it was not powered for comparisons between the different patient groups. As a major consequence the sample size, talking about the ACO patients subgroup particularly, is quite small so that the results cannot be generalized. However the subjects included in the study come from a random sample, thus they can be considered a representative population subgroup. Furthermore this study provides useful data on ACO, an area in which information is relatively lacking. Differently from other previous studies, lung function test data in addition to information from questionnaires has been included.

Conclusion

Based on an ACO definition of bronchial obstruction or FEV₁/FVC <LLN, highly positive BD test (increase in FEV₁ ≥15% and FVC ≥400 mL), and personal history of asthma and atopy, the prevalence of ACO in Northern Italy was estimated at 2.1%, similar to previous estimates in other countries. In contrast to previous data, ACO patients were very similar to those with COPD and asthma in terms of symptoms and other patient and clinical characteristics. On the other hand, our spirometry data revealed significant differences between ACO and COPD patients in terms of lung function parameters. The most significant difference was that FEV₁ reversibility after BD administration was similar in ACO and asthma patients, whereas patients with COPD alone did not respond to BD therapy. Further epidemiological research is required to thoroughly evaluate the burden of ACO and rate of misdiagnoses, and identify the characteristics, risk factors, and needs of these patients in order to improve ACO management.

Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

- Blackwell DL, Lucas JW, Clarke TC. Summary health statistics for U.S. adults: national health interview survey, 2012. Vital and Health Statist Series 10: Data from the Nat Health Survey. 2014;1–171.
- Nakawah MO, Hawkins C, Barbandi F. Asthma, chronic obstructive pulmonary disease (COPD), and the overlap syndrome. *J Am Fam Med.* 2013;26:470–7. doi:10.3122/jabfm.2013.04.120256.
- Global Initiative for Asthma. Diagnosis of Diseases of Chronic Airflow Limitation: Asthma COPD and Asthma-COPD Overlap Syndrome (ACOS) 2015. Available from: <http://ginasthma.org/asthma-copd-and-asthma-copd-overlap-syndrome-acos/> [last accessed 1 May 2017].
- Burrows B, Bloom JW, Traver GA, Cline MG. The course and prognosis of different forms of chronic airways obstruction in a sample from the general population. *New Engl J Med.* 1987;317:1309–14. doi:10.1056/NEJM198711193172103.
- Marsh SE, Travers J, Weatherall M, Williams MV, Aldington S, Shirtcliffe PM, et al. Proportional classifications of COPD phenotypes. *Thorax.* 2008;63:761–7. doi:10.1136/thx.2007.089193.
- Viegi G, Matteelli G, Angino A, Scognamiglio A, Baldacci S, Soriano JB, et al. The proportional Venn diagram of obstructive lung disease in the Italian general population. *Chest.* 2004;126:1093–101. doi:10.1378/chest.126.4.1093.
- Postma DS, Anzueto AR, Jenkins C, Make BJ, Similowski T, Östlund O, et al. Factor analysis in predominantly severe COPD: identification of disease heterogeneity by easily measurable characteristics. *Respir Med.* 2013;107:1939–47. doi:10.1016/j.rmed.2013.07.011.
- Desai M, Oppenheimer J, Tashkin DP. Asthma-chronic obstructive pulmonary disease overlap syndrome: what we know and what we need to find out. *Ann Allergy Asthma Immunol.* 2017;118(3):241–45. doi:10.1016/j.anai.2016.12.016.
- Cazzola M, Rogliani P. Do we really need asthma-chronic obstructive pulmonary disease overlap syndrome? *J Allergy Clin Immunol.* 2016;138:977e983. doi:10.1016/j.jaci.2016.04.028.
- Hardin M, Silverman EK, Barr RG, Hansel NN, Schroeder JD, Make BJ, et al. The clinical features of the overlap between COPD and asthma. *Respir Res.* 2011;12:127. doi:10.1186/1465-9921-12-127.
- Hardin M, Cho M, McDonald ML, Beaty T, Ramsdell J, Bhatt S, et al. The clinical and genetic features of COPD-asthma overlap syndrome. *Eur Respir J.* 2014;44:341–50. doi:10.1183/09031936.00216013.
- Menezes AM, Montes de Oca M, Pérez-Padilla R, Nadeau G, Wehrmeister FC, Lopez-Varela MV, et al. Increased risk of exacerbation and hospitalization in subjects with an overlap phenotype: COPD-asthma. *Chest.* 2014;145:297–304. doi:10.1378/chest.13-0622.
- Soler-Cataluna JJ, Cosio B, Izquierdo JL, JL López-Campos, JM Marín, R Agüero, et al. Consensus document on the overlap phenotype COPD-asthma in COPD. *Arch Bronconeumol.* 2012;48:331–7. doi:10.1016/j.arbr.2012.06.017.
- Kauppi P, Kupiainen H, Lindqvist A, Tammilehto L, Kilpeläinen M, Kinnula VL, et al. Overlap syndrome of asthma and COPD predicts low quality of life. *J Asthma.* 2011;48:279–85. doi:10.3109/02770903.2011.555576.
- Kurashima K, Takaku Y, Ohta C, Takayanagi N, Yanagisawa T, Sugita Y. COPD assessment test and severity of airflow limitation in patients with asthma, COPD, and asthma-COPD overlap syndrome. *Int J Chron Obstruct Pulmon Dis.* 2016;11:479–87. doi:10.2147/COPD.S97343.
- Papi A, Romagnoli M, Baraldo S, Braccioni F, Guzzinati I, Saetta M, et al. Partial reversibility of airflow limitation and

- increased exhaled NO and sputum eosinophilia in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2000;162:1773–7. doi:[10.1164/ajrccm.162.5.9910112](https://doi.org/10.1164/ajrccm.162.5.9910112).
17. Siva R, Green RH, Brightling CE, Shelley M, Hargadon B, McKenna S, et al. Eosinophilic airway inflammation and exacerbations of COPD: a randomised controlled trial. *Eur Respir J*. 2007;29:906–13. doi:[10.1183/09031936.00146306](https://doi.org/10.1183/09031936.00146306).
 18. Miravittles M, Calle M, Soler-Cataluna JJ. Clinical phenotypes of COPD: identification, definition and implications for guidelines. *Arch Bronconeumol*. 2012;48:86–98. doi:[10.1016/j.arbres.2011.10.007](https://doi.org/10.1016/j.arbres.2011.10.007).
 19. Karamitsakos T, Gourgoulakis KI. Asthma-COPD Overlap Syndrome (ACOS): single disease entity or not? Could exhaled nitric oxide be a useful biomarker for the differentiation of ACOS, asthma and COPD? *Med Hypotheses*. 2016;91:20–3. doi:[10.1016/j.mehy.2016.04.008](https://doi.org/10.1016/j.mehy.2016.04.008).
 20. Miravittles M, Soler-Cataluña JJ, Calle M, Molina J, Almagro P, Quintano JA, et al. Spanish COPD guidelines (GesEPOC): pharmacological treatment of stable COPD. Spanish Society of Pulmonology and Thoracic Surgery. *Arch Bronconeumol*. 2012;48:247–57. doi:[10.1016/j.arbres.2012.04.001](https://doi.org/10.1016/j.arbres.2012.04.001).
 21. Miravittles M, Soler-Cataluña JJ, Calle M, Molina J, P Almagro, JA Quintano, et al. Spanish guideline for COPD (GesEPOC). Update 2014. *Arch Bronconeumol*. 2014;50 Suppl 1:1–16.
 22. Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention (updated 2017). Available from: <http://www.ginasthma.org/> 2017. [last accessed 20 May 2017].
 23. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (updated 2017). Available from: <http://www.goldcopd.org/> 2017 [last accessed 20 May 2017].
 24. Postma DS, Rabe KF. The Asthma-COPD Overlap Syndrome. *New Engl J Med*. 2015;373:1241–49. doi:[10.1056/NEJMr1411863](https://doi.org/10.1056/NEJMr1411863).
 25. Global Initiative for Chronic Obstructive Lung Disease. Diagnosis of Diseases of Chronic Airflow Limitation: Asthma, COPD and Asthma-COPD Overlap Syndrome (ACOS). Available from: <http://goldcopd.org/asthma-copd-asthma-copd-overlap-syndrome/> 2015 [last accessed 20 May 2017].
 26. Guerriero M, Caminati M, Viegi G, Senna G, Cesana G, Pomari C. COPD prevalence in a north-eastern Italian general population. *Respir Med*. 2015;109:1040–7. doi:[10.1016/j.rmed.2015.05.009](https://doi.org/10.1016/j.rmed.2015.05.009).
 27. de Marco R, Pesce G, Marcon A, Accordini S, Antonicelli L, Bugiani M, 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. doi:[10.1371/journal.pone.0062985](https://doi.org/10.1371/journal.pone.0062985).
 28. Miravittles M, Soriano JB, Ancochea J, Muñoz L, Duran-Tauleria E, Sánchez G, et al. Characterisation of the overlap COPD-asthma phenotype. Focus on physical activity and health status. *Respir Med*. 2013;107:1053–60. doi:[10.1016/j.rmed.2013.03.007](https://doi.org/10.1016/j.rmed.2013.03.007).
 29. Izquierdo-Alonso JL, Rodríguez-González-moro JM, de Lucas-Ramos P, Unzueta I, Ribera X, Antón E, et al. Prevalence and characteristics of three clinical phenotypes of chronic obstructive pulmonary disease (COPD). *Respir Med*. 2013;107:724–31. doi:[10.1016/j.rmed.2013.01.001](https://doi.org/10.1016/j.rmed.2013.01.001).
 30. Albert P, Agusti A, Edwards L, Tal-Singer R, Yates J, Bakke P, et al. Bronchodilator responsiveness as a phenotypic characteristic of established chronic obstructive pulmonary disease. *Thorax*. 2012;67:701–8. doi:[10.1136/thoraxjnl-2011-201458](https://doi.org/10.1136/thoraxjnl-2011-201458).
 31. Lange P, Halpin DM, O'Donnell DE, MacNee W. Diagnosis, assessment, and phenotyping of COPD: beyond FEV₁. *Int J Chron Obstruct Pulmon Dis*. 2016;11 Spec Iss:3–12.
 32. Vestbo J, Anderson W, Coxson HO, Crim C, Dawber F, Edwards L, et al. Evaluation of COPD longitudinally to identify predictive surrogate end-points (ECLIPSE). *Eur Respir J*. 2008;31:869–73. doi:[10.1183/09031936.00111707](https://doi.org/10.1183/09031936.00111707).
 33. Wurst KE, Rheault TR, Edwards L, Tal-Singer R, Agusti A, Vestbo J. A comparison of COPD patients with and without ACOS in the ECLIPSE study. *Eur Respir J*. 2016;47(5):1559–62. doi:[10.1183/13993003.02045-2015](https://doi.org/10.1183/13993003.02045-2015).
 34. Wheaton AG, Pleasants RA, Croft JB, Ohar JA, Heidari K, Mannino DM, et al. Gender and asthma-chronic obstructive pulmonary disease overlap syndrome. *J Asthma*. 2016;53(7):720–31.
 35. Kumbhare S, Pleasants R, Ohar JA, Strange C. Characteristics and prevalence of asthma/chronic obstructive pulmonary disease overlap in the United States. *Ann Am Thorac Soc*. 2016;13(6):803–10. doi:[10.1513/AnnalsATS.201508-554OC](https://doi.org/10.1513/AnnalsATS.201508-554OC).
 36. Barbara C, Rodrigues F, Dias H, Cardoso J, Almeida J, Matos MJ, et al. Chronic obstructive pulmonary disease prevalence in Lisbon, Portugal: the burden of obstructive lung disease study. *Rev Port Pneumol*. 2013;19(3):96–105.
 37. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. *Eur Respir J*. 2012;40(6):1324–43.
 38. van Boven JF, Román-Rodríguez M, Palmer JF, Toledo-Pons N, Cosío BG, Soriano JB. Comorbidity, pattern, and impact of Asthma-COPD Overlap Syndrome in real life. *Chest*. 2016;149(4):1011–20. doi:[10.1016/j.chest.2015.12.002](https://doi.org/10.1016/j.chest.2015.12.002).