Research Article

SCIMEDPRESS

Open Access

Email: SSMD@scimedpress.com

SMP Sleep Medicine and Disorders

OSA Effects on Chronic Airway Disease Exacerbations – Missed Opportunities for Improving Outcomes in COPD and Asthma

Marta Marin-Oto[1], Jose M Marin[2,*]

[1]*University of Zaragoza School of Medicine, Hospital Clínico Universitario, Zaragoza, Spain*

[2]*Department of Medicine, University of Zaragoza School of Medicine, Hospital Universitario Miguel Servet, Zaragoza, Spain*

Publication Dates

Received date: January 06, 2024

Accepted date: February 06, 2024

Published date: February 09, 2024

*Corresponding Author

José M Marin, Department of Medicine, University of Zaragoza School of Medicine, Hospital Universitario Miguel Servet, Zaragoza, Spain, Tel.: 646073747, E-mail: jmmarint@unizar.es

Citation

Marta Marin-Oto, Jose M Marin (2024) OSA Effects on Chronic Airway Disease Exacerbations – Missed Opportunities for Improving Outcomes in COPD and Asthma, SMP J Sleep Med Disord 1: 1-10

Key Points

- Obstructive sleep apnea, asthma and COPD are the most prevalent respiratory disorders.
- COPD and asthma exacerbations are fundamental health outcomes in the prognosis of both entities.
- OSA is an independent risk factor to explain the increased prevalence and severity of exacerbations in COPD and asthma.
- In cases of OSA/COPD or OSA/asthma syndrome, CPAP treatment can reduce COPD and asthma exacerbations. This treatment should be indicated in accordance with the available OSA management guidelines.

Keywords: Sleep; Obstructive Sleep Apnea; COPD; Overlap Syndrome; COPD Exacerbation; Asthma; Asthma Exacerbation

Introduction

Chronic obstructive pulmonary disease (COPD), bronchial asthma and obstructive sleep apnea (OSA) constitute the three most prevalent chronic respiratory diseases worldwide. Using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) definition of COPD (forced expiratory volume during the first second (FEV_1) / forced vital capacity (FVC) < 0.7), the current prevalence of COPD is estimated between 9% and 12% [1]. In a recent modeling study, it is projected that COPD prevalence will increase by 23% from now to 2050 especially among women and in low-middle income countries [2]. Asthma prevalence data reported around the world are highly variable, probably because the diagnosis of asthma largely falls on an exclusively clinical definition without the need for confirmation with a specific complementary test. In USA, using Behavioral Risk Factor Surveillance System data it was estimated that for 2020, 9% of adults had been diagnosed of asthma [3]. In the case of OSA, the prevalence depends on the cut-off of the apnea-hypopnea index (AHI) that is considered for its diagnosis. Considering AHI cut-offs greater than 5, OSA figures could currently be around 50% of the adult population in USA [4]. It is evident that the high prevalence of these three entities separately implies the frequent coincidence of COPD/OSA and asthma/OSA in the same patient. However, no population-based epidemiological studies have been carried out to accurately estimate the prevalence of these overlap syndromes in the general population. In any case, it is noteworthy that more than 80% of patients with COPD or OSA are not diagnosed and therefore adequately treated [1, 4]. This has important consequences for health outcomes of patients suffering from these overlap syndromes.

COPD and asthma exacerbations, especially if they require hospitalization, are associated with considerable morbidity and mortality and are the main components of the healthcare costs due to these diseases worldwide [1, 5]. In this article, we review the role of the coexistence of OSA as an aggravating factor to develop exacerbations in patients with asthma or COPD, and how the treatment of OSA can efficiently modify health outcomes of these respiratory diseases.

Definitions

At present, we suspect COPD when a patient presents with respiratory symptoms and a history of risk for COPD (e.g. exposure to tobacco smoke or other toxic inhalants). In these cases, spirometry confirms the diagnosis if the post-bronchodilator ratio FEV_1/FVC is less than 0.7 [1]. On the other hand, according to the Global Initiative for Asthma (GINA) the diagnosis of asthma is defined as the history of respiratory symptoms that vary in intensity and over time together with variable expiratory airflow limitation [5]. There is no global agreement on how to define OSA, but we mostly understand that a patient suffers from OSA when he/she shows more than 5 apneas or hypopneas per hour of sleep (apnea-hypopnea index, AHI) in a sleep study [5]. We define the coincidence of OSA in patients with COPD or Asthma as COPD/OSA and Asthma/OSA overlap syndromes (Marin). Both, COPD and asthma are chronic inflammatory bronchopulmonary diseases. In asthma, inflammation is mostly limited to the airways and airway obstrucion is characteristically variable in most patients. In COPD pulmonary inflammation is also associated with airway remodeling, peribronchial fibrosis, destruction of alveolar airspace (emphysema) and vascular changes with a wide variation among patients [6]. The final consequences of these changes lead to a persistent airflow limitation and impaired functional capacity. A differential aspect between asthma and COPD is the evidence that the latter is associated with frequent comorbidities that will develop at younger ages compared to subjects without COPD [7].

As defined by the GOLD Initiative, an acute exacerbation of COPD (AECOPD) is a clinical event characterized by increased dyspnea and/or cough and sputum that worsens in < 14 days which may be accompanied by tachypnea and/or tachycardia and is often associated with increased local and systemic inflammation caused by infection, pollution, or other insult to the airways [1]. Asthma exacerbations are episodes characterized by progressive increase in respiratory symptoms of dyspnea, cough, wheezing or chest tightness and progressive decrease in lung function, that they represent a change from the patient´s usual status that is sufficient to require a change in treatment [5].

Link between OSA and COPD

In patients with COPD, some frequent comorbid conditions are also OSA risk factors. One third of patients with COPD are active smokers and another 50% are ex-smokers. Patients who are active smokers have more upper airway inflammation and collapsibility than non-smokers [8]. In a croseccion-

al study, cigarette smoking history was associated with early onset of OSA and AHI increased with as mean pack × years rose [9]. Therefore, tobacco is a determinant of the pathogenesis of both entities, COPD and OSA. Quitting tobacco smoking results in a deceleration in disease progression and reduces the risk of exacerbations in smokers with COPD [10].

Unlike in OSA, obesity is not a risk factor for developing COPD. However, a specific phenotype of a COPD patient, bloated, bronchitic, overweight and sleepy, has been defined for decades. This is the typical "blue bloater" patient who characteristically shows a tendency towards hypoxemia and CO_2 retention and who we now know most of the time suffers from OSA [11]. In contrast, there is an inverse relationship between AHI and the percentage of emphysema, which is preferably found in thin COPD patients [12]. As the disease progresses, many COPD patients develop fluid retention as a consequence of the administration of systemic corticosteroids or the development of right heart failure. At night, fluid retention contributes to rostral redistribution into the neck, peripharyngeal fluid accumulation and upper airway narrowing, thereby facilitating OSA [13]. Some therapies for COPD such as systemic steroids may produce accumulation of fat in the parapharyngeal tissues and myopathies of the pharyngeal muscles, which increased upper airway collapsibility [14]. Today, a clear understanding of the pathophysiological links between OSA and COPD remains elusive. However, in patients with COPD-OSA overlap clinical outcomes are poorer than in either disease alone.

Link between OSA and Asthma

OSA increases asthma burden and is associated with poor asthma control [5]. Independent of obesity and other confounders, it appears that OSA aggravates asthma through non-eosinophilic inflammatory pathways [15]. The Global Initiative for Asthma (GINA) recognized the importance of OSA as a comorbid condition for an appropriate management of this disease, and they recommended to perform a sleep study to investigate the coexistence of OSA in patients with severe asthma, difficult to control asthma, and asthma associated with obesity [5].

Obesity is the most common risk factor for OSA, but it is also a risk factor for asthma with a "dose-response" effect of increasing BMI which at the same time, can increase the risk of incident asthma, especially in women [16]. Obstructive sleep apnea is very common in patients with chronic rhinosinusitis and nasopharyngeal polyps because they lead to increasing intrathoracic and pharyngeal negative pressure, which promotes upper airway collapse [17]. Many patients with non-atopic asthma and most patients with atopic asthma suffer from nasal problems including chronic rhinosinusitis and nasal polyps. Therefore, it is possible that asthmatics with this type of chronic nasal pathology simultaneously present OSA, and it is advisable to rule out the coexistence of OSA through a sleep study in patients with a torpid evolution of their asthma. Another risk for OSA among some asthmatics if the frequent burst or continuous use of oral steroids. This treatment can augment the tendency to obesity in addition to produce accumulation of fat in the parapharyngeal tissues and myopathies of the pharyngeal muscles as in COPD [18].

Risk Factors for COPD Exacerbations

One of the main objectives of COPD management is to avoid AECOPD. This is because exacerbations accelerate the lung function decline, worsen patients' quality of life and increase mortality [19]. In general, as patients with COPD progress in their natural history, they present an increase in AECOPD. However, there is a great inter-individual variability in the frequency and severity of exacerbations. There are well-established risk factors for AECOPD such as: being an active smoker [20], being exposed to breathing in a polluted environment [21] or having a history of previous exacerbations [22]. Risk factors for AECOPD related to the characteristics of the disease itself include greater functional impairment [23], emphysema on chest CT [24], and coexistence of pulmonary hypertension [25]. COPD patients who have a chronic bronchitic phenotype [26] or coexistent bronchiectasis [27] also are at increased risk of AECOPD. Among the many blood biomarkers studies carried out in recent years, it has been shown that a higher level of eosinophils is associated with a greater risk of exacerbations and are predictor of a better therapeutic response to inhaled corticosteroids [28-30].

As stated above, patients with COPD suffer more comorbidities and at a younger age than subjects in the population without COPD [7]. Among more than 72 comorbidities significantly present in patients with COPD compared to subjects without COPD, there is a group of 12 entities ("comorbidome") that are associated with a greater risk of exacerbations and death [31]. An exhaustive review of each comorbid condi-

tion is not the purpose of this manuscript.

OSA As A Risk Factor for COPD Exacerbations Obesity

Under and overweight is an important predictor of poor outcomes in COPD. In the Genetic Epidemiology of COPD (COPDGene) study, a large multicenter cohort of subjects with GOLD stages 2 through 4 COPD, increasing severity of obesity was associated independently with greater odds of AECOPD [32]. In one retrospective study, Goto et al, showed that COPD patients undergoing bariatric surgery had a reduced risk of hospitalization for acute exacerbations of COPD [33]. However, at baseline, sleep study was not performed in these studies so OSA cannot be ruled out and therefore the specific role of obesity with/without OSA on incident AECOPD could not be assessed. The intermediate mechanisms that explain the increase/reduction of AECOPD with obesity and its treatment with bariatric surgery, respectively, have not been established. It is known that obesity and associated metabolic dysfunction increase the levels of circulating inflammatory biomarkers such as white blood cell count, C-reactive protein and fibrinogen levels which are characteristically elevated in patients with frequent COPD exacerbations [34]. On the other hand, obesity reduces the lung's defense capacity against viruses and bacteria [35-36]. Therefore, it is possible that weight loss reduces exacerbations in patients with obesity (with/without associated OSA) by restoring immune function against respiratory infections. In any case, the relationship between obesity and AECOPD is far from being elucidated since some randomized control trials (RCTs) have shown that overweight or obese patients do not have an increased risk of AECOPD than normal weight COPD patients [37]. But again, no sleep studies were done in those RCTs to identify the coexistence of OSA in obese participants.

Obstructive Sleep Apnea

Few studies have evaluated if COPD patients with OSA (overlap syndrome), with or without associated obesity have more risk of exacerbations than COPD without OSA. In our observational cohort which includes subjects referred to Sleep Clinic for suspected OSA, spirometry in addition to sleep study was performed at baseline and patients were treated according with current OSA and COPD guidelines [38]. Three groups were pre-specified: OSA with CPAP, OSA without CPAP, and COPD alone. All three groups had similar markers of COPD severity. After a mean of 9.6-year follow-up, at least one hospitalization because of COPD exacerbation occurred in 39.5% patients with COPD alone and 61.4% in patients with COPD/OSA overlap untreated with positive airway pressure (PAP) (adjusted relative risk, 1.70 [95% CI, 1.21 - 2.38]). These patients also had a greater risk of hospital readmission. In line with these results, a recent retrospective study showed that among patients hospitalized for COPD exacerbation, those with OSA had higher readmission and mortality rates than those without OSA [39]. Finally, among COPD patients included in the Long-Term Oxygen Treatment Trial, those at intermediate to high risk of OSA (modified STOP-BANG score ≥ 3) relative to low risk (score < 3), had increased frequency of COPD exacerbations (adjusted incidence rate ratio: 1.78, 95% CI, 1.10 - 2.89) [40]. This evidence, however, is considered insufficient by the GOLD to recommend performing sleep studies in all patients with COPD who are admitted for an exacerbation. However, this initiative advocates for assessment of OSA-specific sleep symptoms among patients with severe COPD [1].

Observational and population studies also suggest that the increased risk for AECOPD in patients with overlap syndrome may be mitigated with PAP [38, 40-43]. For example, in our mentioned prospective clinical-based study, patients with overlap syndrome treated with CPAP had no increased risk for severe exacerbations compared with patients with COPD-only [38]. In addition, overlap patients treated with CPAP had a reduction of mortality. A lower risk of AECOPD was also obtained in retrospective studies with COPD/OSA overlap patients engaged in Health Plans and Medicare, treated versus non-treated with CPAP [40, 42]. In these studies the impact on mortality was not assessed. These real-life studies in any case indicate "association" and not "causation" of the effect of CPAP on the reduction of exacerbations in patients with overlap syndrome. Given the impact of AECOPD on health care cost and on progression of the disease, it is fully justified to confirm these findings through a randomized trial. Also, because BiPAP therapy is widely used for severe AECOPD and for stable hypercapnic COPD patients, this form of PAP therapy should be evaluated in OSA/COPD overlap syndrome.

OSA is associated with explanatory factors that may favor AECOPD in patients with overlap syndrome. Characteristically, in patients with OSA, diabetes and metabolic syndrome are

more prevalent, and it is known that these comorbidities favor the development of AECOPD [44]. In OSA, depressive disorders are frequent and related with the OSA severity [45]. Similarly, anxiety or depression in COPD patients is also a risk factor for AECOPD [46]. Daytime sleepiness and fatigue are not frequent in COPD alone but in those with overlap syndrome, these daytime symptoms can decrease physical activity and worsen health outcomes [47]. What is very relevant when recognizing the presence of these intermediate mechanisms that aggravate the risk of AECOPD is that many of them are reversed by weight reduction and/or with CPAP treatment in cases of overlap syndrome. This is what happens with the improvement of diabetes [48], anxiety/depression [49] with CPAP therapy in OSA patients, but it remains to be clarified whether this beneficial effect of CPAP also occurs in patients with overlap syndrome.

OSA as a Risk Factor for Asthma Exacerbations

The main trigger for asthma exacerbations are external agents such as microorganisms, pollens, or pollutants). However, these episodes are more frequent in patients with uncontrolled asthma symptoms or with poor adherence to appropriate therapy and/or significant comorbidities [5]. Among the comorbidities that increase the risk of exacerbations, the GINA consensus points to obesity, chronic rhinosinusitis, and gastroesophageal reflux [5]. Interestingly, these comorbidities are also very common in subjects with OSA and therefore, in patients with OSA/asthma overlap, they may act as potentiating mechanisms of asthmatic exacerbations.

In a large observational series of patients with asthma, logistic regression analysis on comorbid factors shows that psychological dysfunctioning (odd ratio OR 10.8), recurrent respiratory tract infections (OR 6.9), gastro-esophageal reflux (OR 4.9), severe nasal sinus disease (OR 3.7) and OSA (OR 3.4) were significantly associated with frequent exacerbations [50]. These results are not surprising since it is known that snoring and OSA trigger nocturnal asthma attacks in patients with OSA/asthma [51]. In the World Trade Center Health Registry, among patients with asthma there was a higher OSA prevalence with worse asthma control adjusting for body mass index [52]. Among Chinese patients with asthma, OSA was associated with higher risk of severe asthma exacerbations compare to non-OSA asthmatics (relative risk 14.23) [53]. The intermediate mechanisms by which OSA may worsen the health outcomes of people with asthma are unknown. We previously demonstrated that OSA is associated with upper airway inflammation as evidenced by an increase in inflammatory biomarkers obtained from pharyngeal lavage [54]. This fact is in agreement with a high exhaled FeNO level obtained in untreated OSA patients [55]. Of interest is that these airway inflammatory markers were reduced with CPAP treatment in both studies.

CPAP therapy in patients with OSA/asthma overlap syndrome appears to improve quality of life, especially in severe OSA and poorly controlled asthma [56]. However, evidence is mainly derived from observational studies of short duration. In fact, a meta-analysis found CPAP improved daytime or night-time asthma symptoms but did not show an improvement in asthma control or asthma exacerbations [57]. So, at the moment, the topic of the effect of CPAP on the health outcomes in patients with asthma and OSA has not been elucidated and randomized trials are necessary to definitively evaluate this effect. For the moment in patients with OSA/asthma overlap syndrome, the management of both entities separately (asthma and OSA) should be carried out in accordance with the clinical management guidelines for each of the entities.

Summary

In patients with COPD and asthma, exacerbations determine the natural history of both diseases. Patients with both respiratory diseases who suffer from OSA as a comorbidity (overlap syndromes) have a higher risk of exacerbations and hospitalization. In cases of OSA/COPD and OSA/asthma in which CPAP treatment is indicated. Adequate adherence to therapy appears to reduce exacerbations and their severity, especially in OSA/COPD overlap. However, there is a lack of randomized trials that definitively demonstrate this evidence.

Clinics Care Points

- Both, in patients with COPD or with asthma, exacerbations are frequent, worsen the quality of life, accelerate functional deterioration and increase morbidity and mortality.
- Among the main risk factors for developing more frequent and more severe exacerbations, the coexistence of certain comorbidities such as OSA is

well established in COPD and its importance in asthma is less evident.

- OSA is a modifiable risk factor through effective treatment using CPAP or other specific therapies (e.g. weight reduction) and therefore a sleep study should be considered in cases of COPD or asthma with severe exacerbations.

- There is no robust evidence based on randomized trials of the long-term effect of CPAP on the potential reduction of COPD or asthma exacerbations. Until then, the management of the coexistence of OSA in patients with OSA/COPD or OSA/asthma overlap syndromes should be carried out according to the OSA clinical management guidelines.

Disclosure Statement

Both authors report no conflicts of interest.

References

1. Global Initiative for Chronic Obstructive Lung Disease (GOLD) (2023). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease.

2. Boers E, Barrett M, Su JG, et al. (2023) Global Burden of Chronic Obstructive Pulmonary Disease Through 2050. JAMA Netw Open, 6: e2346598.

3. Qin X, Pate CA, Zahran HS (2023) Adult asthma prevalence and trend analysis by urban-rural status across sociodemographic characteristics-United States, 2012-20. J Allergy Clin Immunol Glob 2023; 2: 100085.

4. Benjafield AV, Ayas NT, Eastwood PR, et al. (2019) Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. Lancet Respir Med, 7: 687–98.

5. Global Initiative for Asthma (2023) Global Strategy for Asthma Management and Prevention.

6. Agustí A, Hogg JC (2019) Update on the Pathogenesis of Chronic Obstructive Pulmonary Disease. N Engl J Med, 381: 1248-56.

7. Divo MJ, Celli BR, Poblador-Plou B, et al. (2018) Chronic Obstructive Pulmonary Disease (COPD) as a disease of early aging: Evidence from the EpiChron Cohort. PLoS One. 13: e0193143.

8. Kim KS, Kim JH, Park SY, et al. (2012) Smoking induces oropharyngeal narrowing and increases the severity of obstructive sleep apnea syndrome. J Clin Sleep Med, 8: 367-74.

9. Varol Y, Anar C, Tuzel OE, et al. (2015) The impact of active and former smoking on the severity of obstructive sleep apnea. Sleep Breath, 19: 1279-84.

10. Scanlon PD, Connett JE, Waller LA, et al. (2000) Lung Health Study Research Group. Smoking cessation and lung function in mild-to-moderate chronic obstructive pulmonary disease. The Lung Health Study. Am J Respir Crit Care Med, 161:381-90.

11. Flenley DC (1985) Sleep in chronic obstructive lung disease. Clin Chest Med, 6: 651-61.

12. Krachman SL, Tiwari R, Vega ME, et al. (2016) Effect of emphysema severity on the apnea-hypopnea index in smokers with obstructive sleep apnea. Ann Am Thorac Soc, 13: 1129–35.

13. Yumino D, Redolfi S, Ruttanaumpawan P, et al. (2010) Nocturnal rostral fluid shift: a unifying concept for the pathogenesis of obstructive and central sleep apnea in men with heart failure. Circulation, 121: 1598–605.

14. McNicholas WT (2009) Chronic obstructive pulmonary disease and obstructive sleep apnea: overlaps in pathophysiology, systemic inflammation, and cardiovascular disease. Am J Respir Crit Care Med, 180: 692–700.

15. Teodorescu M, Broytman O, Curran-Everett D, et al. (2015) Obstructive sleep apnea risk, asthma burden, and lower airway inflammation in adults in the Severe Asthma Research Program (SARP) II. J Allergy Clin Immunol Pract, 3: 566–75.

16. Beuther DA, Sutherland ER (2007) Overweight, obesity, and incident asthma: a meta-analysis of prospective epidemiologic studies. Am J Respir Crit Care Med, 175: 661–6.

17. Young T, Finn L, Kim H. Nasal obstruction as a risk factor for sleep disordered breathing. J Allergy Clin Immunol 1997; 99 (2):S757–S762

18. Yigla M, Tov N, Solomonov A, et al. (2003) Difficult-to--control asthma and obstructive sleep apnea. J Asthma, 40: 865–71.

19. Seemungal TA, Donaldson GC, Paul EA, et al. (1998) Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med, 157: 1418-22.

20. Sundh J, Johansson G, Larsson K, et al. (2015) The phenotype of concurrent chronic bronchitis and frequent exacerbations in patients with severe COPD attending Swedish secondary care units. Int J Chron Obstruct Pulmon Dis, 10: 2327–34.

21. Li J, Sun S, Tang R, et al. (2016) Major air pollutants and risk of COPD exacerbations: a systematic review and meta-analysis. Int J Chron Obstruct Pulmon Dis, 11: 3079–91.

22. Hurst JR, Vestbo J, Anzueto A, et al. (2010) Susceptibility

to exacerbation in chronic obstructive pulmonary disease. N Engl J Med, 363: 1128–38.

23. Marin JM, Carrizo SJ, Casanova C, et al. (2009) Prediction of risk of COPD exacerbations by the BODE index. Respir Med, 103: 373-8.

24. Han MK, Kazerooni EA, Lynch DA, et al. (2011) Chronic obstructive pulmonary disease exacerbations in the COPDGene study: associated radiologic phenotypes. Radiology, 261: 274-82.

25. Wells JM, Washko GR, Han MK, et al. (2012) Pulmonary arterial enlargement and acute exacerbations of COPD. N Engl J Med, 367: 913-21.

26. Burgel PR, Nesme-Meyer P, Chanez P, et al. (2009) Cough and sputum production are associated with frequent exacerbations and hospitalizations in COPD subjects. Chest, 135: 975-82.

27. Ni Y, Shi G, Yu Y, et al. (2015) Clinical characteristics of patients with chronic obstructive pulmonary disease with comorbid bronchiectasis: a systemic review and meta-analysis. Int J Chron Obstruct Pulmon Dis, 10: 1465–75.

28. Bafadhel M, Peterson S, De Blas MA, et al. (2018) Predictors of exacerbation risk and response to budesonide in patients with chronic obstructive pulmonary disease: a post-hoc analysis of three randomised trials. Lancet Respir Med, 6: 117-26.

29. Pascoe S, Locantore N, Dransfield MT, Barnes NC, Pavord ID (2015) Blood eosinophil counts, exacerbations, and response to the addition of inhaled fluticasone furoate to vilanterol in patients with chronic obstructive pulmonary disease: a secondary analysis of data from two parallel randomised controlled trials. Lancet Respir Med; 3: 435-42.

30. Singh D, Agusti A, Martinez FJ, et al. (2022) Blood Eosinophils and Chronic Obstructive Pulmonary Disease: A Global Initiative for Chronic Obstructive Lung Disease Science Committee 2022 Review. Am J Respir Crit Care Med, 206: 17-24.

31. Divo M, Cote C, de Torres JP, et al. (2012) Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med, 186: 155-61.

32. Lambert AA, Putcha N, Drummond MB, et al. (2017) COPDGene Investigators. Obesity is associated with increased morbidity in moderate to severe COPD. Chest, 151: 68–77.

33. Goto T, Tsugawa Y, Faridi MK, et al. (2018) Reduced risk of acute exacerbation of COPD after bariatric surgery: a self--controlled case series study. Chest. 153: 611-7.

34. Thomsen M, Ingebrigtsen TS, Marott JL, et al. (2013) Inflammatory biomarkers and exacerbations in chronic obstructive pulmonary disease. JAMA, 309: 2353-61.

35. Neidich SD, Green WD, Rebeles J, et al. (2017) Increased risk of influenza among vaccinated adults who are obese. Int J Obes (Lond), 41:1324-30.

36. Ubags ND, Burg E, Antkowiak M, et al. (2016) A comparative study of lung host defense in murine obesity models. Insights into neutrophil function. Am J Respir Cell Mol Biol, 55: 188-200.

37. Putcha N, Anzueto AR, Calverley PMA, et al. (2022) Mortality and exacerbation risk by body mass index in patients with COPD in TIOSPIR and UPLIFT. Ann Am Thorac Soc, 19: 204–213.

38. Marin JM, Soriano JB, Carrizo SJ, et al. (2010) Outcomes in patients with chronic obstructive pulmonary disease and obstructive sleep apnea: the overlap syndrome. Am J Respir Crit Care Med, 182: 325-31.

39. Naranjo M, Willes L, Prillaman BA, et al. (2020) Undiagnosed OSA may significantly affect outcomes in adults admitted for COPD in an inner-city hospital. Chest, 158: 1198-207.

40. Donovan LM, Feemster LC, Udris EM, et al. (2019) Poor outcomes among patients with chronic obstructive pulmonary disease with higher risk for undiagnosed obstructive sleep apnea in the LOTT Cohort. J Clin Sleep Med, 15: 71-7.

41. Ioachimescu OC, Janocko NJ, Ciavatta M-M, et al. (2020) Obstructive Lung Disease and Obstructive Sleep Apnea (OLDOSA) cohort study: 10-year assessment. J Clin Sleep Med, 16: 267–77.

42. Singh G, Agarwal A, Zhang W, et al. (2019) Impact of PAP therapy on hospitalization rates in Medicare beneficiaries with COPD and coexisting OSA. Sleep Breath,

23:193-200.

43. Sterling KL, Pépin JL, Linde-Zwirble W, et al. (2022) Impact of positive airway pressure therapy adherence on outcomes in patients with obstructive sleep apnea and chronic obstructive pulmonary disease. Am J Respir Crit Care Med, 206: 197-205.

44. Castan-Abad MT, Montserrat-Capdevila J, Godoy P, et al. (2020) Diabetes as a risk factor for severe exacerbation and death in patients with COPD: A prospective cohort study. Eur. J. Public Health, 30: 822–7.

45. Chen YH, Keller JK, Kang JH, et al. (2013) Obstructive sleep apnea and the subsequent risk of depressive disorder: a population-based follow-up study. J Clin Sleep Med, 9: 417-23.

46. Yohannes AM, Mulerova H, Lavoie K, et al. (2017) The association of depressive symptoms with rates of acute exacerbations in patients with COPD: results from a 3-year longitudinal follow-up of the ECLIPSE Cohort. J Am Med Dir Assoc, 18: 955–9.

47. Ramon MA, Ter Riet G, Carsin AE, et al. (2018) PAC--COPD Study Group. The dyspnoea-inactivity vicious circle in COPD: development and external validation of a conceptual model. Eur Respir J, 52: 1800079.

48. Martınez-Ceron E, Barquiel B, Bezos AM, et al. (2016) Effect of continuous positive airway pressure on glycemic control in patients with obstructive sleep apnea and type 2 diabetes. A randomized clinical trial. Am J Respir Crit Care Med, 194:476–85.

49. Jackson ML, Tolson J, Schembri R, et al. (2021) Does continuous positive airways pressure treatment improve clinical depression in obstructive sleep apnea? A randomized wait-list controlled study. Depress Anxiety, 38: 498–507.

50. ten Brinke A, Sterk PJ, Masclee AA, et al. (2015) Risk factors of frequent exacerbations in difficult-to-treat asthma. Eur Respir J, 26: 812-8.

51. Chan CS, Woolcock AJ, Sullivan CE (1998) Nocturnal asthma: role of snoring and obstructive sleep apnea. Am Rev Respir Dis, 137: 1502–4.

52. Jordan HT, Stellman SD, Reibman J, et al. (2015) Factors associated with poor control of 9/11-related asthma 10-11 years after the 2001 World Trade Center terrorist attacks. J Asthma, 52: 630-7.

53. Wang Y, Liu K, Hu K, et al. (2016) Impact of obstructive sleep apnea on severe asthma exacerbations. Sleep Med, 26: 1-5.

54. Vicente E, Marin JM, Carrizo SJ, et al. (2016) Upper airway and systemic inflammation in obstructive sleep apnoea. Eur Respir J, 48: 1108-17.

55. Chua AP, Aboussouan LS, Minai OA, et al. (2013) Long-term continuous positive airway pressure therapy normalizes high exhaled nitric oxide levels in obstructive sleep apnea. J Clin Sleep Med, 9: 529-35.

56. Serrano-Pariente J, Plaza V, Soriano JB, et al. (2017) Asthma outcomes improve with continuous positive airway pressure for obstructive sleep apnea. Allergy, 72: 802–12.

57. Davies SE, Bishopp A, Wharton S, et al. (2018) Does Continuous Positive Airway Pressure (CPAP) treatment of obstructive sleep apnoea (OSA) improve asthma-related clinical outcomes in patients with co-existing conditions?- A systematic review. Respir Med, 143: 18-30.

SMP Family Medicine and Primary Care

SMP Cardiology and Cardiovascular Medicine

SMP Human Nutrition and Dietetics

SMP Pediatrics and Child Health

SMP Journal of Cancer Research

SMP Biotechnology and Bioengineering

SMP Nanotechnology and Nanomedicine

SMP Chemical Engineering Science