Asthma and COPD "overlap": a treatable trait or common several treatable-traits?

Abstract

In the last years, disease classification of chronic respiratory diseases (CRD) has been vivaciously discussed and new concepts have been introduced, namely asthma-chronic obstructive pulmonary disease (COPD) overlap (ACO). Controversially the GOLD consensus document of 2020 considered that we should no longer refer to ACO, as they constitute two different diseases that may share some common traits and clinical features.

The treatable traits approach has numerous strengths that are applicable to several levels of health care. In this paper we review the application of the treatable traits to CRD and describe in detail the ones already identified in patients with asthma and COPD. Treatable traits in CRD can be divided in pulmonary, extra-pulmonary and behavior/lifestyle risk factors. Patients with both asthma and COPD have clearly recognized treatable traits in all these subtypes with a pattern of severe and frequent exacerbations, associated cardiovascular disease and low health related quality of life and productivity.

Introduction

In recent years the disease classification of chronic respiratory diseases has been put into debate (1, 2). Classical classification used pre-20th century descriptions and concepts, based on symptoms, signs and functional abnormalities instead of pathophysiological mechanisms. Diagnostic terms such as asthma, chronic obstructive pulmonary disease (COPD) and chronic bronchitis were originally proposed to define a clinical presentation that appeared to encompass a more or less distinct disease process (1). These labels were defined in a subjective manner taking into account non-specific symptoms and signs such as cough, wheeze and breathlessness. As our knowledge of disease mechanisms progressed to a detailed molecular level the general approach to chronic respiratory diseases has been to try and match these abnormalities to the original disease classification rather than taking into consideration the pathophysiologic mechanisms themselves as the basis for classification (1, 2).

In the last years there has been a renewed debate about how asthma and COPD may likely represent a continuum of different diseases that may share biological mechanisms (i.e. endotypes) and present similar clinical, functional, imaging and/or biological features that can be observed, (i.e. phenotypes) which require precision medicine treatment(2). Current consensus documents about asthma and COPD assume that "heterogeneity" and "complexity" are both part of both diseases and even went further including these characteristics in disease definition (3, 4). Our inability to understand the complexity of airway diseases is clinically relevant as it may conduct to suboptimal management due to the potentially need of different therapeutic strategies and may constraint our pathophysiologic investigation about patients whose clinical phenotype is not easily classified. Additionally, this "Oslerian diagnostic label" may jeopardize drug development for specific endotypes and it limits the generalizability of the results of most randomized controlled trials (2). Despite the identified limitations, the diagnostic labels approach has many advantages: they are useful to discriminate grossly defined groups of patients, are an "easy basis" for teaching students as well as explaining to patients and to use in interventional studies to convince authorities to fund medications. In clinical practice, they are also useful to identify a syndrome but this will probably lead

to empirical management. With nowadays knowledge the labels should represent the start of the assessment process, not the end (5).

The concept of "treatable trait" has been proposed by A. Agusti in 2016, encompassing a label-free, precision medicine approach to the diagnosis and management of chronic airway diseases (2). This strategy has the purpose of "treatable traits" identification in each patient and these traits can be "treatable" based on "phenotypic" recognition or on deep understanding of the critical causal pathways (2). From a patient perspective it is important to recognize that a given patient may have more than one treatable trait and actually this is often the case. A treatable-trait should fulfil the following three characteristics: 1. *Clinical relevant*: (requires to be clinically important, associated with specific disease outcomes); 2. *Identifiable and measurable* (should have a marker to objectively be identified, typically would be a biomarker) and 3. *Treatable* (should be effectively treated and this effect should ideally be measured in randomized controlled trials; traits not currently treatable or partly treatable are research opportunities)(6). One of the main potential strengths of this approach is that it does not start on the assumption that the diagnosis (asthma or COPD) is well established and clear, a situation which is not the case in many instances in clinical practice, particularly in primary care. In the "treatable traits" approach specific diagnostic criteria are defined for these "traits" and this may have a considerable impact in patient treatment assuming an expected larger therapeutic response. Another relevant aspect is that this approach may stimulate best translational research by identifying knowledge gaps that can be in future addressed (2).

In Table I we present the potential advantages and disadvantages (2, 5) of traditionally "Oslerian approach" versus a "Treatable-traits approach" in chronic respiratory diseases:

Another interesting point is that until recently a new phenotypic entity has re-emerged, the asthma-COPD overlap (ACO) (7). This entity has been put into debate due to the evidence that in clinical practice there is a significant number of patients who exhibit features of both diseases (7). Taking into consideration the well-known heterogeneity of both diseases our question is why should patients with overlap of both diseases be "homogeneous" and not also rather "heterogeneous"?

The purpose of our review is to discuss nowadays criteria of asthma-COPD overlap and possible treatable traits among this group of patients.

Asthma-COPD overlap definition

The possible first description of ACO is thought to be proposed by Orie and Sluiter in 1961, the well-know "Dutch hypothesis". This hypothesis theorized that asthma and COPD may have a mutual origin and subsequent expression of each disease is explained by individual variables encompassing genetic factors and environmental exposures (7). On the other hand, an opposite theory has been called the "British hypothesis", which postulates separate origins for asthma and COPD driven by its own individual genetic traits, inflammatory profile and treatment (7). In 2015 a consensus document elaborated together by GINA (Global Initiative for Asthma) and GOLD (Global Initiative for Chronic Obstructive Lung Disease) proposed a clinical description of patients who exhibited features of both asthma and COPD and called this entity the asthma-COPD overlap syndrome (ACOS)(8). In this document it was already emphasized that ACOS was not a single disease entity, including different forms of airways diseases. This constitutes one of the first and main misleading concepts associated with this subject as a syndrome by definition is "a recognizable complex of symptoms and physical findings which indicate a specific condition for which a direct cause is not necessarily understood" (9). In the context of the overlap between asthma and COPD we could argue that the causes are not necessarily understood but by no means the symptoms and physical findings indicate a specific condition.

Recent reviews also concluded that the ACOS does not represent a unique form of disease, and that the inclusion of patients with different endotypes and phenotypes under this umbrella term may not facilitate treatment decisions (10). Although the conceptual interest about ACOS is totally understandable it is now recognized that another syndrome is not needed in the already complex matrix of airways disease and that its use in clinical practice is likely to require a treatable-traits approach (10). Current GINA consensus document also discourages the use of previously described term ACOS given the propensity to consider this entity as a single disease, emphasizing the heterogeneity of patients with ACO (3). The GOLD consensus document of 2020 went even further, considering that we should no longer refer to ACO as asthma and COPD are different disorders. Also, according to this document, a patient with the diagnosis of both diseases should be seen as having concurrent diagnosis that may share common traits and clinical features (4). From our point of view this approach may be too simplistic and disregards all the data available where was shown that patients with concurrent asthma and COPD do not have a simple addiction of both diseases and an "interaction" between both diseases may occur as it will be further detailed.

One clear and paradigmatic example of how ACO cannot be considered one single disease is the vast number of published definitions. In the last recent years, we can find several examples of an "Oslerian approach" in "consensus" or "guidelines" to define ACO. In Table II are detailed the several proposed criteria for asthma-COPD overlap (adapted from (11)):

Apart from the above cited definitions several other definitions have been used for clinical research purpose and this is by sure one of the main limitations about ACO clinical research (16-22). In 2018, using a Delphi structured survey of Portuguese specialists in respiratory diseases, it was published other ACO diagnostic criteria. This group of physicians established a consensus for these criteria: a fixed airflow obstruction (FEV1/FVC<0.7) associated with 2 major criteria (previous history of asthma; presence of a previous history of smoking exposure and/or exposure to biomass combustion;

positive bronchodilation test (increase in FEV_1 of at least 200mL and 12%) on more than 1 occasion) plus 1 minor criteria (history of atopy; age ≥40 years; peripheral eosinophilia (>300 eosinophils/µL or >5% of leukocytes); elevation of specific IgEs or positive skin tests for common allergens)(23). The proposed criteria, as compared to the above definitions, are quite similar to what had been proposed by guidelines/consensus (11). This study, as others published using only expert opinion clearly use an "Oslerian approach", but have the interest of setting the stage about the national general agreement about ACO definition adapted to our local context.

The clinical research (including also clinical trials) about asthma and COPD always used useful approaches to define both conditions in order to exclude patients that did not fulfil the "pure form" of both diseases (24). Though is an easy going approach it limits available evidence and does not fully depict the spectrum of obstructive airway disease that is seen in clinical practice (24). If in the recent years several studies have tried to answer this knowledge gap, the methodologic issue associated with ACO definition may prejudice achieved conclusions.

Treatable traits among asthma-COPD overlap

Currently available data about asthma-COPD overlap has increased in the last years and several conclusions can be discussed. From our conceptual point of view and assuming that the "treatable-traits approach" of diseases is the update method to define patient characteristics we will now discuss the treatable traits identified among ACO patients. In this paper we review the available data published until 2018 about treatable traits identified in patients with ACO. We performed a Pubmed search of all the papers published from 2010 to 2018 that included simultaneously all the search terms "COPD", "Asthma" and "Overlap". A total of 436 papers were selected for a first analysis. All the guidelines, consensus, reviews and editorials were excluded from our review. After exclusion of the previous mentioned papers a total of 304 papers were included in our review and we here discuss the papers that describe treatable traits in ACO.

As previously described by Agusti et al. treatable traits of chronic airway diseases can be divided in pulmonary, extrapulmonary and behaviour/lifestyle risk factors treatable traits (2).

Pulmonary treatable traits in ACO

In Table III are listed the pulmonary treatable traits described in patients with asthma-COPD overlap:

Revising the pulmonary treatable traits described in patients with ACO we can clearly notice that airflow limitation, airway smooth muscle contraction and eosinophilic airway inflammation are constantly found in the literature. This makes perfect sense and is expectable as nowadays available ACO definitions continually include them as diagnostic criteria (12-15). This evidence underlines the interest about bronchodilators treatment in patients with ACO as recommended by nowadays documents of GINA and GOLD (3, 4).

Evidence about eosinophilic airway inflammation in ACO patients has emerged from several studies, not only studies considering it a diagnostic criterion but also an evaluated outcome. Evidence about eosinophilic airway inflammation has emerged using different methodologies: eosinophils in induced sputum but also with eosinophils in peripheral blood and fractional exhaled nitric oxide (FeNO) as surrogate markers (19, 20, 29, 31, 41, 42, 44, 47, 48, 58, 61-64, 67, 71, 73, 74, 77-79, 85-87, 90). The presence of eosinophilic airways inflammation in patients with COPD/ACO is a nowadays matter of debate and may have a therapeutic consequence with the recommendation for the need of inhaled corticosteroids treatment (3, 4). The interest about FeNO evaluation in ACO patients management is also a trending topic and more studies are needed. A study from Chen et al. in 2016 found a FeNO optimal diagnostic cut-off of 22.5 ppb in differentiating patients with ACO from COPD patients, with 70% sensitivity and 75% specificity (38). More recently in 2018 Takayama et al. described that a composite cut-off of FeNO≥25 ppb combined with blood eosinophils counts≥250 cels./µL showed a 96.1% specificity for differentiating ACO from COPD.

Another interesting point of debate about ACO patients is their rate and severity of exacerbations. Although evidence is not consistent in all the published papers there is clearly a trend for considering that ACO patients have not only more frequent exacerbations, as more severe, with increased mortality and associated costs (19, 20, 29, 31, 41, 42, 44, 47, 48, 58, 61-64, 67, 71, 73, 74, 77-79, 85-87, 90). The study from Gerhardsson de Verdier et al. showed that patients with asthma and COPD had nearly double health care costs compared to patients with asthma without COPD, and this large difference was mainly driven by the rates of hospitalizations and emergency department visits (95). A fascinating study from Lange et al. published in 2016 concludes that regarding long-term prognosis of individuals with ACO, we can even identify a more susceptible and severe subgroup with late-onset asthma with an extraordinarily poor prognosis according to FEV_1 decline, exacerbations, pneumonias, and survival (49). All this information together highlights that ACO patients should be carefully managed as an inappropriate management will have a high individual burden but also for the healthcare system.

Emphysema is another pulmonary treatable trait found in patients with ACO but with a frequency apparently lower than in patients with COPD (16, 19, 20, 30, 40, 41, 53, 54, 67, 71, 73, 77, 83, 88, 91). Two different papers published by Yeh et al. in 2016 analyzing the National Health Insurance Research Database of Taiwan found attention-grabbing associations of ACO with pulmonary embolism and incident tuberculosis (102, 103). The association of ACO with increased risk of pulmonary embolism was independent of age, sex, comorbidities and corticosteroids use. The proposed explanation for this risk is that the eosinophilic and neutrophilic inflammation of the airways with pulmonary artery inflammation might be the predisposing factors of pulmonary embolism (102). ACO was also found to be associated with incident tuberculosis in another paper published by Yeh analyzing the same database. The authors found an adjusted hazard ratio for tuberculosis of 2.41 (95% confidence interval: 2.19–2.66) in the ACOS cohort and the tuberculosis risk was significantly higher in the ACOS cohort than in the non-ACOS cohort when stratified by age, sex, comorbidities, and atopy. The authors proposed as probable explanations for this association the possible high doses of corticosteroid and likely

frequent intensive care unit hospitalizations due to recurrent and severe exacerbations of ACO (103).

There has been extensive investigation about the possibility of a biomarker or composite biomarkers to diagnose ACO, apart from what has been discussed for FeNO and blood eosinophils. In 2016, Gao et al. described sputum neutrophil gelatinase-associated lipocalin (NGAL) levels as potentially differentiators of ACO from asthma and COPD, as ACO patients had increased values of this biomarker compared to the other groups of patients. Although NGAL is also a COPD-related biomarker, NGAL is not only attributed to activated neutrophils but could also be secreted by the respiratory epithelial cells in response to inflammatory stimuli and by myeloid and epithelial cells in response to toll-like receptor activation during bacterial infections. Therefore, the high sputum NGAL levels found in ACO might be related to airway inflammation and low-grade microbial colonization, which predispose these patients to acute viral infections and exacerbations (42). Although this result seems promising induced sputum unfortunately is not settled as desired in routine clinical practice and this is a challenge to the implementation of this biomarker and others using this technique. More recently, in 2018, Wang et al. described that plasma YKL-40 also referred to as chitinase-3-like-1 protein (CHI3L1) is a promising candidate for distinguishing between patients with features of ACO and COPD patients, while plasma NGAL may be a valuable biomarker for differentiating between patients with features of ACO and asthma patients (87).

Extra-pulmonary treatable traits in ACO

In Table IV are listed the extra-pulmonary treatable traits described in patients with asthma-COPD overlap:

The association of ACO with allergic rhinoconjunctivitis (16, 30, 48, 58, 70, 71, 73, 80, 88, 103), atopic dermatitis (57, 70, 88, 103) and atopy (20, 27, 31, 33, 41, 42, 44, 48, 52, 57, 58, 62, 63, 66, 71, 73, 74, 76-79, 81, 85, 87, 90, 96) is also intuitive and in some papers were considered diagnostic criteria for ACO. There is some heterogeneous data about the frequency of these treatable traits in ACO patients in comparison with asthma patients, some pointing out less frequency and others similar results. More consistent is the evidence that these treatable traits occur with superior frequency compared to patients with "pure" COPD and are even a factor to consider when comparing both diseases. Considering the other extra-pulmonary treatable traits associated with ACO and their relative frequency compared to "pure" asthma and COPD patient's data is somewhat discordant. The rates of obesity (20, 33, 57, 59, 65, 73, 78, 80, 81, 84, 96, 97, 104), diabetes (22, 25, 39, 40, 57-59, 70, 73, 76, 77, 86, 94, 95, 98, 99, 102, 103), dyslipidemia (40, 59, 66, 70, 73, 95, 102, 103), cataracts (99), gastroesophageal reflux disease (39, 58, 59, 66, 71, 95), cerebrovascular disease (22, 25, 91, 98-100, 103), osteoarthritis (20, 22, 59), osteoporosis/fractures (20, 58, 59, 66, 68, 71, 85, 94, 102), depression (19, 20, 40, 57, 91, 94, 106), anxiety (19, 20, 40, 57, 99, 100), autoimmune diseases (20) and malignancies (35, 98) are in general superior to "pure" asthma and COPD patients although some papers have conflicting results. The noteworthy association of ACO with malignancies has been shown not only for lung cancer but also to other malignancies (35, 98). Cardiovascular disease is an exception to what was previously mentioned as in this case the frequency of disease is consistently superior in ACO patients compared to patients with only asthma or COPD. This evidence has been shown in several forms of cardiovascular disease, including hypertension, ischemic heart disease, angina, acute myocardial infarction and congestive heart failure (20, 22, 25, 28, 29, 39, 40, 57-59, 66, 70, 71, 73, 76, 77, 84, 86, 91, 94, 95, 98-100, 102, 103, 105). The pathophysiology of this association may be related to the persistent systemic inflammation found in patients with ACO (20, 29, 77). In the paper of Fu et al. published

281 in 2014 it was suggested that systemic inflammation is commonly present in ACO, and
282 ACO resembled COPD in terms of systemic inflammation. The evidence about systemic
283 inflammation in COPD is for long known and matter of debate sincere early 2000s (107,
284 108). In the same study it was shown that IL-6 is a pivotal inflammatory mediator that
285 may be involved in airflow obstruction and cardiovascular disease and may be an
286 independent treatment target for ACO. The systemic inflammation that occurs in ACO
287 has also been proposed as a possible mechanism involved in osteoporosis associated
288 with ACO. In the study of Oh et al. patients with ACO had a significantly lower bone
289 mineral density than did those with asthma, after adjusting for age, sex, body mass
290 index, smoking and corticosteroid use (85).

Behaviour/lifestyle risk factors treatable traits in ACO

In Table V are listed the behavior/lifestyle risk factors treatable traits described in patients with asthma-COPD overlap:

The role of smoking exposure in ACO´s pathophysiology is clear and is emphasized in several publications about ACO. Although the data is somewhat contradictory if patients with ACO have different smoking exposure than patients with "pure" COPD, compared with patients with only asthma it is convincing that ACO patients have an increased smoking exposure (16, 17, 19, 20, 25-27, 30, 31, 33, 35, 38-41, 44, 45, 47, 48, 54-58, 60, 62, 63, 65-67, 69, 71-78, 80, 81, 84, 86-89, 93, 96, 97, 101, 104, 105, 110). This evidence is so clear that smoking exposure is included as a diagnostic criteria for ACO in some of the proposed guidelines (12, 13). From a clinical and management perspective this association should highlight the need for effective smoking cessation strategies in patients with ACO, as a truly disease modifying approach. Nonetheless other exposures have been associated with ACO and constitute identified treatable traits, including exposure to pollution (98) and childhood respiratory infections (33). The familiar history of asthma is an identified treatable trait (30, 77, 80, 88) although the potential to be "treated" nowadays is still somewhat debatable.

Another remarkable discussion is the low health related quality of life found in patients with ACO, that has been described in general health related quality of life as well as in respiratory related quality of life (17, 18, 25, 30, 37, 52, 82, 83). This evidence may be probably related to the high number and to the severity of the exacerbations but also to the several comorbidities described in patients with ACO.

At last but not least, there are some behavioral/lifestyle risk factors treatable traits that current evidence cannot clearly describe as cause or consequence of ACO although their association is clear. Sedentarism (17, 80, 97), low education level (22, 78, 82, 97, 101, 104, 110), low productivity (83), low household income and unemployment (65, 104,

110) are consistently described in ACO. From a common sense perspective, we can speculate that the low education level can act as a risk factor for ACO development probably related to an unhealthy lifestyle, smoking and sedentarism. On the other hand, taking into consideration the high disease burden of ACO, it is perfectly conceivable that it will cause low productivity and consequently low household income and unemployment.

In Figure 1 is a summary of the main treatable traits described in patients with asthma-COPD overlap:

Conclusions

The recently proposed concept of “treatable traits” will definitely substitute our traditional “Oslerian approach” of diseases. The identification of “treatable traits” in each patient should be based on deep understanding of the critical causal pathways. There are several potential advantages of this approach, valuable for all levels of care and different areas of medicine. Chronic respiratory diseases management are always included among this approach, particularly the asthma-COPD patients due to the lack of definitive diagnostic criteria in an “Oslerian approach”. There are several pulmonary, extra-pulmonary and behavioral treatable traits associated to patients with both asthma and COPD. The deep knowledge of these treatable traits will possible permit a better disease management in order to diminish the high disease burden described in patients with these features.

REFERENCES

1. Wardlaw AJ, Silverman M, Siva R, Pavord ID, Green R. Multi-dimensional phenotyping: towards a new taxonomy for airway disease. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology. 2005;35(10):1254-62.
2. Agusti A, Bel E, Thomas M, Vogelmeier C, Brusselle G, Holgate S, et al. Treatable traits: toward precision medicine of chronic airway diseases. The European respiratory journal. 2016;47(2):410-9.
3. Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) 2019 [Available from: http://www.ginasthma.org/].
4. Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2020 [Available from: http://www.goldcopd.org/].
5. Agusti A, Bafadhel M, Beasley R, Bel EH, Faner R, Gibson PG, et al. Precision medicine in airway diseases: moving to clinical practice. The European respiratory journal. 2017;50(4).
6. McDonald VM, Fingleton J, Agusti A, Hiles SA, Clark VL, Holland AE, et al. Treatable traits: a new paradigm for 21st century management of chronic airway diseases: Treatable Traits Down Under International Workshop report. The European respiratory journal. 2019;53(5).
7. Venkata AN. Asthma-COPD overlap: review of diagnosis and management. Current opinion in pulmonary medicine. 2019.
8. Initiatives GaG. Diagnosis of Diseases of Chronic Airfow Limitation: Asthma, COPD and Asthma-COPD Overlap Syndrome (ACOS) 2015 [Available from: https://goldcopd.org/wp-content/uploads/2016/04/GOLD_ACOS_2015.pdf.
9. Calvo F, Karras BT, Phillips P, Kimball AM, Wolf F. Diagnoses, syndromes, and diseases: a knowledge representation problem. AMIA Annu Symp Proc. 2003:802.
10. Fingleton J, Hardy J, Beasley R. Treatable traits of chronic airways disease. Current opinion in pulmonary medicine. 2018;24(1):24-31.
11. Nunez A, Sarasate M, Loeb E, Esquinas C, Miravitlles M, Barrecheguren M. Practical Guide to the Identification and Diagnosis of Asthma-COPD Overlap (ACO). Copd. 2019;16(1):1-7.
12. Plaza V, Alvarez F, Calle M, Casanova C, Cosio BG, Lopez-Vina A, et al. Consensus on the Asthma-COPD Overlap Syndrome (ACOS) Between the Spanish COPD Guidelines (GesEPOC) and the Spanish Guidelines on the Management of Asthma (GEMA). Archivos de bronconeumologia. 2017;53(8):443-9.
13. Sin DD, Miravitlles M, Mannino DM, Soriano JB, Price D, Celli BR, et al. What is asthma-COPD overlap syndrome? Towards a consensus definition from a round table discussion. The European respiratory journal. 2016;48(3):664-73.
14. Kankaanranta H, Harju T, Kilpelainen M, Mazur W, Lehto JT, Katajisto M, et al. Diagnosis and pharmacotherapy of stable chronic obstructive pulmonary disease: the finnish guidelines. Basic Clin Pharmacol Toxicol. 2015;116(4):291-307.
15. Koblizek V, Chlumsky J, Zindr V, Neumannova K, Zatloukal J, Zak J, et al. Chronic Obstructive Pulmonary Disease: official diagnosis and treatment guidelines of the Czech Pneumological and Phthisiological Society; a novel phenotypic approach to

COPD with patient-oriented care. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2013;157(2):189-201.
16. Hardin M, Silverman EK, Barr RG, Hansel NN, Schroeder JD, Make BJ, et al. The clinical features of the overlap between COPD and asthma. Respiratory research. 2011;12:127.
17. Miravitlles M, Soriano JB, Ancochea J, Munoz L, Duran-Tauleria E, Sanchez G, et al. Characterisation of the overlap COPD-asthma phenotype. Focus on physical activity and health status. Respiratory medicine. 2013;107(7):1053-60.
18. Menezes AMB, Montes de Oca M, Perez-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(2):297-304.
19. Barrecheguren M, Roman-Rodriguez M, Miravitlles M. Is a previous diagnosis of asthma a reliable criterion for asthma-COPD overlap syndrome in a patient with COPD? International journal of chronic obstructive pulmonary disease. 2015;10:1715-22.
20. 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. The European respiratory journal. 2016;47(5):1559-62.
21. Perez de Llano L, Cosio BG, Miravitlles M, Plaza V, group Sc. Accuracy of a New Algorithm to Identify Asthma-COPD Overlap (ACO) Patients in a Cohort of Patients with Chronic Obstructive Airway Disease. Archivos de bronconeumologia. 2018;54(4):198-204.
22. Chung JW, Kong KA, Lee JH, Lee SJ, Ryu YJ, Chang JH. Characteristics and self-rated health of overlap syndrome. International journal of chronic obstructive pulmonary disease. 2014;9:795-804.
23. Padrao E, Araujo D, Todo Bom A, Robalo Cordeiro C, Correia de Sousa J, Cardoso J, et al. Asthma-COPD overlap: A Portuguese survey. Pulmonology. 2018.
24. Gibson PG, Simpson JL. The overlap syndrome of asthma and COPD: what are its features and how important is it? Thorax. 2009;64(8):728-35.
25. Kauppi P, Kupiainen H, Lindqvist A, Tammilehto L, Kilpelainen M, Kinnula VL, et al. Overlap syndrome of asthma and COPD predicts low quality of life. The Journal of asthma : official journal of the Association for the Care of Asthma. 2011;48(3):279-85.
26. Verrills NM, Irwin JA, He XY, Wood LG, Powell H, Simpson JL, et al. Identification of novel diagnostic biomarkers for asthma and chronic obstructive pulmonary disease. American journal of respiratory and critical care medicine. 2011;183(12):1633-43.
27. Kim TB, Oh YM, Chang YS, Cho YS, Jang AS, Cho SH, et al. The reality of an intermediate type between asthma and COPD in practice. Respiratory care. 2012;57(8):1248-53.
28. Fu JJ, Gibson PG, Simpson JL, McDonald VM. Longitudinal changes in clinical outcomes in older patients with asthma, COPD and asthma-COPD overlap syndrome. Respiration; international review of thoracic diseases. 2014;87(1):63-74.
29. Fu JJ, McDonald VM, Gibson PG, Simpson JL. Systemic Inflammation in Older Adults With Asthma-COPD Overlap Syndrome. Allergy, asthma & immunology research. 2014;6(4):316-24.
30. Hardin M, Cho M, McDonald ML, Beaty T, Ramsdell J, Bhatt S, et al. The clinical and genetic features of COPD-asthma overlap syndrome. The European respiratory journal. 2014;44(2):341-50.

31. Iwamoto H, Gao J, Koskela J, Kinnula V, Kobayashi H, Laitinen T, et al. Differences in plasma and sputum biomarkers between COPD and COPD-asthma overlap. The European respiratory journal. 2014;43(2):421-9.
32. Lim HS, Choi SM, Lee J, Park YS, Lee SM, Yim JJ, et al. Responsiveness to inhaled corticosteroid treatment in patients with asthma-chronic obstructive pulmonary disease overlap syndrome. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology. 2014;113(6):652-7.
33. de Marco R, Marcon A, Rossi A, Anto JM, Cerveri I, Gislason T, et al. Asthma, COPD and overlap syndrome: a longitudinal study in young European adults. The European respiratory journal. 2015;46(3):671-9.
34. Ghebre MA, Bafadhel M, Desai D, Cohen SE, Newbold P, Rapley L, et al. Biological clustering supports both "Dutch" and "British" hypotheses of asthma and chronic obstructive pulmonary disease. The Journal of allergy and clinical immunology. 2015;135(1):63-72.
35. Harada T, Yamasaki A, Fukushima T, Hashimoto K, Takata M, Kudani M, et al. Causes of death in patients with asthma and asthma-chronic obstructive pulmonary disease overlap syndrome. International journal of chronic obstructive pulmonary disease. 2015;10:595-602.
36. Kim MA, Noh CS, Chang YJ, Hong YK, Lee JS, Lee SW, et al. Asthma and COPD overlap syndrome is associated with increased risk of hospitalisation. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2015;19(7):864-9.
37. Suzuki T, Tada Y, Kawata N, Matsuura Y, Ikari J, Kasahara Y, et al. Clinical, physiological, and radiological features of asthma-chronic obstructive pulmonary disease overlap syndrome. International journal of chronic obstructive pulmonary disease. 2015;10:947-54.
38. Chen FJ, Huang XY, Liu YL, Lin GP, Xie CM. Importance of fractional exhaled nitric oxide in the differentiation of asthma-COPD overlap syndrome, asthma, and COPD. International journal of chronic obstructive pulmonary disease. 2016;11:2385-90.
39. Cosentino J, Zhao H, Hardin M, Hersh CP, Crapo J, Kim V, et al. Analysis of Asthma-Chronic Obstructive Pulmonary Disease Overlap Syndrome Defined on the Basis of Bronchodilator Response and Degree of Emphysema. Ann Am Thorac Soc. 2016;13(9):1483-9.
40. Cosio BG, Soriano JB, Lopez-Campos JL, Calle M, Soler JJ, de-Torres JP, et al. Distribution and Outcomes of a Phenotype-Based Approach to Guide COPD Management: Results from the CHAIN Cohort. PloS one. 2016;11(9):e0160770.
41. Cosio BG, Soriano JB, Lopez-Campos JL, Calle-Rubio M, Soler-Cataluna JJ, de-Torres JP, et al. Defining the Asthma-COPD Overlap Syndrome in a COPD Cohort. Chest. 2016;149(1):45-52.
42. Gao J, Iwamoto H, Koskela J, Alenius H, Hattori N, Kohno N, et al. Characterization of sputum biomarkers for asthma-COPD overlap syndrome. International journal of chronic obstructive pulmonary disease. 2016;11:2457-65.
43. Goto T, Camargo CA, Jr., Hasegawa K. Fractional exhaled nitric oxide levels in asthma-COPD overlap syndrome: analysis of the National Health and Nutrition

Examination Survey, 2007-2012. International journal of chronic obstructive pulmonary disease. 2016;11:2149-55.
44. Huang AX, Lu LW, Liu WJ, Huang M. Plasma Inflammatory Cytokine IL-4, IL-8, IL-10, and TNF-alpha Levels Correlate with Pulmonary Function in Patients with Asthma-Chronic Obstructive Pulmonary Disease (COPD) Overlap Syndrome. Med Sci Monit. 2016;22:2800-8.
45. Kalinina EP, Denisenko YK, Vitkina TI, Lobanova EG, Novgorodtseva TP, Antonyuk MV, et al. The Mechanisms of the Regulation of Immune Response in Patients with Comorbidity of Chronic Obstructive Pulmonary Disease and Asthma. Canadian respiratory journal : journal of the Canadian Thoracic Society. 2016;2016:4503267.
46. Kang J, Yao W, Cai B, Chen P, Ling X, Shang H. Current situation of asthma-COPD overlap syndrome (ACOS) in Chinese patients older than 40 years with airflow limitation: rationale and design for a multicenter, cross-sectional trial (study protocol). Journal of thoracic disease. 2016;8(12):3744-51.
47. Kitaguchi Y, Yasuo M, Hanaoka M. Comparison of pulmonary function in patients with COPD, asthma-COPD overlap syndrome, and asthma with airflow limitation. International journal of chronic obstructive pulmonary disease. 2016;11:991-7.
48. Kobayashi S, Hanagama M, Yamanda S, Ishida M, Yanai M. Inflammatory biomarkers in asthma-COPD overlap syndrome. International journal of chronic obstructive pulmonary disease. 2016;11:2117-25.
49. Lange P, Colak Y, Ingebrigtsen TS, Vestbo J, Marott JL. Long-term prognosis of asthma, chronic obstructive pulmonary disease and asthma-chronic obstructive pulmonary disease overlap in the Copenhagen City Heart study: a prospective population-based analysis. Lancet Respir Med. 2016;4(6):454-62.
50. Montes de Oca M, Aguirre C, Lopez Varela MV, Laucho-Contreras ME, Casas A, Surmont F. Exacerbations and health care resource utilization in patients with airflow limitation diseases attending a primary care setting: the PUMA study. International journal of chronic obstructive pulmonary disease. 2016;11:3059-67.
51. Ozkaya S, Diricar A, Tuna T. The objective evaluation of obstructive pulmonary diseases with spirometry. International journal of chronic obstructive pulmonary disease. 2016;11:2009-15.
52. Soriano C, Pedone C, Scichilone N. Fifteen-year mortality of patients with asthma-COPD overlap syndrome. Eur J Intern Med. 2016;34:72-7.
53. Wang W, Xie M, Dou S, Cui L, Xiao W. Computer quantification of "angle of collapse" on maximum expiratory flow volume curve for diagnosing asthma-COPD overlap syndrome. International journal of chronic obstructive pulmonary disease. 2016;11:3015-22.
54. Xie M, Wang W, Dou S, Cui L, Xiao W. Quantitative computed tomography measurements of emphysema for diagnosing asthma-chronic obstructive pulmonary disease overlap syndrome. International journal of chronic obstructive pulmonary disease. 2016;11:953-61.
55. Baarnes CB, Kjeldgaard P, Nielsen M, Miravitlles M, Ulrik CS. Identifying possible asthma-COPD overlap syndrome in patients with a new diagnosis of COPD in primary care. NPJ Prim Care Respir Med. 2017;27:16084.

56. Bai JW, Mao B, Yang WL, Liang S, Lu HW, Xu JF. Asthma-COPD overlap syndrome showed more exacerbations however lower mortality than COPD. QJM. 2017;110(7):431-6.
57. Caillaud D, Chanez P, Escamilla R, Burgel PR, Court-Fortune I, Nesme-Meyer P, et al. Asthma-COPD overlap syndrome (ACOS) vs 'pure' COPD: a distinct phenotype? Allergy. 2017;72(1):137-45.
58. Cosio BG, Perez de Llano L, Lopez Vina A, Torrego A, Lopez-Campos JL, Soriano JB, et al. Th-2 signature in chronic airway diseases: towards the extinction of asthma-COPD overlap syndrome? The European respiratory journal. 2017;49(5).
59. Ding B, Small M. Treatment trends in patients with asthma-COPD overlap syndrome in a COPD cohort: findings from a real-world survey. International journal of chronic obstructive pulmonary disease. 2017;12:1753-63.
60. Feng JX, Lin Y, Lin J, He SS, Chen MF, Wu XM, et al. Relationship between Fractional Exhaled Nitric Oxide Level and Efficacy of Inhaled Corticosteroid in Asthma-COPD Overlap Syndrome Patients with Different Disease Severity. J Korean Med Sci. 2017;32(3):439-47.
61. Gao J, Zhou W, Chen B, Lin W, Wu S, Wu F. Sputum cell count biomarkers in the differentiation of asthma, COPD and asthma-COPD overlap. International journal of chronic obstructive pulmonary disease. 2017;12:2703-10.
62. Inoue H, Nagase T, Morita S, Yoshida A, Jinnai T, Ichinose M. Prevalence and characteristics of asthma-COPD overlap syndrome identified by a stepwise approach. International journal of chronic obstructive pulmonary disease. 2017;12:1803-10.
63. Jo YS, Lee J, Yoon HI, Kim DK, Yoo CG, Lee CT. Different prevalence and clinical characteristics of asthma-chronic obstructive pulmonary disease overlap syndrome according to accepted criteria. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology. 2017;118(6):696-703 e1.
64. Joo H, Han D, Lee JH, Rhee CK. Heterogeneity of asthma-COPD overlap syndrome. International journal of chronic obstructive pulmonary disease. 2017;12:697-703.
65. Kim J, Kim YS, Kim K, Oh YM, Yoo KH, Rhee CK, et al. Socioeconomic impact of asthma, chronic obstructive pulmonary disease and asthma-COPD overlap syndrome. Journal of thoracic disease. 2017;9(6):1547-56.
66. Koblizek V, Milenkovic B, Barczyk A, Tkacova R, Somfay A, Zykov K, et al. Phenotypes of COPD patients with a smoking history in Central and Eastern Europe: the POPE Study. The European respiratory journal. 2017;49(5).
67. Murashima K, Takaku Y, Ohta C, Takayanagi N, Yanagisawa T, Kanauchi T, et al. Smoking history and emphysema in asthma-COPD overlap. International journal of chronic obstructive pulmonary disease. 2017;12:3523-32.
68. Lee DW, Jin HJ, Shin KC, Chung JH, Lee HW, Lee KH. Presence of sarcopenia in asthma-COPD overlap syndrome may be a risk factor for decreased bone-mineral density, unlike asthma: Korean National Health and Nutrition Examination Survey (KNHANES) IV and V (2008-2011). International journal of chronic obstructive pulmonary disease. 2017;12:2355-62.
69. Montes de Oca M, Victorina Lopez Varela M, Laucho-Contreras ME, Casas A, Schiavi E, Mora JC. Asthma-COPD overlap syndrome (ACOS) in primary care of four Latin America countries: the PUMA study. BMC Pulm Med. 2017;17(1):69.

572 70. Park HJ, Byun MK, Kim HJ, Ahn CM, Lee JH, Shin KC, et al. Asthma-COPD Overlap
573 Shows Favorable Clinical Outcomes Compared to Pure COPD in a Korean COPD Cohort.
574 Allergy, asthma & immunology research. 2017;9(5):431-7.
575 71. Perez-de-Llano L, Cosio BG, group Cs. Asthma-COPD overlap is not a
576 homogeneous disorder: further supporting data. Respiratory research. 2017;18(1):183.
577 72. Riesco JA, Alcazar B, Trigueros JA, Campuzano A, Perez J, Lorenzo JL. Active
578 smoking and COPD phenotype: distribution and impact on prognostic factors.
579 International journal of chronic obstructive pulmonary disease. 2017;12:1989-99.
580 73. Tommola M, Ilmarinen P, Tuomisto LE, Lehtimaki L, Haanpaa J, Niemela O, et al
581 Differences between asthma-COPD overlap syndrome and adult-onset asthma. The
582 European respiratory journal. 2017;49(5).
583 74. Alcazar-Navarrete B, Trigueros JA, Riesco JA, Campuzano A, Perez J. Geographic
584 variations of the prevalence and distribution of COPD phenotypes in Spain: the
585 ESPIRAL-ES study". International journal of chronic obstructive pulmonary disease.
586 2018;13:1115-24.
587 75. Ayub, II, Arshad AM, Sekar P, Manimaran N, Thangaswamy D, Chockalingam C.
588 Predictors of asthma-chronic obstructive pulmonary disease overlap syndrome in
589 patients with chronic obstructive pulmonary disease from a tertiary care center in
590 India. Lung India. 2018;35(2):137-42.
591 76. Bikov A, Horvath A, Tomisa G, Bartfai L, Bartfai Z. Changes in the Burden of
592 Comorbidities in Patients with COPD and Asthma-COPD Overlap According to the
593 GOLD 2017 Recommendations. Lung. 2018;196(5):591-9.
594 77. Duong-Quy S, Tran Van H, Vo Thi Kim A, Pham Huy Q, Craig TJ. Clinical and
595 Functional Characteristics of Subjects with Asthma, COPD, and Asthma-COPD Overlap:
596 A Multicentre Study in Vietnam. Canadian respiratory journal : journal of the Canadian
597 Thoracic Society. 2018;2018:1732946.
598 78. Ekerljung L, Mincheva R, Hagstad S, Bjerg A, Telg G, Stratelis G, et al.
599 Prevalence, clinical characteristics and morbidity of the Asthma-COPD overlap in a
600 general population sample. The Journal of asthma : official journal of the Association
601 for the Care of Asthma. 2018;55(5):461-9.
602 79. Guo Y, Hong C, Lu Y, Chen H, Huang X, Hong M. Diagnostic value of fractional
603 exhaled nitric oxide for asthma-chronic obstructive pulmonary disease overlap
604 syndrome. Medicine (Baltimore). 2018;97(23):e10857.
605 80. Henriksen AH, Langhammer A, Steinshamn S, Mai XM, Brumpton BM. The
606 Prevalence and Symptom Profile of Asthma-COPD Overlap: The HUNT Study. Copd.
607 2018;15(1):27-35.
608 81. Tania A, Krenke R, Kuziemski K, Czajkowska-Malinowska M, Celejewska-Wojcik
609 N, Kuznar-Kaminska B, et al. Distribution and characteristics of COPD phenotypes -
610 results from the Polish sub-cohort of the POPE study. International journal of chronic
611 obstructive pulmonary disease. 2018;13:1613-21.
612 82. Kim MH, Rhee CK, Kim K, Kim SH, Lee JY, Kim YH, et al. Heterogeneity of asthma
613 and COPD overlap. International journal of chronic obstructive pulmonary disease.
614 2018;13:1251-60.
615 83. Llanos JP, Ortega H, Germain G, Duh MS, Lafeuille MH, Tiggelaar S, et al. Health
616 characteristics of patients with asthma, COPD and asthma-COPD overlap in the
617 NHANES database. International journal of chronic obstructive pulmonary disease.
618 2018;13:2859-68.

84. Mendy A, Forno E, Niyonsenga T, Carnahan R, Gasana J. Prevalence and features of asthma-COPD overlap in the United States 2007-2012. The clinical respiratory journal. 2018;12(8):2369-77.
85. Oh JY, Lee YS, Min KH, Lee SY, Shim JJ, Kang KH, et al. Osteoporosis in Patients with Asthma-Chronic Obstructive Pulmonary Disease Overlap Syndrome. Tuberc Respir Dis (Seoul). 2018;81(1):73-9.
86. Takayama Y, Ohnishi H, Ogasawara F, Oyama K, Kubota T, Yokoyama A. Clinical utility of fractional exhaled nitric oxide and blood eosinophils counts in the diagnosis of asthma-COPD overlap. International journal of chronic obstructive pulmonary disease. 2018;13:2525-32.
87. Wang J, Lv H, Luo Z, Mou S, Liu J, Liu C, et al. Plasma YKL-40 and NGAL are useful in distinguishing ACO from asthma and COPD. Respiratory research. 2018;19(1):47.
88. Wang YC, Jaakkola MS, Lajunen TK, Lai CH, Jaakkola JJK. Asthma-COPD Overlap Syndrome among subjects with newly diagnosed adult-onset asthma. Allergy. 2018;73(7):1554-7.
89. Kiljander T, Helin T, Venho K, Jaakkola A, Lehtimaki L. Prevalence of asthma-COPD overlap syndrome among primary care asthmatics with a smoking history: a cross-sectional study. NPJ Prim Care Respir Med. 2015;25:15047.
90. Kawamatawong T, Charoenniwassakul S, Reekpattanapipat T. The asthma and chronic obstructive pulmonary disease overlap syndrome in tertiary care setting Thailand. Asia Pac Allergy. 2017;7(4):227-33.
91. Vaz Fragoso CA, Murphy TE, Agogo GO, Allore HG, McAvay GJ. Asthma-COPD overlap syndrome in the US: a prospective population-based analysis of patient-reported outcomes and health care utilization. International journal of chronic obstructive pulmonary disease. 2017;12:317-27.
92. Andersen H, Lampela P, Nevanlinna A, Saynajakangas O, Keistinen T. High hospital burden in overlap syndrome of asthma and COPD. The clinical respiratory journal. 2013;7(4):342-6.
93. 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(5):e62985.
94. Rhee CK, Yoon HK, Yoo KH, Kim YS, Lee SW, Park YB, et al. Medical utilization and cost in patients with overlap syndrome of chronic obstructive pulmonary disease and asthma. Copd. 2014;11(2):163-70.
95. Gerhardsson de Verdier M, Andersson M, Kern DM, Zhou S, Tunceli O. Asthma and Chronic Obstructive Pulmonary Disease Overlap Syndrome: Doubled Costs Compared with Patients with Asthma Alone. Value Health. 2015;18(6):759-66.
96. Ding B, DiBonaventura M, Karlsson N, Ling X. Asthma-chronic obstructive pulmonary disease overlap syndrome in the urban Chinese population: prevalence and disease burden using the 2010, 2012, and 2013 China National Health and Wellness Surveys. International journal of chronic obstructive pulmonary disease. 2016;11:1139-50.
97. 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.

98. To T, Zhu J, Larsen K, Simatovic J, Feldman L, Ryckman K, et al. Progression from Asthma to Chronic Obstructive Pulmonary Disease. Is Air Pollution a Risk Factor? American journal of respiratory and critical care medicine. 2016;194(4):429-38.
99. Wurst KE, St Laurent S, Hinds D, Davis KJ. Disease Burden of Patients with Asthma/COPD Overlap in a US Claims Database: Impact of ICD-9 Coding-based Definitions. Copd. 2017;14(2):200-9.
100. Shantakumar S, Pwu RF, D'Silva L, Wurst K, Kuo YW, Yang YY, et al. Burden of asthma and COPD overlap (ACO) in Taiwan: a nationwide population-based study. BMC Pulm Med. 2018;18(1):16.
101. Mindus S, Malinovschi A, Ekerljung L, Forsberg B, Gislason T, Jogi R, et al. Asthma and COPD overlap (ACO) is related to a high burden of sleep disturbance and respiratory symptoms: Results from the RHINE and Swedish GA2LEN surveys. PloS one. 2018;13(4):e0195055.
102. Yeh JJ, Wang YC, Kao CH. Asthma-Chronic Obstructive Pulmonary Disease Overlap Syndrome Associated with Risk of Pulmonary Embolism. PloS one. 2016;11(9):e0162483.
103. Yeh JJ, Wang YC, Kao CH. Asthma-Chronic Obstructive Pulmonary Diseases Overlap Syndrome Increases the Risk of Incident Tuberculosis: A National Cohort Study. PloS one. 2016;11(7):e0159012.
104. To T, Zhu J, Gray N, Feldman LY, Villeneuve PJ, Licskai C, et al. Asthma and Chronic Obstructive Pulmonary Disease Overlap in Women. Incidence and Risk Factors. Ann Am Thorac Soc. 2018;15(11):1304-10.
105. Yeh JJ, Wei YF, Lin CL, Hsu WH. Association of asthma-chronic obstructive pulmonary disease overlap syndrome with coronary artery disease, cardiac dysrhythmia and heart failure: a population-based retrospective cohort study. BMJ Open. 2017;7(10):e017657.
106. Yeh JJ, Lin CL, Hsu WH, Kao CH. The relationship of depression in asthma-chronic obstructive pulmonary disease overlap syndrome. PloS one. 2017;12(12):e0188017.
107. Agusti AG. Systemic effects of chronic obstructive pulmonary disease. Novartis Found Symp. 2001;234:241-9; discussion 50-4.
108. Bugalho A, JN. Association between bronchial reversibility and airway inflammation in patients with Chronic Obstructive Pulmonary Disease. Rev Port Pneumol (2006). 2002;7(6):547-80.
109. Yamauchi Y, Yasunaga H, Matsui H, Hasegawa W, Jo T, Takami K, et al. Comparison of in-hospital mortality in patients with COPD, asthma and asthma-COPD overlap exacerbations. Respirology (Carlton, Vic). 2015;20(6):940-6.
110. Baarnes CB, Andersen ZJ, Tjonneland A, Ulrik CS. Determinants of incident asthma-COPD overlap: a prospective study of 55,110 middle-aged adults. Clin Epidemiol. 2018;10:1275-87.

706 **Table I. Potential advantages and disadvantages of traditionally "Oslerian approach" versus a**
707 **"Treatable-traits approach" in chronic respiratory diseases:**

	"Oslerian approach"	"Treatable-traits approach"
Advantages	• Simpler definition patients' groups (convenient for students teaching, patient education) • Easy to use in interventional studies • Useful syndrome identification	• No diagnostic assumptions • Precise definition of the "traits" • Disease mechanisms based • Expected larger therapeutic response • Stimulates translational research • Helps the identification of key criteria for future RCT
Disadvantages	• Fails to provide optimal care (no consideration to endotypes) • No appreciation of common patterns of disease • Increases clinical practice variability • Inhibits research progress	• Nowadays only partially based on evidence • Requires comparison about efficacy, safety and cost-effectiveness with "classic strategies" • Uncertainty about patients, physicians and stakeholder acceptance

708 Legend: RCT – Randomized clinical trials

709 **Table II. Proposed criteria for asthma-COPD overlap (adapted from (11)):**

Consensus	Diagnostic Criteria for ACO	Ref.
GesEPOC-GEMA (2017)	- Age≥35 years old - Tobacco exposure ≥10 pack-years - Post BDT FEV1/FVC < 0.70 - Diagnosis of asthma - In absence of asthma diagnosis: - very positive BDT(≥400 mL and 15%) - and/or blood eosinophilia≥300 cells/mL	(12)
Sin et al. (2016)	ACO is confirmed by the presence of three major and at least one minor criteria <u>Major criteria</u> - Post BDT FEV1/FVC <0.70 in individuals>40 years of age - At least 10 pack-years of tobacco smoking - Documented history of asthma before 40 years of age - BDT of >400 mL in FEV1 <u>Minor criteria</u> - Documented history of atopy or allergic rhinitis - BDR of FEV1≥200 mL and 12% from baseline values on 2 or more visits - Peripheral blood eosinophil count of ≥300 cells/uL	(13)
Finnish guidelines (2015)	ACO is confirmed by presenting two main criteria or one main criteria and two additional criteria: <u>Main criteria:</u> - Very positive BDT FEV1 >15 % and >400 ml - Sputum eosinophilia or elevated FENO (>50 ppb) - Previous asthma symptoms (starting age at < 40 y) <u>Additional criteria</u> - Elevated total IgE - Atopy - Repeated significant positive BDT (FEV1 >12 % and >200ml) - Peak expiratory flow follow-up typical of asthma	(14)
Czech guidelines (2013)	ACO is confirmed by the presence of two major criteria or one major plus two minor criteria: Definitive diagnosis of COPD <u>Major criteria:</u> - Very positive BDT FEV1 >15% and >400 mL - FENO≥45–50 ppb and/or sputum eosinophils≥3% - history of asthma <u>Minor criteria:</u>	(15)

	-	Positive BDT (FEV1 >12% and >200 mL)
	-	Elevated total IgE
	-	History of atopy

710 ACO: asthma-COPD overlap; GesEPOC-GEMA: Spanish COPD guidelines-Spanish Asthma Guidelines; BDT:

711 Bronchodilator test; Ref.: reference

712 **Table III. Pulmonary treatable traits described in asthma-COPD overlap:**

	References
Airflow limitation	(16-20, 25-88)
Airway smooth muscle contraction	(16-20, 26, 27, 29-32, 36, 41-45, 47, 50-58, 61-64, 66, 67, 69, 70, 73-79, 81, 85-90)
Hyperinflation	(44, 47, 57)
Emphysema	(16, 19, 20, 30, 40, 41, 53, 54, 67, 71, 73, 77, 83, 88, 91)
Eosinophilic airway inflammation	(19, 20, 29, 31, 41, 42, 44, 47, 48, 58, 61-64, 67, 71, 73, 74, 77-79, 85-87, 90)
Severe and frequent exacerbations	(16-20, 30, 36, 40, 49, 50, 52, 57, 63, 64, 69, 75, 76, 78, 82-84, 92-100)
Chronic bronchitis	(19, 20, 41, 57, 65, 75-77, 80, 83, 88, 91, 101)
Bronchiectasias	(81, 88)
Chronic respiratory failure	(60)
Pulmonary embolism	(102)
Pulmonary hypertension	(75)
Pneumonia	(99)
Incident Tuberculosis	(103)

713

714 **Table IV. Extra-Pulmonary treatable traits described in asthma-COPD overlap:**

	References
Allergic Rhinoconjunctivitis	(16, 30, 48, 58, 70, 71, 73, 80, 88, 103)
Atopic Dermatitis	(57, 70, 88, 103)
Atopy	(20, 27, 31, 33, 41, 42, 44, 48, 52, 57, 58, 62, 63, 66, 71, 73, 74, 76-79, 81, 85, 87, 90, 96)
Obstructive Sleep Apnoea Syndrome	(39, 40, 57, 77)
Obesity	(25, 39, 57, 59, 65, 73, 78, 80, 81, 84, 96, 97, 101)
Cardiovascular disease	(20, 22, 25, 28, 29, 39, 40, 57-59, 66, 70, 71, 73, 76, 77, 84, 86, 91, 94, 95, 98-100, 102, 103, 105)
Diabetes	(22, 25, 39, 40, 57-59, 70, 73, 76, 77, 85, 94, 95, 98, 99, 102, 103)
Dyslipidemia	(40, 59, 66, 70, 73, 95, 102, 103)
Cataracts	(99)
Gastroesophageal reflux disease	(39, 58, 59, 66, 71, 95)
Cerebrovascular disease	(22, 25, 91, 98-100, 103)
Osteoarthritis	(20, 22, 59)
Osteoporosis/Fractures	(20, 58, 59, 66, 68, 71, 85, 94, 102)
Depression	(19, 20, 40, 57, 91, 94, 106)
Anxiety	(19, 20, 40, 57, 99, 100)
Dementia	(100)
Autoimmune diseases	(20)
Malignancies	(35, 98)
Persistent systemic inflammation	(20, 29, 77)

715

716 **Table V. Behaviour/lifestyle risk factors treatable traits described in asthma-COPD overlap:**

	References
Smoking exposure	(16, 17, 19, 20, 25-27, 30, 31, 33, 35, 38-41, 44, 45, 47, 48, 54-58, 60, 62, 63, 65-67, 69, 71-78, 80, 81, 84, 86-89, 93, 96, 97, 101, 104, 109, 110)
Exposure to pollution	(98)
Childhood respiratory infections	(33)
Familiar history of asthma	(30, 77, 80, 88)
Low health related quality of life	(17, 18, 25, 30, 37, 52, 82, 83)
Sedentarism	(17, 80, 97)
Low education level	(22, 78, 82, 97, 101, 104, 110)
Low productivity	(83)
Low household income / unemployment	(65, 104, 110)

717

718 **Figure 1. Main treatable traits described in patients with asthma-COPD overlap:**