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Chronic kidney disease in European patients with obstructive sleep apnea: the ESADA cohort study

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SUMMARY

The cross-sectional relationship of obstructive sleep apnea with moderate to severe chronic kidney disease, defined as an estimated glomerular filtration rate <60 mL min^{-1}•1.73 m^{-2}, was investigated in a large cohort of patients with suspected obstructive sleep apnea studied by nocturnal polysomnography or cardiorespiratory polygraphy. Data were obtained from the European Sleep Apnea Database, where information from unselected adult patients with suspected obstructive sleep apnea afferent to 26 European sleep centres had been prospectively collected. Both the Modification of Diet in Renal Disease and the Chronic Kidney Disease-Epidemiology Collaboration equations were used for the assessment of estimated glomerular filtration rate. The analysed sample included 7700 subjects, 71% male, aged 51.9 ± 12.5 years. Severe obstructive sleep apnea (apnea–hypopnea index ≥30) was found in 34% of subjects. The lowest nocturnal oxygen saturation was 81 ± 10.2%. Chronic kidney disease prevalence in the whole sample was 8.7% or 6.1%, according to the Modification of Diet in Renal Disease or the Chronic Kidney Disease-Epidemiology Collaboration equations, respectively. Subjects with lower estimated glomerular filtration rate were older, more obese, more often female, had worse obstructive sleep apnea and more co-morbidities ($P < 0.001$, each). With both equations, independent predictors of estimated glomerular filtration rate <60 were: chronic heart failure; female gender; systemic hypertension; older age; higher body mass index; and worse lowest nocturnal oxygen saturation. It was concluded that in obstructive sleep apnea, chronic kidney disease is largely predicted by co-morbidities and anthropometric characteristics. In addition, severe nocturnal hypoxaemia, even for only a small part of the night, may play an important role as a risk factor for kidney dysfunction.

INTRODUCTION

Obstructive sleep apnea (OSA) is characterized by repeated upper airway obstruction during sleep, leading to intermittent hypoxaemia and sleep fragmentation. Patients with OSA show an increased risk for several diseases, including cardiovascular and metabolic disorders (Kendzerska *et al.*, 2014).

Patients with OSA could also develop renal disorders. Risk factors for renal dysfunction, for example, advanced age, obesity, systemic hypertension and diabetes, are common in patients with OSA, and OSA is a risk factor for sympathetic hyperactivation, central arteries stiffness, atherosclerosis, subclinical inflammation, endothelial dysfunction and various types of metabolic alterations, which may concur to impair renal function (Abuyassin *et al.*, 2015). Importantly, hypoxia is considered a potential initiator of events leading to renal failure, causing inflammatory, apoptotic and fibrotic responses, with increasing tubulo-interstitial injury and loss of peritubular capillaries with further hypoxia and the institution of a vicious circle, leading to progressive renal dysfunction (Fine and Norman, 2008). In fact, in patients with OSA, increased filtration fraction (Kinebuchi *et al.*, 2004; Nicholl *et al.*, 2014) and altered renal artery haemodynamics (Nicholl *et al.*, 2014; Sardo *et al.*, 2015), two conditions that may appear early in the history of chronic kidney disease (CKD), have been described and were correlated to nocturnal oxygen saturation (Kinebuchi *et al.*, 2004; Sardo *et al.*, 2015). Similarly, according to some studies, albumin excretion in OSA is correlated to nocturnal oxygen saturation (Bulcun *et al.*, 2015; Iliescu *et al.*, 2001).

Although it is usually accepted that OSA contributes to the onset and progression of CKD, studies performed in patients with OSA have not always been in agreement, and do not always clarify which characteristics of OSA could play a role as renal risk factors. Conflicting results have been reported in a number of small studies (Chou *et al.*, 2011; Fleischmann *et al.*, 2010; Kanbay *et al.*, 2012; Tsioufis *et al.*, 2008). Of two larger studies comparing subjects with OSA and controls, one performed in Japan (Iseki *et al.*, 2008) and the other one in Turkey (Uyar *et al.*, 2016), only one reported a worse renal function in the OSA subjects (Iseki *et al.*, 2008). Two recent large epidemiological studies, one performed in Taiwan (Lee *et al.*, 2015) and the other one in USA (Molnar *et al.*, 2015), have shown an increased incidence of CKD in patients diagnosed with OSA compared with controls: both studies relied on previous diagnoses recorded on population registries that did not report the degree of severity of OSA and of nocturnal hypoxia. Only one longitudinal observation showed that time with oxygen saturation <90% exceeding 12%, but not apnea–hypopnea index (AHI), was associated with a faster decline in glomerular filtration rate (GFR) (Ahmed *et al.*, 2011). Different study designs, sample sizes, ethnicity and lifestyles, which varied among countries where the studies were performed, could account for the apparent disagreements. In addition, as shown in a large study in elderly subjects, the relationship between OSA and CKD may appear different depending on the equation adopted to estimate GFR (Canales *et al.*, 2008). So far, in most studies (Ahmed *et al.*, 2011; Chou *et al.*, 2011; Fleischmann *et al.*, 2010; Iseki *et al.*, 2008; Tsioufis *et al.*, 2008), GFR has been only estimated with the Modification of Diet in Renal Disease (MDRD) equation (Levey *et al.*, 2006), while only two studies (Molnar *et al.*, 2015; Uyar *et al.*, 2016) have used the more recent CKD-Epidemiology Collaboration (CKD-EPI) equation (Levey *et al.*, 2009) that today is considered more reliable than the MDRD equation to estimate GFR.

It was hypothesized that OSA could be associated with CKD. To test this hypothesis, the relationship between severity of nocturnal respiratory disorders with moderate to severe CKD (stages 3–5) was investigated in a cross-sectional setting. For this purpose, a large European cohort of patients with suspected OSA was studied using both the MDRD and the CKD-EPI equations for the assessment of GFR.

MATERIALS AND METHODS

The European Sleep Apnea Database (ESADA) prospectively records data from unselected adult patients (age 18–80 years) with suspected OSA afferent to several European sleep centres (Hedner *et al.*, 2011). It contains data relevant to sleep recordings, clinical features and biochemical determinations. Exclusion criteria are previous OSA diagnosis, limited life expectancy, and current alcohol or drug abuse. Enrolment started in March 2007. Cross-sectional data recorded up to July 2012 were analysed. Written informed consent to anonymous use of data was obtained from all patients. Each centre obtained approval from the Ethical Committee of its own institution.

In addition to common anthropometric measurements, information on sleepiness, measured with the Epworth Sleepiness Scale, medical history, and recent biochemical analyses, including serum creatinine, were recorded. Methods used for creatinine determination were not recorded. Patients were subjected to either unattended cardiorespiratory polygraphy (PG) or full attended nocturnal polysomnography (PSG), following routine procedures applied in each centre.

The 2007 American Academy of Sleep Medicine scoring rules were adopted for scoring (Iber *et al.*, 2007). All recordings were manually revised. Nocturnal variables taken into account were AHI, oxygen desaturation index (ODI), mean oxyhaemoglobin saturation (mean SpO_2) and lowest oxyhaemoglobin saturation (lowest SpO_2). In the PSG recordings, AHI was calculated as the average number of apneas and hypopneas per hour of sleep time measured on the electroencephalogram. In the PG recordings, the same variable was calculated in relationship to the sleep period, considered as the estimated time between sleep initiation and final awakening. Time with $SpO_2 < 90\%$ (T90) was recorded in a minority of subjects who were subdivided into a group with T90 $\leq$ 12% and a group with T90 > 12%.

Estimated GFR (eGFR) was calculated both with the MDRD and the CKD-EPI equation.

Values of eGFR <60 mL min^{-1}•1.73 m^{-2} were used as a threshold to separate subjects with CKD (stage 3 or worse) from subjects with normal or mildly altered kidney function, respectively [NICE (National Institute for Health and Care Excellence), 2014].

Statistical analysis

Statistical analysis was carried out using IBM SPSS Statistics software (release 21 for Windows). Data are presented as mean ± SD. Univariate analyses were performed to compare subjects with eGFR ≥60 and <60 mL min^{-1}•1.73 m^{-2}. Proportions were analysed by chi-square test, and differences in means between groups were analysed by unpaired *t*-test or one-way ANOVA followed by Bonferroni *post hoc* test for pairwise comparisons. Then, logistic regression analyses, with eGFR < 60 mL min^{-1}•1.73 m^{-2} as the dependent variable, calculated with each of the two equations, were performed. *P*-values <0.05 were considered to be statistically significant.

In building logistic regression models, a hierarchical method was chosen. Possible predictors of CKD [age, sex, systemic hypertension, diabetes, cardiac failure, body mass index (BMI)] were selected and entered into the hierarchical regression in order of their importance, based on previous literature evidence. Thereafter, PG/PSG variables, i.e. AHI, ODI, mean SpO_2 and lowest SpO_2, were added to the model. In order to avoid collinearity between sleep variables, four models were built: one for each PG/PSG variable. The Hosmer–Lemeshow goodness-of-fit statistic was used to test how the data fit the chosen models. Furthermore, the chosen models were tested for multicollinearity using the variance inflation factor and the 'tolerance' statistic.

RESULTS

At the time of the analysis, the ESADA cohort included 12 635 subjects from 26 sleep centres of 18 countries. Altogether, 4935 subjects were excluded because they showed at least one of the following: missing creatinine data ($n = 4092$); missing or insufficient PG/PSG or anthropometric data ($n = 850$). The final dataset included 7700 subjects. Although included and excluded subjects significantly differed in many respects, most differences were small (Table 1). Among the included subjects, one-third showed severe OSA (AHI ≥ 30), and PG was performed in 4052 cases.

Subjects with eGFR <60 accounted for 8.7% of the total sample based on the MDRD equation, and 6.1% based on the CKD-EPI equation. Table 2 shows differences between subjects with eGFR ≥60 and <60. The subjects with lower eGFR were older ($P < 0.001$), more obese ($P < 0.001$), more often female ($P < 0.001$), and had worse OSA according to AHI ($P < 0.001$), ODI ($P < 0.001$), mean and lowest SpO_2 ($P < 0.001$). Besides, hypertension, type 2 diabetes, chronic obstructive pulmonary disease and chronic heart failure were observed more often in subjects with lower eGFR ($P < 0.001$, each).

The model that best predicted eGFR < 60 according to the logistic hierarchical analysis, after testing for multicollinearity, included the following variables: age; gender; BMI; systemic hypertension; chronic heart failure; and lowest SpO_2. This result was similar irrespective of the equation used for eGFR calculations. Data showed a satisfactory fit with the model ($P = 0.45$ for both CKD-EPI and MDRD). Other PG/PSG variables did not enter the model.

Table 1 Anthropometrics, OSA characteristics and main co-morbidities in included and excluded subjects

	Included subjects	Excluded subjects	P-value
Age (years)	51.9 ± 12.5	52.4 ± 13.2	0.031
BMI (kg m^{-2})	30.9 ± 6.5	32.1 ± 7.0	<0.001
Male gender	71.0%	73.3%	0.005
Epworth Sleepiness Scale	9.9 ± 5.1	10.1 ± 5.5	0.006
AHI (n h^{-1})	26.4 ± 25.4	27.1 ± 24.5	0.181
AHI >30	33.7%	36.5%	0.003
ODI (n h^{-1})	21.3 ± 24.1	23.5 ± 25.4	<0.001
Mean SpO_2 (%)	93.5 ± 2.9	92.8 ± 4.0	<0.001
Lowest SpO_2 (%)	81.0 ± 10.2	79.9 ± 11.1	<0.001
Systemic hypertension	41.9%	44.5%	0.005
Type 2 diabetes	8.7%	11.8%	<0.001
Chronic obstructive pulmonary disease	5.0%	5.5%	0.235
Chronic heart failure	2.2%	2.2%	0.967
T90 >12%*	17.9%	23.5%	0.031

Data are presented as mean ± standard deviation, or percentage of whole.
AHI, apnea–hypopnea index; BMI, body mass index; ODI, oxygen desaturation index; SpO_2, oxyhaemoglobin saturation.
*Data available for 1496 included and 268 excluded subjects.

The results of the logistic regressions are shown in Fig. 1. All variables entered in the analysis resulted in significant predictors of eGFR < 60, irrespective of the equation adopted. Lowest SpO_2 showed an odds ratio of 0.98, indicating that each unit decrease in lowest SpO_2 was associated with a 2% higher probability of CKD.

Because measures of AHI were not exactly equivalent in subjects studied by PG or PSG, the two groups were separated to verify if AHI could predict eGFR < 60 within each group. Even in the two groups taken apart, AHI did not independently predict eGFR at the logistic analysis.

Data about T90 were available in 1480 subjects. Fewer subjects with eGFR ≥ 60 than with eGFR < 60 showed T90 values >12% (respectively, 16.7% versus 32.5% with the MDRD equation, and 16.7% versus 38.6% with the CKD-EPI, $P < 0.001$). However, T90 did not predict eGFR in the multivariate analysis when it was forced in the model in the place of lowest SpO_2.

DISCUSSION

In the current cohort of patients referred for suspected OSA and studied cross-sectionally, OSA was associated with CKD. Well-known risk factors for CKD in the general population, such as older age, higher BMI, female gender, chronic heart failure and systemic hypertension, were

Table 2 Differences in characteristics between subjects with eGFR ≥60 and <60 mL min^{-1}·1.73 m^{-2} calculated with the MDRD or the CKD-EPI equation

	eGFR ≥60 MDRD	eGFR <60 MDRD	P-value	eGFR ≥60 CKD-EPI	eGFR <60 CKD-EPI	P-value
Age (years)	50.9 ± 12.2	62.0 ± 10.7	<0.001	51.0 ± 12.1	64.7 ± 10.2	<0.001
BMI (kg m^{-2})	30.7 ± 6.4	32.3 ± 6.6	<0.001	30.8 ± 6.5	32.5 ± 6.5	<0.001
Male gender	72.3%	57.1%	<0.001	71.6%	61.8%	<0.001
Epworth Sleepiness Scale	9.9 ± 5.1	9.4 ± 5.2	0.034	9.9 ± 5.1	9.4 ± 5.1	0.064
AHI (n h^{-1})	25.9 ± 25.3	31.8 ± 26.0	<0.001	25.9 ± 25.3	33.9 ± 25.5	<0.001
ODI (n h^{-1})	20.8 ± 23.9	26.9 ± 25.2	<0.001	20.9 ± 24.0	28.5 ± 24.3	<0.001
Mean SpO_2 (%)	93.6 ± 2.9	92.5 ± 3.4	<0.001	93.6 ± 2.9	92.2 ± 3.4	<0.001
Lowest SpO_2 (%)	81.3 ± 10.1	77.4 ± 11.3	<0.001	81.3 ± 10.1	76.4 ± 11.2	<0.001
Systemic hypertension	39.5%	67.1%	<0.001	39.9%	73.2%	<0.001
Type 2 diabetes	8.1%	15.9%	<0.001	8.1%	18.5%	<0.001
Chronic obstructive pulmonary disease	4.7%	7.9%	<0.001	4.7%	8.9%	<0.001
Chronic heart failure	1.7%	7.6%	<0.001	1.7%	9.8%	<0.001

Data are presented as mean ± standard deviation, or percentage of whole.
AHI, apnea–hypopnea index; BMI, body mass index; CKD-EPI, chronic kidney disease-epidemiology collaboration; eGFR, estimated glomerular filtration rate; MDRD, modification of diet in renal disease; ODI, oxygen desaturation index; SpO_2, oxyhaemoglobin saturation.

significant predictors for CKD in the current sample. In addition, severity of nocturnal hypoxaemia, evaluated by lowest SpO_2, proved an independent predictor of CKD. The frequency of ventilatory disorders (AHI) or of oxygen desaturations (ODI) was related to a higher prevalence of CKD only at univariate analysis. The prevalence of CKD appeared slightly higher when using the MDRD compared with the CKD-EPI equation, similarly to what has been reported in other populations (Matsushita *et al.*, 2012). However, the variables predicting CKD did not differ between equations.

The relationship between OSA and CKD has been the object of great interest. In patients with end-stage renal disease (Forni Ogna *et al.*, 2015; Kuhlmann *et al.*, 2000; Unruh *et al.*, 2006), as well as with less severe forms of CKD (Nicholl *et al.*, 2012; Sakaguchi *et al.*, 2011), a high prevalence of OSA has been reported. Among other mechanisms, renal failure could promote OSA by causing increased chemoresponsiveness or increased fluid retention and upper airway collapsibility through rostral fluid shift when assuming a recumbent position (Abuyassin *et al.*, 2015; Lyons *et al.*, 2015). Other studies in OSA subjects found some association between OSA and increased albumin excretion (Daskalopoulou *et al.*, 2011; Faulx *et al.*, 2007; Iliescu *et al.*, 2001; Tsioufis *et al.*, 2008) or decreased GFR (Ahmed *et al.*, 2011; Chou *et al.*, 2011; Iseki *et al.*, 2008; Kanbay *et al.*, 2012; Lee *et al.*, 2015; Molnar *et al.*, 2015), but factors contributing to kidney deterioration varied among studies.

The current results indicate that the most important predictors of CKD in patients with OSA are similar to kidney risk factors in the general population. As expected, age was significantly related to CKD occurrence. In fact, ageing is associated with renal structural and functional alterations (Esposito and Dal Canton, 2010), which may contribute to explain the progressive increase in CKD prevalence with increasing age. Female gender predicted CKD occurrence, as already demonstrated in a large number of studies in the general population (Zhang and Rothenbacher, 2008). Furthermore, obesity (Hunley *et al.*, 2010) and co-morbidities like chronic heart failure and systemic hypertension, which are well-known risk factors for CKD (Ronco and Ronco, 2012), proved significant predictors of CKD in the current population. Unexpectedly, diabetes was not an independent predictor of CKD. Further observations are necessary to verify if that was a peculiarity of the current sample, or if that finding applies also to other OSA populations. Possibly, most diabetic subjects were evaluated for OSA early in the course of their disease, and were still in a hyperfiltration state. In addition, hypertension, which very often coexists with diabetes, could obscure the role of diabetes as a risk factor for CKD.

Although common risk factors were strong independent predictors of CKD, a role of OSA was suggested by the finding that lowest nocturnal SpO_2 independently participated to predict CKD. This is in agreement with theories that hypoxia may endanger renal function (Fine and Norman, 2008). A previous large study also pointed out a role of nocturnal hypoxia in the deterioration of renal function in OSA (Ahmed *et al.*, 2011). Among the SpO_2 parameters, only lowest SpO_2 was independently associated with CKD. Other parameters could be considered more representative of SpO_2 nocturnal behaviour. However, in the current sample, neither ODI nor mean SpO_2 resulted independent predictors of CKD. Actually, ODI is an expression of the number of oxygen desaturations, and not of their severity, whereas mean SpO_2 may be similar in subjects with very different degrees of oxygen saturation falls, due to the influence of the high values of SpO_2 in its calculation. Therefore, among the parameters measured, lowest SpO_2 could be the most representative of the severity of nocturnal hypoxia, which

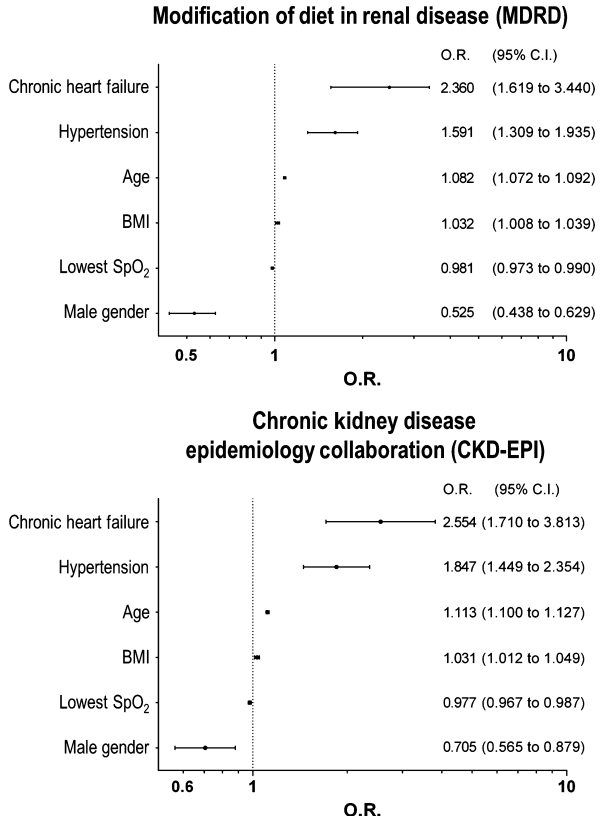

Figure 1. Logistic regression analysis with estimated glomerular filtration rate (eGFR) < 60 mL min^{-1}•1.73 m^{-2} as dependent variable. Upper panel: predictors of GFR < 60 mL min^{-1}•1.73 m^{-2} estimated by the modification of diet in renal disease (MDRD) equation. R^2 by Cox and Snell = 0.088, R^2 by Nagelkerke = 0.197, $P < 0.001$; −2 log likelihood: 3598.6. Lower panel: predictors of GFR < 60 mL min^{-1}•1.73 m^{-2} estimated by the chronic kidney disease-epidemiology collaboration (CKD-EPI) equation. R^2 by Cox and Snell = 0.093, R^2 by Nagelkerke = 0.253, $P < 0.001$; −2 log likelihood: 2604.5. BMI, body mass index; SpO_2, oxyhaemoglobin saturation.

could warrant its relationship with CKD. As in this study, a recent investigation showed that lowest SpO_2, but not mean SpO_2, could predict carotid atherosclerosis in OSA (Gunnarsson *et al.*, 2015).

This study has some limitations. A slight underestimation of the prevalence of CKD in real life patients with OSA was possible, as patients excluded from the study were older and had more co-morbidities than the included patients. However, this study was more interested in looking for an association between OSA and CKD rather than to demonstrate the actual prevalence of CKD in OSA. The influence of central and obstructive events was not separately analysed. The prevalence of central sleep apnea in CKD is about 10% (Nigam *et al.*, 2016). Central apneas could be consequences of CKD, as in end-stage renal disease they are more common in the predialysis nights. Future studies may discover if central apneas may also represent risk factors for CKD. Due to its cross-sectional design, this study does not provide information on a possible long-term effect of nocturnal hypoxaemia on renal dysfunction. In the current sample, T90 appeared related to CKD only at univariate analysis, but this measurement was available just in a minority of patients, preventing strong conclusions. Some possible predictors of CKD, like inflammatory markers (Fassett *et al.*, 2011) or smoking (Briganti *et al.*, 2002), were not evaluated. However, this study explored the role of chronic obstructive pulmonary disease, which is strongly related to smoking, and found no independent effect. Because more than 90% of the subjects were of Caucasian origin, the results may not apply to other ethnic groups. Furthermore, the study lacks information on albuminuria or albumin/creatinine ratio, a marker of kidney disease. Finally, it is not known whether GFR estimates could be influenced by methods used for creatinine determination in some patients, as measurement techniques were not recorded.

The most important strength of the current study is its very large sample. To the authors' knowledge, it is the largest study performed so far on kidney function in OSA where PG/PSG data were available. Other large studies that pointed out a role of OSA as a risk factor for CKD could not clearly indicate which characteristics of OSA were related to kidney function deterioration (Iseki *et al.*, 2008), or did not have data from nocturnal recordings that could clearly suggest a detrimental role of an altered nocturnal respiratory function (Lee *et al.*, 2015; Molnar *et al.*, 2015). The subjects studied in this investigation are representative of a wide range of unselected patients with suspected OSA. In this sample, potential confounding effects of lifestyle on renal function may have been blunted, as average lifestyle significantly varies in the countries where data were collected, located between Northern Europe and the Mediterranean area. Finally, the current findings are corroborated by the use of two different equations for the estimate of GFR, which gave similar results.

In conclusion, in this large sample of European patients, OSA had a significant cross-sectional relationship with CKD. This result did not vary with the equations used for GFR estimation. Among variables related to OSA severity, lowest SpO_2 was independently associated with moderate to severe CKD, suggesting that severe hypoxaemia, even for only a small part of the night, may be more important than average oxygen saturation levels or frequency of nocturnal respiratory events as a risk factor for kidney dysfunction in OSA.

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CONFLICTS OF INTEREST

The following authors declare no competing interests: O. Marrone, O. K. Basoglu, J. A. Kvamme, S. Ryan, J. L. Pepin, J. Verbraecken and M. R. Bonsignore. S. Battaglia declares grant/research support from Chiesi farmaceutici. L. Grote declares these potential conflicts of interest: study equipment support from Itamar, Philips and Weinmann; speakers bureau: Weinmann, Resmed, Philips; consultant: Breas, Resmed and Mundipharma. J. Hedner declares speakers bureau from Weinmann, Almirall, Astra-Zeneca, MSD.

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AUTHORS' CONTRIBUTIONS

O. M. conceived the study, contributed to its design and drafted the manuscript; S. B. performed the statistical analysis; M. R. B. contributed to the design of the study and to data analysis; all the authors contributed to data interpretation, gave important intellectual contribution, critically revised the article and gave their final approval. Data were collected by all ESADA collaborators.

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