Sleep and cardiometabolic comorbidities in the OSA-COPD overlap syndrome: Data from ESADA

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Title: Sleep and cardiometabolic comorbidities in the OSA-COPD overlap syndrome: Data from ESADA

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Summary

OSA-COPD overlap syndrome (OVS) patients, compared to OSA patients, had lower sleep quality, which was associated with FEV$_1$ and diurnal PaO$_2$. The sleep-related hypoxia presented in OVS was associated with increased risk of heart failure.

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**Abbreviations:**

AHI = apnoea-hypopnea index; ABG = arterial blood gases; BMI = body mass index; CRP = C-reactive protein; CGI = Clinical Global Impression; COPD = Chronic Obstructive Pulmonary Disease; ESADA = European Sleep Apnoea Database; ESS = Epworth Sleepiness Scale; FEV₁ = Forced Expiratory Volume in one second; FVC = Forced Vital Capacity; GLMM = Generalized linear mixed effects models; HCO₃⁻ = hydrogen bicarbonate; ODI = oxygen desaturation index; OSA = Obstructive sleep apnoea; OVS = Overlap Syndrome; PaCO₂ = arterial partial pressure of carbon dioxide; PaO₂ = arterial partial pressure of oxygen; REM = rapid eye movement; SpO₂ = mean peripheral oxyhemoglobin saturation; SD = standard deviation; SWS = slow wave sleep; T90 = time below SpO₂ of 90%; 95%CI = 95% confidence intervals;
Abstract

Aim: The impact of OSA-COPD overlap syndrome (OVS) on sleep quality and cardiovascular outcomes has not been fully explored. We aimed to compare clinical and polysomnographic characteristics of OVS vs OSA patients, and to explore pathophysiological links between OVS and comorbidities.

Study design and methods: This cross-sectional analysis initially included data from 5,600 patients with OSA and lung function in the European Sleep Apnoea Database (ESADA). Two subgroups of patients with OSA (n=1109) or OVS (n=509) were matched (2:1) based on sex, age, body mass index (BMI), and apnoea-hypopnea index (AHI) at baseline.

Results: After matching, OVS patients had more severe hypoxia, lower sleep efficiency and presented higher prevalence of arterial hypertension, ischemic heart disease and heart failure compared to OSA patients.

OVS was associated with a significant decrease in sleep efficiency (β -3.0% (95%CI -4.7, -1.3) and in nocturnal mean SpO₂ (β -1.1% (95%CI -1.5, -0.7). Further analysis revealed that a decrease in FEV₁ and PaO₂ was related with a decrease in sleep efficiency and in mean nocturnal SpO₂.

A COPD diagnosis increased by 1.75 and 1.36 the odds of having heart failure (95%CI 1.15, 2.67) and systemic hypertension (95%CI 1.07, 1.73), respectively.

Nocturnal hypoxia was strongly associated with comorbidities, interestingly, the mean nocturnal SpO₂ and T90 were associated with increase odds of systemic hypertension, diabetes, and heart failure but ODI was only related to hypertension and diabetes.

Conclusion: OVS patients presented with more sleep-related hypoxia, a reduced sleep quality and a higher risk for heart failure and hypertension.
Introduction

Obstructive sleep apnoea (OSA) and Chronic Obstructive Pulmonary Disease (COPD) represent two of the most prevalent respiratory disorders in clinical practice. Their coexistence is often referred to as the “Overlap Syndrome” (OVS) [1], a condition that affects at least 1% of the adult population [2,3]. Both COPD and OSA are associated with a range of overlapping physiological [4] and biological disturbances that include hypoxia and inflammation [5]. Hypoxemia, both intermittent and sustained, is more pronounced in the OVS [6], as is hypercapnia and adverse clinical outcomes when compared with COPD or OSA alone [7].

The OVS has been associated with cardiac arrhythmias [8], pulmonary hypertension and right heart failure [9]. OVS patients seem to show higher odds for prevalent coronary heart disease, heart failure and peripheral arteriopathy [10], and overall, this condition was associated with higher rates of cardiovascular morbidity and all-cause mortality [11,12].

However, it remains unknown if the overlap of each disorder amplifies the inflammatory responses and if the pro-inflammatory state is mainly triggered by intermittent nocturnal hypoxia or by comorbid risk factors like obesity or frequent exposure to smoking [13, 14].

In patients with overlap syndrome, it is likely that the added impact on sleep, ventilation, pulmonary hemodynamics, and comorbidities, could affect the clinical burden of disease [15]. The Clinical Global Impressions (CGI) scale, previously used in OSA patients [16] provides the physicians' global impression of disease severity in a patient, considering the medical history, psychosocial circumstances, symptoms,
behavior, as well as the impact of the symptoms [17]. The use of CGI scale in overlap patients could contribute as a clinical tool to reflect the significance of clinical disease. In the present study we aimed to analyze potential clinical and polysomnographic differences in OSA, and OVS patients registered in the large European Sleep Apnoea Database (ESADA). To evaluate the impact of COPD on OSA patients and, if significant, to explore its possible links, particularly the role of intermittent and sustained hypoxia and lung function.

**Methods**

**Study population**

Data from patients included in the European Sleep Apnoea Database (ESADA) were analyzed. Enrollment in the ESADA started in March 2007. The ESADA study prospectively collects data from unselected patients aged 18–80 years with suspected OSA referred to European sleep centers. Exclusion criteria in the ESADA include a previous OSA diagnosis, limited estimated life expectancy, and current alcohol or drug abuse. Data recorded in the ESADA include anthropometrics, information on comorbidities, blood tests, lung function, degree of daytime somnolence assessed by the Epworth Sleepiness Scale (ESS) score, and baseline polysomnography or cardiorespiratory polygraphy data.

Written informed consent to analyzed pseudo-anonymous data in the ESADA was obtained from all patients prior to study start. Each sleep center obtained approval from the ethical committee of their own institution.
In the current study we considered data from 30,235 (entire quality-controlled data content) participants captured between March 2007 and December 2019. The methods used for sleep and apnoea scoring have previously been reported in detail [18, 19].

Data on the Clinical Global Impression (CGI) score was specifically addressed in the current analysis. The CGI scale has been developed and used to assess the global burden of disease severity in an individual patient [17] and its use has been previously described in OSA patients included in the ESADA database [16].

After excluding participants without lung function data (23,393 patients), without an OSA diagnosis or with respiratory diseases other than COPD, data from 5,600 participants were available in the current analysis. Patients with an apnoea-hypopnea index (AHI) of at least 5 events/hour, a diagnosis of COPD confirmed by a physician and corroborated by a Forced Expiratory Volume in one second (FEV$_1$) and a computed Forced Vital Capacity (FVC) ratio (FEV$_1$/FVC) lower than 0.7 were allocated to the OVS patient group. Each overlap patient (n=509) was matched with two patients without COPD based on similar sex, age, BMI, and AHI. Thus, 1,527 patients were included in our main analysis cohort (509 OVS plus 1,018 OSA). The study flowchart is shown in Figure 1.

**Statistical analysis**

Patient data, sleep characteristics and arterial blood gases (ABG) analysis data are presented as mean ± standard deviation (SD) for continuous variables and in percentages for categorical data, for OVS (OSA plus COPD) patients and OSA.
Most centers in the ESADA, as academic institutions, collect lung function data regardless of a reported presence of a respiratory disease. To avoid a potential data collection bias, a logistic regression model was fitted to test if both groups (OVS and OSA) had similar probability of having a lung function test performed. No significant difference between groups could be demonstrated.

In the unmatched cohort, comparisons between the two groups were performed using independent samples t-tests as appropriate for continuous variables, or the Chi-square tests for categorical variables. After pairing, additional adjustment for sleep center and other confounders was made. In this case, variance significance was evaluated through ANOVA method for nested models.

Generalized linear mixed effects models (GLMM) using binomial distribution were fitted to evaluate the association between cardiometabolic comorbidities in OSA patients with and without COPD. Different characteristics with plausibility to influence the outcome (cigarette smoking, excessive daytime sleepiness, hypertension, heart failure, ischemic heart disease, diabetes, atrial fibrillation, sleep center) were analyzed and whenever significantly associated with the outcome, included in the model. Thus, models were adjusted for sleep center, cigarette smoking, diabetes, and systemic hypertension whenever those were confirmed to have an impact. Results were presented through odds ratios (OR) and the respective 95% confidence intervals (95%CI) and the different confounders included in the model are described. Moreover, to evaluate if having COPD impacted differently the prevalence of comorbidities in different severity classes of AHI, a sensitivity analysis stratified by AHI classes (AHI < 30 events/h and AHI ≥ 30 events/h) was performed.
To evaluate the association between polysomnography and ABG results and having COPD, a GLMM using gaussian family was fitted. Results were presented as mean differences (β) and the respective 95% confidence intervals (95%CI). As previously applied for comorbidities, we performed a further analysis to evaluate the impact of OSA severity. This methodology was also used to investigate if arterial partial pressure of oxygen (PaO₂), and FEV₁ impacted on the sleep efficiency and the mean peripheral oxyhemoglobin saturation (SpO₂) results.

A significance level of 5% was assumed. Analyses were performed using the R software version 3.6.3, and Statistical Package for the Social Sciences (SPSS), version 26.

Results
Among OSA patients of the ESADA cohort, the OVS prevalence, verified by sleep test and lung function data was 7.9%.

Patient characteristics and sleep quality
In the case-control analysis of OVS and OSA patients matched for age, sex, BMI and AHI, daytime PaO₂, mean SpO₂, sleep efficiency, and % of REM sleep were all significantly lower in patients with OVS (Table 1). The degree of subjective daytime sleepiness (ESS score) was comparable between groups.

In a multiple regression analysis controlling for center and current smoking, OVS was associated with a significant decrease in sleep efficiency (β -3.0% (95%CI -4.7, -1.3), in nocturnal mean SpO₂ (β -1.1% (95%CI -1.5, -0.7), and in daytime PaO₂ (β -4.9 mmHg
(95%CI -6.5, -3.2) (Table 2). There was a tendency for a more pronounced impact of having COPD on sleep efficiency and PaO₂ in patients with mild-to-moderate OSA (Table 3). Further analysis of matched overlap and OSA patients revealed that a decrease in FEV₁ and PaO₂ was related with a decrease in sleep efficiency and lower mean SpO₂ (Table 4).

There was no significant difference in the prevalence of insomnia (p=0.196) and OVS patients did not have significantly higher odds of using prescribed psychotropic drugs (OR 1.2 (0.65, 2.28)) compared to OSA patients.

Cardiometabolic comorbidities and burden of disease

Following matching, the prevalence of arterial hypertension, ischemic heart disease and heart failure was significantly higher in the OVS group; no differences were found in diabetes prevalence (Table 1). A COPD diagnosis increased by 1.75 the odds of having heart failure (95%CI 1.15, 2.67), by 1.36 (95%CI 1.07, 1.73) the odds of having systemic hypertension and by 1.35 (95%CI 1.00, 1.84) the odds of having systemic hypertension (Figure 2). Notably, the influence of COPD on a comorbid heart failure was higher in patients with mild-to-moderate OSA (AHI<30 events/h) (OR-3.30 (95%CI 1.62, 6.93)) than in the severe OSA group (OR-1.67 (95%CI 1.06, 2.61)) (Table 3).

Several measures of nocturnal hypoxia were associated with increased risk of systemic hypertension, diabetes, and heart failure (Table 5). A decrease in mean SpO₂ and an increase in time below SpO₂ of 90% (T90) were associated with both systemic hypertension, diabetes, and heart failure. An increase of 10 events/h in the oxygen desaturation index (ODI) was associated with a 1.10 and a 1.13-fold, respectively, increased odds of
arterial hypertension and diabetes. Notably, no relationship between ODI and heart failure or ischemic heart diseases was found. Moreover, a 5 mmHg increase in daytime PaO$_2$ was associated with a reduced risk of systemic hypertension and diabetes, but not for heart failure or ischemic heart disease after adjusting for cardiac risk factors.

Patients with OVS presented higher rates of a “moderate to markedly ill” scores in the CGI scale, and with lower rates of “mild scores” compared with OSA patients (p<0.001). (Figure 3).

In the unmatched cohort, OVS patients compared with OSA patients were significantly older, were more often male, and had a higher prevalence of hypertension, diabetes, heart failure, or ischemic heart disease (Supplementary material). Sleep in patients with OVS was characterized by a higher percentage of sleep stage N1, a lower percentage of rapid eye movement (REM) sleep and generally more intermittent and sustained hypoxia.

**Discussion**

Our study in the ESADA cohort identified an OVS prevalence of 7.9% in OSA patients with recorded lung function data. OVS was associated with more severe nocturnal hypoxia, elevated cardiometabolic comorbidity, in particular heart failure, and worsened sleep quality when compared with OSA patients. An important strength in the current study was the accuracy of the OVS classification by standard pulmonary function test in both cases and controls.

**Prevalence of OVS**
Some of the apparent discrepancies between studies regarding COPD prevalence in OSA can be explained by differences in selection criteria, population characteristics design and disease definition used. Chaouat and colleagues [9] prospectively investigated OSA patients and reported that 11% had an obstructive spirometric pattern, and Bednareck and colleagues found OVS in 9.2% of subjects with OSA [2].

More recently, a cross-sectional study in the French Sleep Apnoea Registry found a prevalence of 13% of overlap syndrome in patients with moderate to severe OSA [10]. In the present study, we exclude all participants without lung function data, without OSA diagnosis and with respiratory diseases other than COPD, including obstructive airway diseases such as asthma. This allowed us to analyze well defined groups of patients, to control for the possibility of misdiagnosis [20] and avoiding possible bias of other respiratory disease known to impact sleep and breathing [21]. Furthermore, mild OSA patients were included in our study.

**Clinical characteristics in OVS**

The decision to match OVS and OSA patients based on sex, age, BMI and AHI at baseline was necessary since OVS patients were significantly older and more often male then OSA patients, which is in line with previous reports [10], as expected according to disease epidemiology [22]. Obesity is a main risk factor for OSA, since BMI was in a comparable range in both groups the observed differences in comorbidities, nocturnal hypoxia and sleep quality are mainly attributable to COPD and not to overweight or obesity.
The total ESS score gives an estimate of the personal average sleep propensity across a wide range of activities in the daily life [23]. In this study, we did not identify significant differences between OVS and OSA patients. Previous studies that reported less subjective daytime sleepiness in overlap patients compared to OSA-alone, although statistically different, they reported ESS scores under the minimum clinically important difference [10]. Indeed, studies revealed COPD-only patients reporting similar degree of sleepiness as measured by the ESS, when compared to overlap syndrome patients [24]. Also, ESS did not accurately predict OSA in the group of patients with COPD.

Insomnia is a common complaint [25], occurring in approximately 30% of patients with COPD [26, 27], there was no significant difference in diagnosis of insomnia between OSA and overlap patients.

Sleep quality in OVS

Our study allowed the analysis of objective sleep parameters obtained by polysomnography in a large sample of OVS patients. We thereby added important knowledge about sleep in OVS. We found that COPD was associated with a significant decrease in sleep efficiency and in nocturnal mean SpO2. There was a tendency for the added impact of having COPD on sleep efficiency and diurnal PaO2, to be more pronounced in mild-to-moderate OSA, which may reflect a more severe sleep fragmentation in patients with severe OSA that is less influenced by comorbid COPD. Previous studies also reported on compromised sleep quality in patients with COPD [28], including increased sleep fragmentation, reduced slow-wave and REM sleep [29]. Interestingly, previous data suggested that sleep disturbance is largely a consequence of COPD-related fragmentation, and to a lesser extent triggered by coexisting OSA [28].
It has been previously reported that nocturnal oxygen desaturation is more severe in patients with OVS [5]. This finding is expected given the impact of impaired lung function on oxygenation and risk for CO₂ retention in hypoventilation syndromes. Further analysis in our matched OVS and OSA groups revealed that a decrease in daytime PaO₂ and FEV₁ was associated with a decrease in sleep efficiency and a lower mean SpO₂.

Daytime hypoxemia, but not airflow obstruction, have previously been shown to be independently associated with sleep efficiency [30]. Other studies have demonstrated a relationship between the presence of lung disease and poor sleep, but FEV₁ was not correlated with the changes in sleep architecture [31]. In severe COPD patients, severity of dynamic lung hyperinflation has been associated with worse sleep efficiency, independent of apnoea and nocturnal hypoxemia [32]. Therefore, further studies on this topic are necessary to fully evaluate the possible relationship between compromised lung function and sleep quality in overlap patients. Likewise, there is a need to further explore the reasons why, even if sleep macrostructure in OVS patients is more affected, they did not show significant increased subjective excessive daytime sleepiness.

**Cardiometabolic comorbidity in OVS**

In the present study the prevalence of hypertension, heart failure, and ischemic heart disease was elevated in OVS patients, a finding which is in line with several previous studies [8, 9, 10, 11]. Having COPD increased the odds of arterial hypertension and heart failure. Interestingly, the influence of COPD on comorbid heart failure was particularly high in patients with mild-to-moderate OSA compared with severe OSA.
Previous studies have demonstrated that measures of nocturnal hypoxemia, more strongly predicted cardiovascular disease and all-cause mortality than the AHI [33]. Also, differences between nocturnal desaturation patterns of OSA, COPD and OVS patients have been described [34]. In OSA, there are episodes of hypoxia (intermittent hypoxia) with normal saturation levels between apnoeas/hypopnoeas. In COPD, the pattern is modest sustained oxygen desaturation with deterioration during REM sleep.

In this study, measures of nocturnal hypoxia were strongly associated with comorbidities, the mean nocturnal SpO$_2$ and T90 were associated with increase odds of systemic hypertension, diabetes, and heart failure but ODI was only related to hypertension and diabetes, suggesting that hypoxic pattern (intermittent or sustained) associated with alterations in mechanics of ventilation (obstructive upper airway events) can affect autonomic and cardiovascular modulation in different ways. Importantly, our results may suggest that coexistence of sustained desaturation (COPD) and intermittent desaturations linked to OSA is associated with more severe cardiovascular burden (including heart failure). Obviously, due to the cross-sectional design of our analysis we cannot determine a cause-effect relationship. Also, the different preponderance of intermittent or sustained desaturations, could explain the higher impact of COPD on less severe OSA patients, but further studies are needed for a more comprehensive explanation.

Our study analyzed for the first time the clinical global impression scale in OVS patients. In general, CGI scores were higher in OVS indicating a more negative perception of overall disease severity in OVS compared with matched OSA patients.
Further application of the CGI scale for instance in interventional trials might be highly relevant, particularly for OVS patients.

Our study has strengths and limitations. The study sample is large, including a high-quality dataset collected in leading academic centres reporting polysomnographic data. The methodology used allowed for well-defined groups allocations which increases validity of our results. Also, although current smoking was considered on the analysis it was not possible to evaluate the impact of former smoking versus never smoking since there was no data available. On the other hand, the lack of longitudinal data prevents analysis of cause–effect relationships. The major limitation is the unavailability of data on COPD symptoms, exacerbations, or phenotypes. Different clinical COPD phenotypes influence the likelihood of co-existing OSA [13] in that the increased lung volumes and low BMI associated with the predominant emphysema phenotype protects against OSA [35, 36]. On the other hand, the higher likelihood of peripheral edema and increased BMI associated with the predominant chronic bronchitis phenotype promotes OSA [37].

In conclusion, we found evidence that comorbid COPD was associated with a significant decrease in sleep efficiency, more severe nocturnal oxygen desaturation and exhibited higher odds for hypertension and heart failure in OSA patients. Furthermore, overlap patients presented worse scores at the clinical impression scale denoting increased clinical burden. The present report highlights the importance of a comprehensive approach in patients with chronic multimorbid conditions and the need for further studies on this topic to fully evaluate the relationship. This may enable identifying therapeutic interventions that might improve the overall management.
### Table 1 — Characteristics and comorbidities of the patients after pairing, for the final sample of 1527 patients

<table>
<thead>
<tr>
<th></th>
<th>OVS (n=509)</th>
<th>OSA (n=1018)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean ± SD</td>
<td>58.8 ± 11.5</td>
<td>58.6 ± 11.3</td>
<td>0.818</td>
</tr>
<tr>
<td>Sex, female, %</td>
<td>14.9</td>
<td>14.1</td>
<td>0.699</td>
</tr>
<tr>
<td>Smokers %</td>
<td>50.6</td>
<td>28.1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>BMI, kg/m², mean ± SD</td>
<td>32.4 ± 6.5</td>
<td>32.2 ± 5.9</td>
<td>0.547</td>
</tr>
<tr>
<td>AHI, events/h, mean ± SD</td>
<td>40.8 ± 25.0</td>
<td>40.8 ± 24.8</td>
<td>0.996</td>
</tr>
<tr>
<td>FEV₁/FVC, mean ± SD</td>
<td>0.64 ± 0.06</td>
<td>0.80 ± 0.06</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>FEV₁, % predicted, mean ± SD</td>
<td>72.1 ± 20.5</td>
<td>93.6 ± 18.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ESS score, mean ± SD</td>
<td>10.2 ± 5.3</td>
<td>10.1 ± 5.2</td>
<td>0.588</td>
</tr>
<tr>
<td>Systemic hypertension, %</td>
<td>58.5</td>
<td>53.1</td>
<td>0.050</td>
</tr>
<tr>
<td>Ischemic heart disease, %</td>
<td>20.0</td>
<td>15.2</td>
<td>0.020</td>
</tr>
<tr>
<td>AF, %</td>
<td>5.9</td>
<td>5.0</td>
<td>0.467</td>
</tr>
<tr>
<td>Heart failure, %</td>
<td>11.4</td>
<td>6.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>25.7</td>
<td>25.1</td>
<td>0.803</td>
</tr>
<tr>
<td>PaO₂, mmHg, mean ± SD</td>
<td>77.43 ± 11.72</td>
<td>82.71 ± 13.02</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PaCO₂, mmHg, mean ± SD</td>
<td>37.90 ± 5.11</td>
<td>37.30 ± 5.27</td>
<td>0.082</td>
</tr>
<tr>
<td>HCO₃, mmol/L, mean ± SD</td>
<td>24.53 ± 2.85</td>
<td>24.29 ± 2.96</td>
<td>0.241</td>
</tr>
<tr>
<td>pH, mean ± SD</td>
<td>7.42 ± 0.03</td>
<td>7.42 ± 0.03</td>
<td>0.758</td>
</tr>
<tr>
<td>Sleep efficiency, %, median, IQR</td>
<td>76.10, 1.07</td>
<td>78.81, 20.13</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>N1 sleep, %, mean ± SD</td>
<td>7.37 ± 4.06</td>
<td>6.00 ± 2.94</td>
<td>0.074</td>
</tr>
<tr>
<td>N2 sleep, %, mean ± SD</td>
<td>59.27 ± 7.49</td>
<td>62.34 ± 9.65</td>
<td>0.187</td>
</tr>
<tr>
<td>SWS, %, mean ± SD</td>
<td>10.59 ± 4.55</td>
<td>11.14 ± 5.48</td>
<td>0.155</td>
</tr>
<tr>
<td>REM sleep, %, mean ± SD</td>
<td>7.95 ± 4.03</td>
<td>9.10 ± 6.41</td>
<td>0.01</td>
</tr>
<tr>
<td>Mean SpO₂, %, mean ± SD</td>
<td>91.45 ± 1.04</td>
<td>92.22 ± 1.09</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Lowest SpO₂, %, mean ± SD</td>
<td>77.45 ± 3.36</td>
<td>78.16 ± 2.81</td>
<td>0.413</td>
</tr>
<tr>
<td>T90, %, mean ± SD</td>
<td>20.60 ± 27.20</td>
<td>18.61 ± 25.84</td>
<td>0.14</td>
</tr>
<tr>
<td>T90 &gt;10%, %</td>
<td>46.4</td>
<td>42.7</td>
<td>0.257</td>
</tr>
<tr>
<td>SpO₂, events/h, mean ± SD</td>
<td>35.30 ± 11.01</td>
<td>36.06 ± 11.00</td>
<td>0.13</td>
</tr>
</tbody>
</table>

---

* a – Nested ANOVA, b - Chi-square Test, c - adjusted to sleep center

AF = atrial fibrillation, AHI= apnoea-hypopnea index, BMI= body mass index, ESADA = European Sleep Apnoea Database, ESS = Epworth Sleepiness Scale, FEV₁ = Forced expiratory volume in one second, FVC = forced vital capacity, HCO₃ = hydrogen bicarbonate, ODI = oxygen desaturation index, OSA= obstructive sleep apnoea, OVS = Overlap Syndrome, PaCO₂ = partial arterial pressure of carbon dioxide, PaO₂ = partial arterial pressure of oxygen, REM = rapid eye movement, SD = standard deviation, SpO₂ = peripheral oxyhemoglobin saturation, SWS – slow wave sleep, T90 = time below SpO₂ of 90%.
Table 2 - Association between having COPD and polysomnography characteristics and arterial blood gases analysis in the GLMM

<table>
<thead>
<tr>
<th>COPD</th>
<th>Sleep efficiency, %</th>
<th>Mean SpO₂, %</th>
<th>Lowest SpO₂, %</th>
<th>Stage N1+N2, %</th>
<th>SWS, %</th>
<th>Stage REM, %</th>
<th>PaO₂ mmHg</th>
<th>PaCO₂ mmHg</th>
<th>HCO₃ mmol/L</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>β (95%CI)</td>
<td>β (95%CI)</td>
<td>β (95%CI)</td>
<td>β (95%CI)</td>
<td>β (95%CI)</td>
<td>β (95%CI)</td>
<td>β (95%CI)</td>
<td>β (95%CI)</td>
<td>β (95%CI)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>-3.0 (-4.7, -1.3)</td>
<td>-1.1 (-1.5, -0.7)</td>
<td>-0.5 (-1.6, 0.5)</td>
<td>-1.2 (-3.3, 0.9)</td>
<td>0.3 (2.2, 2.8)</td>
<td>-0.01 (-0.9, 0.9)</td>
<td>-4.9 (-6.5, -3.2)</td>
<td>0.8 (0.1, 1.4)</td>
<td>0.3 (-0.1, 0.7)</td>
<td>-0.003 (-0.007, 0.001)</td>
</tr>
</tbody>
</table>

β (95%CI) adjusted for sleep center and current smoking

CI=confidence interval, COPD=chronic obstructive pulmonary disease, GLMM = generalized linear mixed effects models, HCO₃ = hydrogen bicarbonate, ODI = oxygen desaturation index, PaCO₂ = partial arterial pressure of carbon dioxide, PaO₂ = partial arterial pressure of oxygen, REM = rapid eye movement, SpO₂ = peripheral oxyhemoglobin saturation, SWS = slow wave sleep
Table 3 - Sensitivity analysis, according to OSA severity, for association between having COPD and sleep efficiency, oxygenation variables and heart failure

<table>
<thead>
<tr>
<th>COPD</th>
<th>Sleep efficiency, %</th>
<th>Mean SpO₂, %</th>
<th>PaO₂ (mmHg)</th>
<th>Heart failure&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AHI&lt;30/h β (95%CI)</td>
<td>AHI ≥ 30/h β (95%CI)</td>
<td>AHI&lt;30/h β (95%CI)</td>
<td>AHI ≥ 30/h β (95%CI)</td>
</tr>
<tr>
<td>No</td>
<td>ref</td>
<td>ref</td>
<td>ref</td>
<td>ref</td>
</tr>
<tr>
<td>Yes</td>
<td>-3.6 (-6.1, -1.0)</td>
<td>-2.7 (-4.9, -0.5)</td>
<td>-1.03 (-1.4, -0.6)</td>
<td>-1.1 (-1.7, -0.6)</td>
</tr>
</tbody>
</table>

β (95%CI) adjusted for sleep center and current smoking
AHI = apnoea-hypopnea index, CI=confidence interval, PaO₂ = partial arterial pressure of oxygen, SpO₂ = peripheral oxyhemoglobin saturation
<sup>a</sup> Model adjusted for sleep center, current smoking, diabetes, and systemic hypertension
Table 4 – Association between PaO$_2$ and FEV$_1$ and sleep efficiency and mean SpO2 during sleep

<table>
<thead>
<tr>
<th></th>
<th>Sleep efficiency, %</th>
<th>Mean SpO$_2$, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β (95%CI)</td>
<td>β (95%CI)</td>
</tr>
<tr>
<td>PaO$_2$ (mmHg)</td>
<td>0.9 (0.02-0.16)</td>
<td>0.1 (0.09, 0.13)</td>
</tr>
<tr>
<td>FEV$_1$ (% of predicted)</td>
<td>0.10 (0.06-0.13)</td>
<td>0.05 (0.04, 0.06)</td>
</tr>
</tbody>
</table>

β (95%CI) adjusted for sleep center and current smoking
AHI = apnoea-hypopnea index, CI=confidence interval, FEV$_1$ - forced expiratory volume in one second, PaO$_2$ = partial arterial pressure of oxygen, SpO$_2$ = peripheral oxyhemoglobin saturation
Table 5 – Association between comorbidities and oxygen parameters

<table>
<thead>
<tr>
<th></th>
<th>Systemic Hypertension</th>
<th>Diabetes</th>
<th>Heart Failure</th>
<th>Ischemic Heart Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Model 1 OR (95%CI)</td>
<td>Model 1 OR (95%CI)</td>
<td>Model 1 OR (95%CI)</td>
<td>Model 1 OR (95%CI)</td>
</tr>
<tr>
<td>MeanSpO₂</td>
<td>0.93 (0.90, 0.96)</td>
<td>0.91 (0.88, 0.94)</td>
<td>0.94 (0.90, 0.99)</td>
<td>0.98 (0.94, 1.02)</td>
</tr>
<tr>
<td>T90</td>
<td>1.02 (1.01, 1.02)</td>
<td>1.02 (1.01, 1.02)</td>
<td>1.01 (1.00-1.02)</td>
<td>1.00 (0.99, 1.01)</td>
</tr>
<tr>
<td>ODI/10</td>
<td>1.10 (1.05,1.15)</td>
<td>1.13 (1.08, 1.18)</td>
<td>1.03 (0.95, 1.12)</td>
<td>1.01 (0.95,1.07)</td>
</tr>
<tr>
<td>PaO₂/5</td>
<td>0.90 (0.85, 0.95)</td>
<td>0.89 (0.83, 0.94)</td>
<td>0.90 (0.80, 1.01)</td>
<td>0.96 (0.89, 1.03)</td>
</tr>
</tbody>
</table>

Model 1 - adjusted for sleep center, current smoking, diabetes, and systemic hypertension
CI=Confidence interval, OR= Odds ratio, ODI = oxygen desaturation index, PaO₂ = partial arterial pressure of oxygen, SD = standard deviation, SpO₂ = peripheral oxyhemoglobin saturation, T90 = time below SpO₂ of 90%.

* ODI/10 for a 10 events/h increase in ODI, *PaO₂/5 = for a 5mmHg increase in PaO₂
References:


Figure Legends

Figure 1—Schematic representation of patients’ inclusion criteria

Figure 1 Legend:
ESADA = European Sleep Apnoea Database, COPD = Chronic Obstructive Pulmonary Disease, OSA = Obstructive Sleep Apnoea, w/ = without.

Figure 2 - Association between COPD and some comorbidities, considering OR and respective 95% CI

Figure 2 Legend:
\(^a\) adjusted for sleep center and current smoking, \(^b\) adjusted for sleep center, current smoking, diabetes and systemic hypertension
CI=Confidence interval, OR= Odds ratio

Figure 3 – Clinical Global Impression scale results in patients with OSA and OVS

Figure 3 Legend:
OSA = obstructive sleep apnoea, OVS – overlap syndrome
Guarantor
Mafalda van Zeller and Marta Drummond take responsibility for the content of the manuscript, including the data and analysis.

Author contributions
Mafalda van Zeller, Ozen K. Basoglu, Johan Verbraecken, Carolina Lombardi, Walter T. McNicholas, Jean-Louis Pepin, Paschalis Steiropoulos, Pawel Sliwinski, Maria R. Bonsignore, Sophia E. Schiza, Jan Hedner, Ludger Grote, Marta Drummond contributed to study concept, data interpretation, and writing and editing of the manuscript. Daniela Correia contributed to data analysis. All the ESADA study group contributed to data collection, study concept and data interpretation and discussion.

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30235 patients entered in the ESADA at Dec 2019

6842 patients with lung function data

428 w/o sleep apnea

6414 patients with sleep apnea

814 with respiratory disease other than COPD or missing data

5600 with complete data

509 OSA + COPD

509 matched

5091 OSA

1018 matched

Figure 1—Schematic representation of patients’ inclusion criteria

Figure 1 Legend:
ESADA = European Sleep Apnoea Database, COPD = Chronic Obstructive Pulmonary Disease, OSA = Obstructive Sleep Apnoea, w/ = without.

180x166mm (144 x 144 DPI)
Figure 2 - Association between COPD and some comorbidities, considering OR and respective 95% CI

Figure 2 Legend:
a adjusted for sleep center and current smoking, b adjusted for sleep center, current smoking, diabetes and systemic hypertension CI=Confidence interval, OR=Odds ratio
Figure 3 – Clinical Global Impression scale results in patients with OSA and OVS

Figure 3 Legend:
OSA = obstructive sleep apnoea, OVS = overlap syndrome
158x71mm (330 x 330 DPI)
**Supplementary material**

Characteristics of patients with OVS and OSA in ESADA unmatched cohort

<table>
<thead>
<tr>
<th></th>
<th>OVS (n=509)</th>
<th>OSA (n=5091)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean ± SD</td>
<td>58.8 ± 11.5</td>
<td>52.6 ± 12.1</td>
<td>&lt; 0.001&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Sex, female, %</td>
<td>14.9</td>
<td>25.6</td>
<td>&lt; 0.001&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Smoker %</td>
<td>50.6</td>
<td>31.6</td>
<td>&lt; 0.001&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>BMI, kg/m&lt;sup&gt;2&lt;/sup&gt;, mean ± SD</td>
<td>32.4 ± 6.5</td>
<td>32.6 ± 6.5</td>
<td>0.488&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>AHI, events/h, mean ± SD</td>
<td>40.8 ± 25.0</td>
<td>39.5 ± 26.0</td>
<td>0.313&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;/FVC, mean ± SD</td>
<td>0.64 ± 0.06</td>
<td>0.8 ± 0.1</td>
<td>&lt; 0.001&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;, % predicted, mean ± SD</td>
<td>72.1 ±20.5</td>
<td>94.8 ± 17.2</td>
<td>&lt; 0.001&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>ESS score, mean ± SD</td>
<td>10.2 ± 5.3</td>
<td>10.1 ± 5.3</td>
<td>0.626&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Arterial hypertension, %</td>
<td>58.5</td>
<td>46.2</td>
<td>&lt; 0.001&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Ischemic heart disease, %</td>
<td>20.0</td>
<td>10.5</td>
<td>&lt; 0.001&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>AF, %</td>
<td>6.0</td>
<td>7.3</td>
<td>0.168&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Heart failure, %</td>
<td>11.4</td>
<td>4.8</td>
<td>&lt; 0.001&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>25.7</td>
<td>19.9</td>
<td>0.001&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Sleep efficiency, %, mean ± SD</td>
<td>76.4 ± 16.1</td>
<td>77.4 ± 14.7</td>
<td>0.226&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>N1 sleep, %, mean ± SD</td>
<td>10.2 ± 11.3</td>
<td>7.1 ± 7.2</td>
<td>&lt; 0.001&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>N2 sleep, %, mean ± SD</td>
<td>59.3 ± 17.1</td>
<td>61.3 ± 16.5</td>
<td>0.021&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>SWS, %, mean ± SD</td>
<td>17.3 ± 14.2</td>
<td>18.1 ± 14.4</td>
<td>0.286&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>REM sleep, %, mean ± SD</td>
<td>11.8 ± 8.0</td>
<td>12.6 ± 7.7</td>
<td>0.046&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mean SpO&lt;sub&gt;2&lt;/sub&gt;, %, mean ± SD</td>
<td>91.5 ±3.9</td>
<td>92.5 ± 3.7</td>
<td>&lt; 0.001&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Lowest SpO&lt;sub&gt;2&lt;/sub&gt;, %, mean ± SD</td>
<td>77.4 ±10.3</td>
<td>78.5 ± 10.6</td>
<td>0.022&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>ODI, events/h, mean ± SD</td>
<td>35.3 ± 27.4</td>
<td>34.2 ± 27.9</td>
<td>0.385&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>PaO&lt;sub&gt;2&lt;/sub&gt;, mmHg, mean ± SD</td>
<td>77.4 ±11.8</td>
<td>84.7 ± 13.2</td>
<td>&lt; 0.001&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> - T-test, <sup>b</sup> - Chi-Square Test

AF = atrial fibrillation, AHI = apnea-hypopnea index, BMI = body mass index, ESADA = European Sleep Apnea Database, ESS = Epworth Sleepiness Scale, FEV<sub>1</sub> = Forced expiratory volume in one second, FVC = forced vital capacity, ODI = oxygen desaturation index, OSA = obstructive sleep apnea, OVS = Overlap Syndrome, PaO<sub>2</sub> = partial pressure of oxygen, SD = standard deviation, SpO<sub>2</sub> = peripheral oxyhemoglobin saturation, REM = rapid eye movement, SWS = slow wave sleep.