



Sleep and cardiometabolic comorbidities in the obstructive sleep apnoea–COPD overlap syndrome: data from the European Sleep Apnoea Database

Mafalda van Zeller ¹, Ozen K. Basoglu², Johan Verbraecken ³, Carolina Lombardi⁴, Walter T. McNicholas ⁵, Jean-Louis Pepin⁶, Paschalis Steiropoulos⁷, Pawel Sliwinski ⁸, Daniela Correia⁹, Maria R. Bonsignore ^{10,11}, Sophia E. Schiza¹², Jan Hedner¹³, Ludger Grote ¹³, Marta Drummond¹ and the European Sleep Apnoea Database study group

¹Sleep and Ventilation Unit, Centro Hospitalar Universitário de São João and Faculty of Medicine, University of Porto, Porto, Portugal. ²Ege University, Department of Chest Diseases, Izmir, Turkey. ³Multidisciplinary Sleep Disorders Centre, Antwerp University Hospital and University of Antwerp, Antwerp, Belgium. ⁴Sleep Disorder Center, Cardiology Department, Istituto Auxologico Italiano IRCCS, Ospedale San Luca and University of Milano Bicocca, Milan, Italy. ⁵Department of Respiratory and Sleep Medicine, St Vincent's Hospital Group, and School of Medicine, University College Dublin, Dublin, Ireland. ⁶Université Grenoble Alpes, INSERM U1300, CHU de Grenoble, Grenoble, France. ⁷Sleep Unit, Department of Pneumology, Democritus University of Thrace, Alexandroupolis, Greece. ⁸Department of Respiratory Medicine, Institute of Tuberculosis and Lung Diseases, Warsaw, Poland. ⁹EPIUnit – Instituto de Saúde Pública, Universidade do Porto, Laboratório para a Investigação Integrativa e Translacional em Saúde Populacional and Departamento de Ciências da Saúde Pública e Forenses, e Educação Médica, Faculdade de Medicina, Universidade do Porto, Porto, Portugal. ¹⁰CNR, Istituto per la Ricerca e l'Innovazione Biomedica, Palermo, Italy. ¹¹Biomedical Department of Internal and Specialistic Medicine (DiBiMIS), Section of Pneumology, University of Palermo, Palermo, Italy. ¹²Sleep Disorders Unit, Department of Respiratory Medicine, Medical School, University of Crete, Heraklion, Greece. ¹³Department of Sleep Medicine, Sahlgrenska University Hospital, and the Sahlgrenska Academy, Gothenburg University, Gothenburg, Sweden.

Corresponding author: Mafalda van Zeller (vanzeller.mafalda@gmail.com)



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Compared with patients with obstructive sleep apnoea (OSA), patients with OSA–COPD overlap syndrome (OVS) have lower sleep quality, which is associated with FEV₁ and diurnal arterial oxygen tension. The sleep-related hypoxia presented in OVS is associated with increased risk of heart failure. <https://bit.ly/3KF4A4I>

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Abstract

Aim The impact of obstructive sleep apnoea (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 patients with OVS *versus* patients with OSA, and to explore pathophysiological links between OVS and comorbidities.

Study design and methods This cross-sectional analysis initially included data from 5600 patients with OSA and lung function in the European Sleep Apnoea Database. Two subgroups of patients with OSA (n=1018) or OVS (n=509) were matched (2:1) based on sex, age, body mass index and apnoea–hypopnea index at baseline.

Results After matching, patients with OVS had more severe hypoxia, lower sleep efficiency and presented with higher prevalences of arterial hypertension, ischaemic heart disease and heart failure compared with patients with OSA. OVS was associated with a significant decrease in sleep efficiency (mean difference (β) –3.0%, 95% CI –4.7 to –1.3) and in nocturnal mean peripheral oxyhaemoglobin saturation (S_{pO₂}) (β –1.1%, 95% CI –1.5 to –0.7). Further analysis revealed that a decrease in forced expiratory volume in 1 s and arterial oxygen tension was related to a decrease in sleep efficiency and in mean nocturnal S_{pO₂}. A COPD diagnosis increased the odds of having heart failure by 1.75 (95% CI 1.15–2.67) and systemic hypertension by 1.36 (95% CI 1.07–1.73). Nocturnal hypoxia was strongly associated with comorbidities; the mean nocturnal S_{pO₂} and T90 (increase in time below S_{pO₂} of 90%) were associated with increased odds of systemic hypertension, diabetes and heart failure but the oxygen desaturation index was only related to hypertension and diabetes.

Conclusion Patients with OVS 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 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]. Hypoxaemia, both intermittent and sustained, is more pronounced in patients with OVS [6], as is hypercapnia and adverse clinical outcomes, when compared with patients with COPD or OSA alone [7].

The OVS has been associated with cardiac arrhythmias [8], pulmonary hypertension and right heart failure [9]. Patients with OVS 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 such as obesity or frequent exposure to smoking [13, 14].

In patients with OVS, it is likely that the added impact on sleep, ventilation, pulmonary haemodynamics and comorbidities could affect the clinical burden of disease [15]. The Clinical Global Impressions (CGI) scale, previously used in patients with OSA [16], provides the physician's global impression of disease severity in a patient, considering the medical history, psychosocial circumstances, symptoms, behaviour, as well as the impact of the symptoms [17]. The use of the CGI scale in patients with OVS could contribute as a clinical tool to reflect the significance of clinical disease.

In the present study we aimed to analyse the potential clinical and polysomnographic differences in patients with OSA and patients with OVS registered in the large European Sleep Apnoea Database (ESADA) to evaluate the impact of COPD on patients with OSA and, if significant, to explore the possible links, particularly the role of intermittent and sustained hypoxia and lung function.

Methods

Study population

Data from patients included in the ESADA were analysed. 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 centres. 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 analyse pseudo-anonymous data in the ESADA was obtained from all patients prior to study start. Each sleep centre obtained approval from the ethical committee of their own institution.

In the current study we considered data from 30 235 participants (the entire quality-controlled data content) 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 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 patients [17] and its use has been previously described in patients with OSA 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 5600 participants were available in the current analysis. Patients with an AHI of at least five events per hour, a diagnosis of COPD confirmed by a physician and corroborated by a forced expiratory volume in 1 s (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 patient with OVS ($n=509$) was matched with two patients without COPD based on similar sex, age, BMI and AHI. Thus, 1527 patients were included in our main analysis cohort (509 OVS plus 1018 OSA). The study flowchart is shown in figure 1.

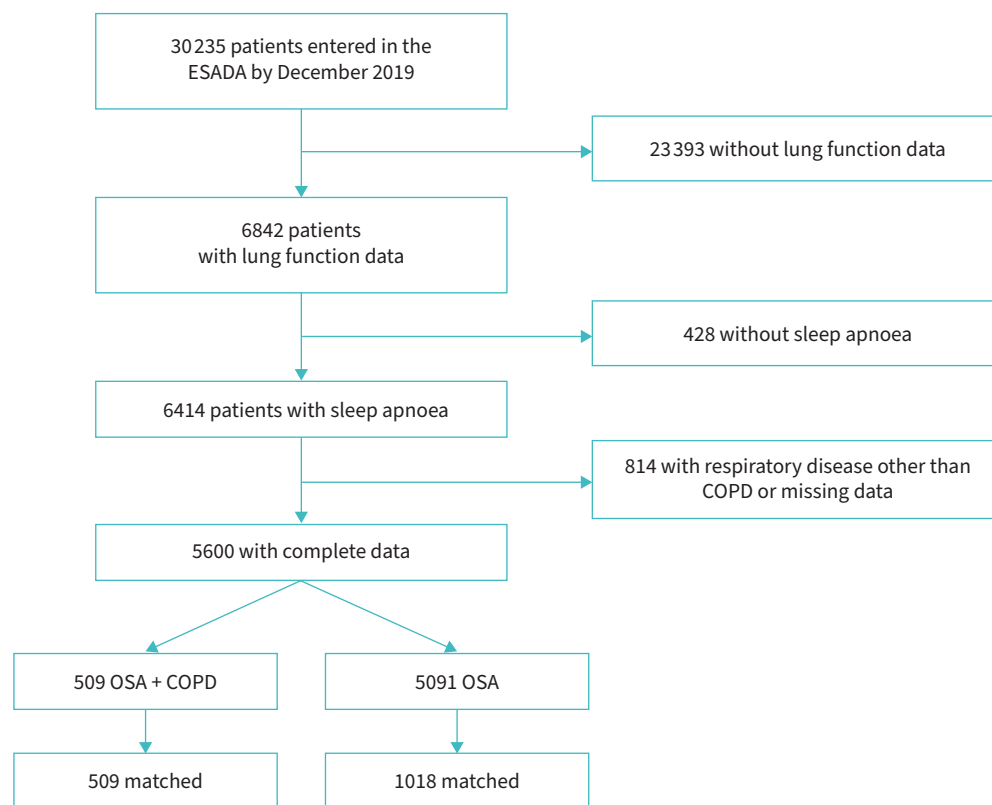


FIGURE 1 Schematic representation of study inclusion criteria. ESADA: European Sleep Apnoea Database, OSA: obstructive sleep apnoea.

Statistical analysis

Patient data, sleep characteristics and arterial blood gases (ABG) analysis data are presented as mean \pm standard deviation (SD) for continuous variables, and in percentages for categorical data, for patients with OVS (OSA plus COPD) and patients with OSA.

Most centres 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 a similar probability of having had 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 centre and other confounders was made, and variance significance was evaluated using the ANOVA method for nested models.

Generalised linear mixed effects models (GLMMs) using binomial distribution were fitted to evaluate the associations between cardiometabolic comorbidities in patients with OSA with and without COPD. Different characteristics with the plausibility to influence the outcome (cigarette smoking, excessive daytime sleepiness, hypertension, heart failure, ischaemic heart disease, diabetes, atrial fibrillation, sleep centre) were analysed and, whenever significantly associated with the outcome, included in the model. Thus, models were adjusted for sleep centre, cigarette smoking, diabetes and systemic hypertension whenever those were confirmed to have an impact. Results are presented as odds ratios (OR) and respective 95% confidence intervals, and the different confounders included in the model are described. Moreover, to evaluate if having COPD differently impacted the prevalence of comorbidities in different severity classes of AHI, a sensitivity analysis stratified by AHI class (AHI <30 events \cdot h $^{-1}$ and AHI ≥ 30 events \cdot h $^{-1}$) was performed.

To evaluate the association between polysomnography and ABG results and having COPD, a GLMM using the gaussian family was fitted. Results were presented as mean differences (β) and respective 95%

confidence intervals. 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 oxygen tension (P_{aO_2}) and FEV_1 impacted on the sleep efficiency and the mean peripheral oxygen saturation (S_{pO_2}) 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 patients with OSA in 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 patients with OVS and patients with OSA matched for age, sex, BMI and AHI, daytime P_{aO_2} , mean S_{pO_2} , sleep efficiency and percentage of rapid eye movement (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 centre and current smoking, OVS was associated with a significant decrease in sleep efficiency (β -3.0% , 95% CI -4.7 to -1.3), in nocturnal mean S_{pO_2} (β -1.1% , 95% CI -1.5 to -0.7) and in daytime P_{aO_2} (β -4.9 mmHg, 95% CI -6.5 to -3.2) (table 2). There was a tendency for a more pronounced impact of having COPD on sleep efficiency and P_{aO_2} in patients with mild-to-moderate OSA (table 3). Further analysis of matched patients with OVS and patients with

TABLE 1 Characteristics and comorbidities of patients after pairing in main analysis cohort (1527 patients)

	OVS (n=509)	OSA (n=1018)	p-value
Age, y, mean \pm sd	58.8 \pm 11.5	58.6 \pm 11.3	0.818 [#]
Sex, female, %	14.9	14.1	0.699 [#]
Smokers %	50.6	28.1	<0.001 [#]
BMI, kg·m ⁻² , mean \pm sd	32.4 \pm 6.5	32.2 \pm 5.9	0.547 [#]
AHI, events·h ⁻¹ , mean \pm sd	40.8 \pm 25.0	40.8 \pm 24.8	0.996 [#]
FEV ₁ /FVC, mean \pm sd	0.64 \pm 0.06	0.80 \pm 0.06	<0.001 [#]
FEV ₁ , % predicted, mean \pm sd	72.1 \pm 20.5	93.6 \pm 18.3	<0.001 [#]
ESS score, mean \pm sd	10.2 \pm 5.3	10.1 \pm 5.2	0.588 [#]
Systemic hypertension, %	58.5	53.1	0.050 [#]
Ischaemic heart disease, %	20.0	15.2	0.020 [#]
AF, %	5.9	5.0	0.467 [#]
Heart failure, %	11.4	6.0	<0.001 [#]
Diabetes, %	25.7	25.1	0.803 [#]
P_{aO_2} , mmHg, mean \pm sd	77.43 \pm 11.72	82.71 \pm 13.02	<0.001 [#]
P_{aCO_2} , mmHg, mean \pm sd	37.90 \pm 5.11	37.30 \pm 5.27	0.082 [#]
HCO ₃ mmol·L ⁻¹ , mean \pm sd	24.53 \pm 2.85	24.29 \pm 2.96	0.241 [#]
pH, mean \pm sd	7.42 \pm 0.03	7.42 \pm 0.03	0.758 [#]
Sleep efficiency, %, median, IQR	76.10, 1.07	78.81, 20.13	<0.001 ^{#,+}
N1 sleep, %, mean \pm sd	7.37 \pm 4.06	6.00 \pm 2.94	0.074 ^{#,+}
N2 sleep, %, mean \pm sd	59.27 \pm 7.49	62.34 \pm 9.65	0.187 ^{#,+}
SWS, %, mean \pm sd	10.59 \pm 4.55	11.14 \pm 5.48	0.155 ^{#,+}
REM sleep, %, mean \pm sd	7.95 \pm 4.03	9.10 \pm 4.61	0.01 ^{#,+}
Mean S_{pO_2} , %, mean \pm sd	91.45 \pm 1.04	92.22 \pm 1.09	<0.001 ^{#,+}
Lowest S_{pO_2} , %, mean \pm sd	77.45 \pm 3.36	78.16 \pm 2.81	0.413 ^{#,+}
T90, %, mean \pm sd	20.60 \pm 27.20	18.61 \pm 25.84	0.14
T90 >10%, %	46.4	42.7	0.257 [#]
ODI, events·h ⁻¹ , mean \pm sd	35.30 \pm 11.01	36.06 \pm 11.00	0.13 [#]

OVS: overlap syndrome; OSA: obstructive sleep apnoea; BMI: body mass index; AHI: apnoea-hypopnea index; FEV₁: forced expiratory volume in 1 s; FVC: forced vital capacity; ESS: Epworth Sleepiness Scale; AF: atrial fibrillation; P_{aO_2} : arterial oxygen tension; P_{aCO_2} : arterial carbon dioxide tension; SWS: slow wave sleep; REM: rapid eye movement; S_{pO_2} : peripheral oxygen saturation; T90: time below S_{pO_2} of 90%; ODI: oxygen desaturation index. [#] nested ANOVA; [#] Chi-square test; ⁺ adjusted to sleep centre.

TABLE 2 Associations between having COPD and polysomnography characteristics and arterial blood gases analysis in the GLMMs

	Sleep efficiency, %	Mean S_{pO_2} , %	Lowest S_{pO_2} , %	Stage N1 +N2, %	SWS, %	Stage REM, %	P_{aO_2} , mmHg	P_{aCO_2} , mmHg	HCO_3^- , mmol·L ⁻¹	pH
No COPD	ref	ref	Ref	ref	ref	ref	ref	ref	ref	ref
COPD	-3.0 (-4.7– -1.3)	-1.1 (-1.5– -0.7)	-0.5 (-1.6– 0.5)	-1.2 (-3.3– 0.9)	0.3 (-2.2– 2.8)	-0.01 (-0.9– 0.9)	-4.9 (-6.5– -3.2)	0.8 (0.1– 1.4)	0.3 (-0.1– 0.7)	-0.003 (-0.007– 0.001)

Data presented as mean difference (β) (95% CI). β (95% CI) adjusted for sleep centre and current smoking. GLMM: generalised linear mixed effects model; S_{pO_2} : peripheral oxygen saturation; SWS: slow wave sleep; REM: rapid eye movement; P_{aCO_2} : arterial carbon dioxide tension; P_{aO_2} : arterial oxygen tension.

TABLE 3 Sensitivity analysis, according to obstructive sleep apnoea severity, for associations between having COPD and sleep efficiency, oxygenation variables and heart failure

	Sleep efficiency, %		Mean S_{pO_2} , %		P_{aO_2} , mmHg		Heart failure [#]	
	AHI <30 h ⁻¹	AHI \geq 30 h ⁻¹	AHI <30 h ⁻¹	AHI \geq 30 h ⁻¹	AHI <30 h ⁻¹	AHI \geq 30 h ⁻¹	AHI <30 h ⁻¹	AHI \geq 30 h ⁻¹
No COPD	ref	ref	ref	ref	ref	ref	ref	ref
COPD	-3.6 (-6.1– -1.0)	-2.7 (-4.9– -0.5)	-1.03 (-1.4– -0.6)	-1.1 (-1.7– -0.6)	-6.8 (-9.5– -4.1)	-3.9 (-5.9– -1.8)	3.30 (1.62– 6.93)	1.67 (1.06– 2.61)

Data presented as mean difference (β) (95% CI). β (95% CI) adjusted for sleep centre and current smoking. AHI: apnoea-hypopnea index; S_{pO_2} : peripheral oxygen saturation; P_{aO_2} : arterial oxygen tension. [#] model adjusted for sleep centre; current smoking, diabetes and systemic hypertension.

OSA revealed that a decrease in FEV_1 and P_{aO_2} was related to a decrease in sleep efficiency and lower mean S_{pO_2} (table 4).

There was no significant difference in the prevalence of insomnia ($p=0.196$), and patients with OVS did not have significantly higher odds of using prescribed psychotropic drugs (OR 1.2, 95% CI 0.65–2.28) compared with patients with OSA.

Cardiometabolic comorbidities and burden of disease

Following matching, the prevalence of arterial hypertension, ischaemic 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 the odds of having heart failure by 1.75 (95% CI 1.15–2.67) and systemic hypertension by 1.36 (95% CI 1.07–1.73) (figure 2). Notably, the influence of COPD on comorbid heart failure was higher in patients with mild-to-moderate OSA (AHI <30 events·h⁻¹) (OR 3.30, 95% CI 1.62–6.93) than in patients with severe OSA (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 S_{pO_2} and an increase in time below S_{pO_2} of 90% (T90) were associated with both systemic hypertension, diabetes and heart failure. An increase of ten events per hour 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

TABLE 4 Associations between P_{aO_2} and FEV_1 , and sleep efficiency and mean S_{pO_2} during sleep

	Sleep efficiency, %	Mean S_{pO_2} , %
P_{aO_2} , mmHg	0.9 (0.02–0.16)	0.1 (0.09–0.13)
FEV_1 , % pred	0.10 (0.06–0.13)	0.05 (0.04–0.06)

Data presented as mean difference (β) (95% CI). β (95% CI) adjusted for sleep centre and current smoking. P_{aO_2} : arterial oxygen tension; FEV_1 : forced expiratory volume in 1 s; S_{pO_2} : peripheral oxygen saturation.

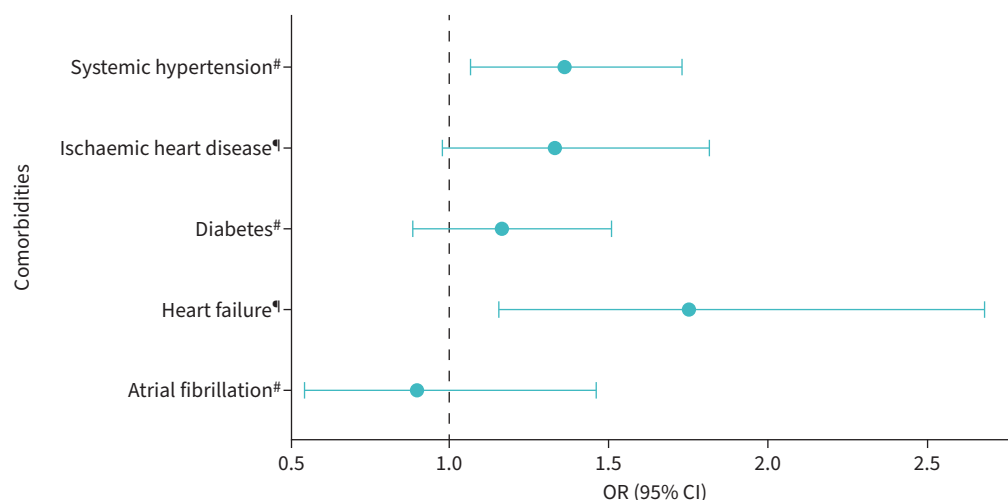


FIGURE 2 Associations between COPD and comorbidities. OR: odds ratio. [#]: adjusted for sleep centre and current smoking; [¶]: adjusted for sleep centre, current smoking, diabetes and systemic hypertension.

and heart failure or ischaemic heart diseases was found. A 5 mmHg increase in daytime P_{aO_2} was associated with a reduced risk of systemic hypertension and diabetes, but not for heart failure or ischaemic heart disease after adjusting for cardiac risk factors.

Patients with OVS presented higher rates of moderate to markedly ill scores on the CGI scale and lower rates of mild scores compared with patients with OSA ($p < 0.001$) (figure 3).

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

Discussion

Our study in the ESADA cohort identified an OVS prevalence of 7.9% in patients with OSA 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 patients with OSA. 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 and disease definition used. CHAOUAT and colleagues [9] prospectively investigated patients with OSA and reported that 11% had an obstructive spirometric pattern, and BEDNARECK and colleagues [2] found OVS in 9.2% of subjects with OSA.

TABLE 5 Associations between comorbidities and oxygen parameters

	Systemic hypertension, OR (95% CI)	Diabetes, OR (95% CI)	Heart failure, OR (95% CI)	Ischaemic heart disease, OR (95% CI)
Mean S_{pO_2}	0.93 (0.90–0.96)	0.91 (0.88–0.94)	0.94 (0.90–0.99)	0.98 (0.94–1.02)
T90	1.02 (1.01–1.02)	1.02 (1.01–1.02)	1.01 (1.00–1.02)	1.00 (0.99–1.01)
ODI/10 [#]	1.10 (1.05–1.15)	1.13 (1.08–1.18)	1.03 (0.95–1.12)	1.01 (0.95–1.07)
$P_{aO_2}/5^{\ddagger}$	0.90 (0.85–0.95)	0.89 (0.83–0.94)	0.90 (0.80–1.01)	0.96 (0.89–1.03)

Data adjusted for sleep centre, current smoking, diabetes and systemic hypertension. OR: odds ratio; S_{pO_2} : peripheral oxyhaemoglobin saturation; T90: time below S_{pO_2} of 90%; ODI: oxygen desaturation index; P_{aO_2} : arterial oxygen tension. [#]: ODI/10 for a 10 events·h⁻¹ increase in ODI; [¶]: $P_{aO_2}/5$ for a 5 mmHg increase in P_{aO_2} .

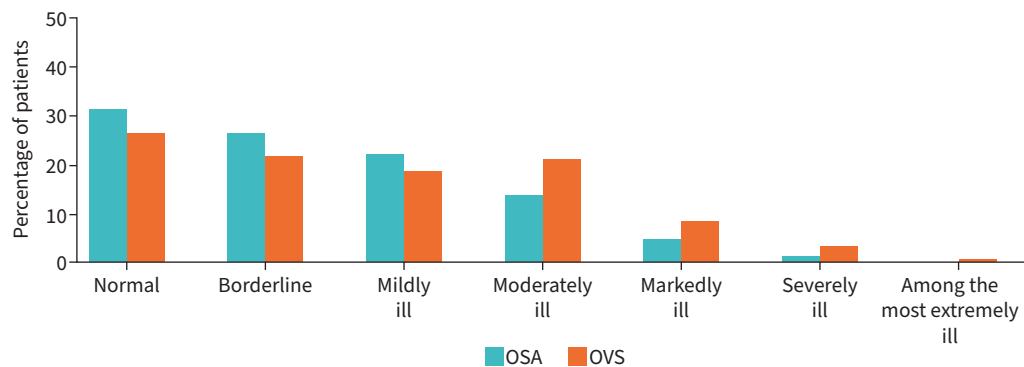


FIGURE 3 Clinical Global Impression scale results in patients with OSA and patients with OVS. OSA: obstructive sleep apnoea, OVS: overlap syndrome.

More recently, a cross-sectional study in the French Sleep Apnoea Registry found a prevalence of 13% of OVS in patients with moderate to severe OSA [10].

In the present study, we exclude all participants without lung function data, without an OSA diagnosis and with respiratory diseases other than COPD, including obstructive airway diseases such as asthma. This allowed us to analyse 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, patients with mild OSA were included in our study.

Clinical characteristics in OVS

The decision to match patients with OVS and patients with OSA based on sex, age, BMI and AHI at baseline was necessary since patients with OVS were significantly older and more often male than patients with OSA, 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 patients with OVS and patients with OSA. Previous studies that reported less subjective daytime sleepiness in patients with OVS compared with patients with OSA alone, although statistically different, they reported ESS scores under the minimum clinically important difference [10]. Indeed, studies revealed patients with COPD-only reported similar degree of sleepiness, as measured by the ESS, when compared with patients with OVS [24]. Also, the 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 patients with OVS.

Sleep quality in OVS

Our study allowed the analysis of objective sleep parameters obtained by polysomnography in a large sample of patients with OVS. We thereby added important knowledge about sleep in patients with OVS. We found that COPD was associated with a significant decrease in sleep efficiency and in nocturnal mean S_{pO_2} . There was a tendency for the added impact of having COPD on sleep efficiency and diurnal P_{aO_2} to be more pronounced in patients with 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 CO_2

retention in hypoventilation syndromes. Further analysis in our matched OVS and OSA groups revealed that a decrease in daytime P_{aO_2} and FEV_1 was associated with a decrease in sleep efficiency and a lower mean S_{pO_2} .

Daytime hypoxaemia, but not airflow obstruction, has 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 FEV_1 was not correlated with the changes in sleep architecture [31]. In patients with severe COPD, severity of dynamic lung hyperinflation has been associated with worse sleep efficiency, independent of apnoea and nocturnal hypoxaemia [32]. Therefore, further studies on this topic are necessary to fully evaluate the possible relationship between compromised lung function and sleep quality in patients with OVS. Likewise, there is a need to further explore the reasons why, even if sleep macrostructure in patients with OVS is more affected, patients did not show significant increased subjective excessive daytime sleepiness.

Cardiometabolic comorbidity in OVS

In the present study the prevalence of hypertension, heart failure and ischaemic heart disease was elevated in patients with OVS, 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 patients with severe OSA.

Previous studies have demonstrated that measures of nocturnal hypoxaemia, more strongly predicted cardiovascular disease and all-cause mortality than the AHI [33]. Also, differences between nocturnal desaturation patterns of OSA, COPD and OVS 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 S_{pO_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 patients with less severe OSA, but further studies are needed for a more comprehensive explanation.

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

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 the 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. However, 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 coexisting OSA [13] in that the increased lung volumes and low BMI associated with the predominant emphysema phenotype protects against OSA [35, 36]. Although, the higher likelihood of peripheral oedema 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 patients with OSA. Furthermore, patients with OVS presented worse scores on the CGI 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.

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The European Sleep Apnoea Database study group: P. Steiropoulos (Sleep Unit, Department of Pneumology, Democritus University of Thrace, Alexandroupolis, Greece), J. Verbraecken (Multidisciplinary Sleep Disorders Centre, Antwerp University Hospital and University of Antwerp, Antwerp, Belgium), E. Petiet (Multidisciplinary Sleep Disorders Centre, Antwerp University Hospital and University of Antwerp, Antwerp, Belgium), G. Trakada (Pulmonary Medicine, National and Kapodistrian University of Athens, Athens, Greece) I. Fietze (Schlafmedizinisches Zentrum, Charité – Universitätsmedizin Berlin, Germany), T. Penzel (Schlafmedizinisches Zentrum, Charité – Universitätsmedizin Berlin, Germany), O. Ludka (Department of Cardiology, University Hospital Brno and International Clinical Research Center, St Ann's University Hospital, Brno, Czech Republic), I. Bouloukaki (Sleep Disorders Unit, Department of Respiratory Medicine, Medical School, University of Crete, Greece), S. Schiza (Sleep Disorders Unit, Department of Respiratory Medicine, Medical School, University of Crete, Greece), W.T. McNicholas (Department of Respiratory Medicine, St. Vincent's University Hospital, Dublin, Ireland), S. Ryan (Pulmonary and Sleep Disorders Unit, St. Vincent's University Hospital, Dublin, Ireland), R.L. Riha (Department of Sleep Medicine, Royal Infirmary Edinburgh, UK), J.A. Kvamme (Sleep Laboratory, ENT Department, Førde Central Hospital, Førde, Norway), L. Grote (Sleep Disorders Center, Pulmonary Department, Sahlgrenska University Hospital, and Center of Sleep and Wake Disorders, Sahlgrenska Academy, Gothenburg University, Gothenburg, Sweden), J. Hedner (Sleep Disorders Center, Pulmonary Department, Sahlgrenska University Hospital, and Center of Sleep and Wake Disorders, Sahlgrenska Academy, Gothenburg University, Gothenburg, Sweden), D. Zou (Sleep Disorders Center, Pulmonary Department, Sahlgrenska University Hospital, and Center of Sleep and Wake Disorders, Sahlgrenska Academy, Gothenburg University, Gothenburg, Sweden), D. Pevernagie (Sleep Disorders Center, Ghent University, Ghent, Belgium), S. Bailly (Université Grenoble Alpes, INSERM HP2 (U1042) and Grenoble University Hospital, Grenoble, France), J-L. Pépin (Université Grenoble Alpes, INSERM HP2 (U1042) and Grenoble University Hospital, Grenoble, France), R. Tamisier (Université Grenoble Alpes, INSERM HP2 (U1042) and Grenoble University Hospital, Grenoble, France), H. Hein (Sleep Disorders Center, St Adolf Stift, Reinbeck, Germany), O.K. Basoglu (Department of Chest Diseases, Ege University, Izmir, Turkey), M.S. Tasbakan (Department of Chest Diseases, Ege University, Izmir, Turkey), J. Buskova (Department of Sleep Medicine, National Institute of Mental Health, Klecany, Czech Republic), P. Joppa (Department of Respiratory Medicine and Tuberculosis, Faculty of Medicine, P.J. Safarik University and L. Pasteur University Hospital, Kosice, Slovakia), R. Staats (Department of Respiratory Medicine, Hospital de Santa Maria, Lisbon, Portugal), D. Testelmans (Sleep Disorders Centre, University Hospital Gasthuisberg, Leuven, Belgium), H. Gouveris (ENT Department at Mainz University Hospital, Mainz, Germany), K. Ludwig (ENT Department at Mainz University Hospital, Mainz, Germany), C. Lombardi (Istituto Auxologico Italiano, IRCCS, Department of Cardiovascular, Neural and Metabolic Sciences, St Luke Hospital, and Department of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy), G. Parati (Istituto Auxologico Italiano, IRCCS, Department of Cardiovascular, Neural and Metabolic Sciences, St Luke Hospital, and Department of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy), M.R. Bonsignore (PROMISE Department, University of Palermo, Palermo, Italy), F. Fanfulla (Unità Operativa di Medicina del Sonno, Istituto Scientifico di Pavia IRCCS, Pavia, Italy), M. Drummond (Sleep and Ventilation Unit, Centro Hospitalar Universitário de São João and Faculty of Medicine, University of Porto, Porto, Portugal), M. van Zeller (Sleep and Ventilation Unit, Centro Hospitalar Universitário de São João and Faculty of Medicine, University of Porto, Porto, Portugal), W. Randerath (Sleep Disorders Centre, Pulmonary Clinic, Solingen, Germany), M. Treml (Respiratory Research Institute, Pulmonary Clinic, Solingen, Germany), Z. Dogas (Sleep Medicine Center, Department of Neuroscience, University of Split School of Medicine, Split, Croatia), R. Pecotic (Sleep Medicine Center, Department of Neuroscience, University of Split School of Medicine, Split, Croatia), A. Pataka (Respiratory Failure Unit, G. Papanikolaou Hospital, Thessalonika, Greece), S. Mihaicuta (Pulmonary Department, Victor Babes University of Medicine and Pharmacy, Victor Babes Hospital, Timisoara, Romania), U. Anttalainen (Division of Medicine, Department of Pulmonary Diseases, Turku University Hospital and Sleep Research Centre, Department of Pulmonary Diseases and Clinical Allergology, University of Turku, Finland), T. Saaresranta (Division of Medicine, Department of Pulmonary Diseases, Turku University Hospital and Sleep Research Centre, Department of Pulmonary Diseases and Clinical Allergology, University of Turku, Finland) and P. Sliwinski (2nd Department of Respiratory Medicine, Institute of Tuberculosis and Lung Diseases, Warsaw, Poland).

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References

- 1 Lee R, McNicholas WT. Obstructive sleep apnea in chronic obstructive pulmonary disease patients. *Curr Opin Pulm Med* 2011; 17: 79–83.
- 2 Bednarek M, Plywaczewski R, Jonczak L, et al. There is no relationship between chronic obstructive pulmonary disease and obstructive sleep apnea syndrome: a population study. *Respiration* 2005; 72: 142–149.
- 3 Weitzenblum E, Chaouat A, Kessler R, et al. Overlap syndrome: obstructive sleep apnea in patients with chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2008; 5: 237–241.
- 4 Verbraecken J, McNicholas WT. Respiratory mechanics and ventilatory control in overlap syndrome and obesity hypoventilation. *Respir Res* 2013; 14: 132.
- 5 McNicholas WT. Chronic obstructive pulmonary disease and obstructive sleep apnea: overlaps in pathophysiology, systemic inflammation, and cardiovascular disease. *Am J Respir Crit Care Med* 2009; 180: 692–700.
- 6 McNicholas WT. Chronic obstructive pulmonary disease and obstructive sleep apnoea—the overlap syndrome. *J Thorac Dis* 2016; 8: 236–242.
- 7 Shteinberg M, Weiler-Ravel D, Adir Y. The overlap syndrome: obstructive sleep apnoea and chronic obstructive pulmonary disease. *Harefuah* 2009; 148: 333–336, 348.
- 8 Shepard JW Jr, Garrison MW, Grither DA, et al. Relationship of ventricular ectopy to nocturnal oxygen desaturation in patients with chronic obstructive pulmonary disease. *Am J Med* 1985; 78:28–34.
- 9 Chaouat A, Weitzenblum E, Krieger J, et al. Association of chronic obstructive pulmonary disease and sleep apnea syndrome. *Am J Respir Crit Care Med* 1995; 151: 82–86.
- 10 Adler D, Bailly S, Benmerad M, et al. Clinical presentation and comorbidities of obstructive sleep apnoea-COPD overlap syndrome. *PLoS One* 2020; 15: e0235331.
- 11 Chudzinska T, Leung RS, Aaron SD, et al. Cardiovascular outcomes and all cause mortality in patients with obstructive sleep apnea and chronic obstructive pulmonary disease (overlap syndrome). *Ann Am Thorac Soc* 2019; 16: 71–81.
- 12 Shah AJ, Quek E, Alqahtani JS, et al. Cardiovascular outcomes in patients with COPD-OSA overlap syndrome: a systematic review and meta-analysis. *Sleep Med Rev* 2022; 63: 101627.
- 13 McNicholas WT. COPD-OSA overlap syndrome: evolving evidence regarding epidemiology, clinical consequences, and management. *Chest* 2017; 152: 1318–1326.
- 14 McNicholas WT. Does associated chronic obstructive pulmonary disease increase morbidity and mortality in obstructive sleep apnoea? *Ann Am Thorac Soc* 2019; 16: 50–53.

- 15 Zamarrón C, García Paz V, Morete E, *et al.* Association of chronic obstructive pulmonary disease and obstructive sleep apnea consequences. *Int J Chron Obstruct Pulmon Dis* 2008; 3: 671–682.
- 16 Dieltjens M, Verbraecken JA, Hedner J, *et al.* Use of the clinical global impression scale in sleep apnoea patients – results from the ESADA database. *Sleep Med* 2019; 59: 56–65.
- 17 Busner J, Targum SD. The clinical global impressions scale: applying a research tool in clinical practice. *Psychiatry (Edgmont)* 2007; 4: 28–37.
- 18 Hedner J, Grote L, Bonsignore M, *et al.* The European Sleep Apnoea Database (ESADA): report from 22 European sleep laboratories. *Eur Respir J* 2011; 38: 635–642.
- 19 Escourrou P, Grote L, Penzel T, *et al.* The diagnostic method has a strong influence on classification of obstructive sleep apnoea. *J Sleep Res* 2015; 24: 730–738.
- 20 Petrie K, Toelle BG, Wood-Baker R, *et al.* Undiagnosed and misdiagnosed chronic obstructive pulmonary disease: data from the BOLD Australia study. *Int J Chron Obstruct Pulmon Dis* 2021; 16: 467–475.
- 21 McNicholas WT, Hansson D, Schiza S, *et al.* Sleep in chronic respiratory disease: COPD and hypoventilation disorders. *Eur Respir Rev* 2019; 28: 190064.
- 22 Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management, and Prevention of COPD: 2023 Report. <https://goldcopd.org/2023-gold-report-2/>
- 23 Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991; 14: 540–545.
- 24 Mermigkis C, Kopanakis A, Foldvary-Schaefer N, *et al.* Health-related quality of life in patients with obstructive sleep apnoea and chronic obstructive pulmonary disease (overlap syndrome). *Int J Clin Pract* 2007; 61: 207–211.
- 25 Vanfleteren LE, Beghe B, Andersson A, *et al.* Multimorbidity in COPD, does sleep matter? *Eur J Intern Med* 2020; 73: 7–15.
- 26 Klink M, Quan SF. Prevalence of reported sleep disturbances in a general adult population and their relationship to obstructive airways diseases. *Chest* 1987; 91: 540–546.
- 27 Budhiraja R, Parthasarathy S, Budhiraja P, *et al.* Insomnia in patients with COPD. *Sleep* 2012; 35: 369–375.
- 28 Cormick W, Olson LG, Hensley MJ, *et al.* Nocturnal hypoxaemia and quality of sleep in patients with chronic obstructive lung disease. *Thorax* 1986; 41: 846–854.
- 29 McSharry DG, Ryan S, Calverley P, *et al.* Sleep quality in chronic obstructive pulmonary disease. *Respirology* 2012; 17: 1119–1124.
- 30 McNicholas WT. Impact of sleep in COPD. *Chest* 2000; 117: Suppl., 48S–53S.
- 31 Sanders MH, Newman AB, Haggerty CL, *et al.* Sleep and sleep-disordered breathing in adults with predominantly mild obstructive airway disease. *Am J Respir Crit Care Med* 2003; 167: 7–14.
- 32 Kwon JS, Wolfe LF, Lu BS, *et al.* Hyperinflation is associated with lower sleep efficiency in COPD with co-existent obstructive sleep apnoea. *COPD* 2009; 6: 441–445.
- 33 Azarbarzin A, Sands SA, Stone KL, *et al.* The hypoxic burden of sleep apnoea predicts cardiovascular disease-related mortality: the Osteoporotic Fractures in Men Study and the Sleep Heart Health Study. *Eur Heart J* 2019; 40: 1149–1157.
- 34 Bouloukaki I, Fanaridis M, Testelmans D, *et al.* Overlaps between obstructive sleep apnoea and other respiratory diseases, including COPD, asthma and interstitial lung disease. *Breathe* 2022; 18: 220073.
- 35 Biselli P, Grossman PR, Kirkness JP, *et al.* The effect of increased lung volume in chronic obstructive pulmonary disease on upper airway obstruction during sleep. *J Appl Physiol (1985)* 2015; 119: 266–271.
- 36 Krachman SL, Tiwari R, Vega ME, *et al.* Effect of emphysema severity on the apnoea-hypopnea index in smokers with obstructive sleep apnoea. *Ann Am Thorac Soc* 2016; 13: 1129–1135.
- 37 White LH, Bradley TD. Role of nocturnal rostral fluid shift in the pathogenesis of obstructive and central sleep apnea. *J Physiol* 2013; 591: 1179–1193.