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## Asthma and COPD “overlap”: a treatable trait or common several treatable-traits?

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### KEY WORDS

*Asthma; Asthma-Chronic Obstructive Pulmonary Disease Overlap Syndrome; comorbidity; diagnosis; differential; pulmonary disease, Chronic Obstructive.*

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### Summary

*In the last years, disease classification of chronic respiratory diseases (CRD) has been vividly 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 subtopics but it is notorious the severe and frequent exacerbations, the associated cardiovascular disease and the low health related quality of life and productivity of these patients.*

### Introduction

In recent years the disease classification of chronic respiratory diseases has been put into debate (1,2). Classical classification used pre-20<sup>th</sup> 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 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 devel-

opment 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 in the last years 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 de-

**Table I** - Potential advantages and disadvantages of traditionally “Oslerian approach” versus a “Treatable-traits approach” in chronic respiratory diseases.

	“Oslerian approach”	“Treatable-traits approach”
<b>Advantages</b>	<ul style="list-style-type: none"> <li>• Simpler definition patients’ groups (convenient for students teaching, patient education)</li> <li>• Easy to use in interventional studies</li> <li>• Useful syndrome identification</li> </ul>	<ul style="list-style-type: none"> <li>• No diagnostic assumptions</li> <li>• Precise definition of the “traits”</li> <li>• Disease mechanisms based</li> <li>• Expected larger therapeutic response</li> <li>• Stimulates translational research</li> <li>• Helps the identification of key criteria for future RCT</li> </ul>
<b>Disadvantages</b>	<ul style="list-style-type: none"> <li>• Fails to provide optimal care (no consideration to endotypes)</li> <li>• No appreciation of common patterns of disease</li> <li>• Increases clinical practice variability</li> <li>• Inhibits research progress</li> </ul>	<ul style="list-style-type: none"> <li>• Nowadays only partially based on evidence</li> <li>• Requires comparison about efficacy, safety and cost-effectiveness with “classic strategies”</li> <li>• Uncertainty about patients, physicians and stakeholder acceptance</li> </ul>

RCT – Randomized clinical trials.

scription 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).

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.

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 (FEV<sub>1</sub>/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<sub>1</sub> 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.

**Table II** - Proposed criteria for asthma-COPD overlap (11).

Consensus	Diagnostic Criteria for ACO	Ref.
<b>GesEPOC-GEMA (2017)</b>	Age ≥35 years old Tobacco exposure ≥10 pack-years Post BDT FEV <sub>1</sub> /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)
<b>Sin et al. (2016)</b>	ACO is confirmed by the presence of three major and at least one minor criteria <b>Major criteria</b> Post BDT FEV <sub>1</sub> /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 <b>Minor criteria</b> Documented history of atopy or allergic rhinitis BDR of FEV <sub>1</sub> ≥200 mL and 12% from baseline values on 2 or more visits Peripheral blood eosinophil count of ≥300 cells/lug	(13)
<b>Finnish guidelines (2015)</b>	ACO is confirmed by presenting two main criteria or one main criteria and two additional criteria: <b>Main criteria</b> Very positive BDT FEV <sub>1</sub> >15 % and >400 mL Sputum eosinophilia or elevated FENO (>50 ppb) Previous asthma symptoms (starting age at < 40 y) <b>Additional criteria</b> Elevated total IgE Atopy Repeated significant positive BDT (FEV <sub>1</sub> >12% and >200ml) Peak expiratory flow follow-up typical of asthma	(14)
<b>Czech guidelines (2013)</b>	ACO is confirmed by the presence of two major criteria or one major plus two minor criteria: Definitive diagnosis of COPD <b>Major criteria</b> Very positive BDT FEV <sub>1</sub> >15% and >400 mL FENO ≥45–50 ppb and/or sputum eosinophils ≥3% history of asthma <b>Minor criteria</b> Positive BDT (FEV <sub>1</sub> >12% and >200 mL) Elevated total IgE History of atopy	(15)

ACO: asthma-COPD overlap; GesEPOC-GEMA: Spanish COPD guidelines-Spanish Asthma Guidelines; BDT: Bronchodilator test; Ref.: reference.

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 Agustí 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 patient’s 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

**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)

in 2018 Takayama et al. described that a composite cut-off of FeNO  $\geq 25$  ppb combined with blood eosinophils counts  $\geq 250$  cels./ $\mu\text{L}$  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 Gerhardtsson 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<sub>1</sub> 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 ACOS (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-as-

sociated 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 heterogenous 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 (25,39,57,59,65,73,78,80,81,84,96,97,104), 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

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

	References
Allergic Rhinconjunctivitis	(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, 104)
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, 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)
Dementia	(100)
Autoimmune diseases	(20)
Malignancies	(35, 98)
Persistent systemic inflammation	(20, 29, 77)

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 in 2014 it was suggested that systemic inflammation is commonly present in ACO, and ACO resembled COPD in terms of systemic inflammation. The evidence about systemic inflammation in COPD is for long known and matter of debate since early 2000s (107,108). In the same study it was shown that IL-6 is a pivotal inflammatory mediator that may be involved in airflow obstruction and cardiovascular disease and may be an independent treatment target for ACO. The systemic inflammation that occurs in ACO has also been proposed as

a possible mechanism involved in osteoporosis associated with ACO. In the study of Oh et al. patients with ACO had a significantly lower bone mineral density than did those with asthma, after adjusting for age, sex, body mass 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, 80,81,84,86-89,93,96,97,101,104,109,110). 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 associa-

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

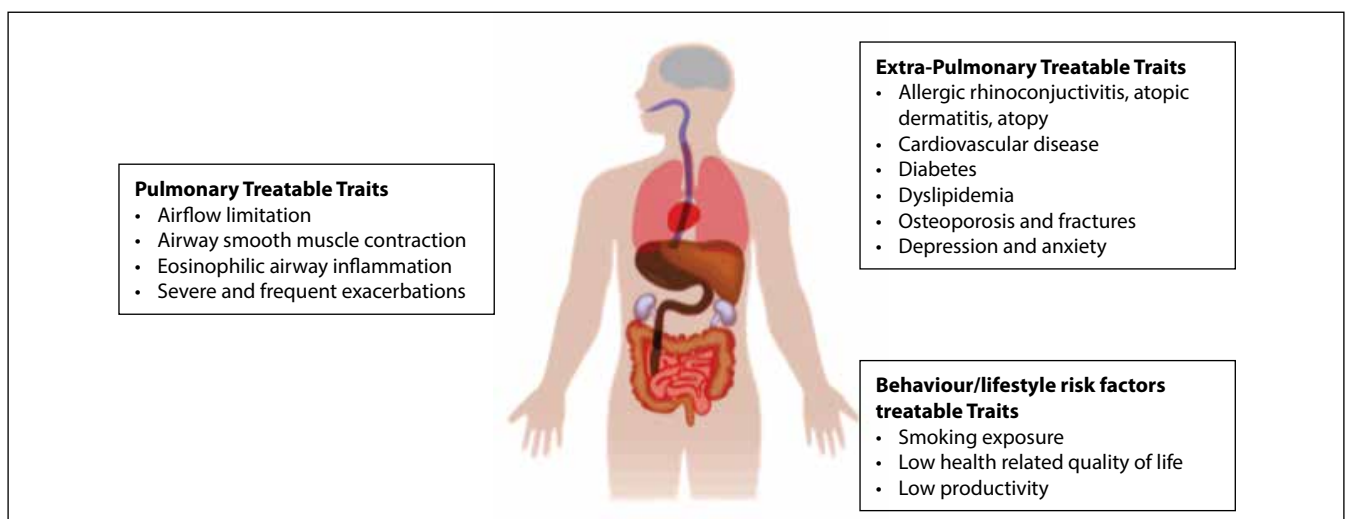
	References
Smoking exposure	(16, 17, 19, 20, 25-27, 30, 31, 33, 35, 38-41, 44, 45, 47, 48, 54-58, 60, 62, 63, 65-67, 69, 71-78, 80, 81, 84, 86-89, 93, 96, 97, 101, 104, 109, 110)
Exposure to pollution	(98)
Childhood respiratory infections	(33)
Familiar history of asthma	(30, 77, 80, 88)
Low health related 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)

tion 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 commonsense perspective, we can speculate that the low education level can act as a risk factor for ACO development probably related to an unhealthy

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

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 re-

spiratory diseases management are always included among this approach, particularly the asthma-COPD overlap due to the lack of definitive diagnostic criteria in an “Oslerian approach”. There are several pulmonary, extra-pulmonary and behavioral treatable traits associated with asthma-COPD overlap. 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 asthma-COPD overlap.

## Conflict of interests

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