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REGULAR RESEARCH PAPER

Determinants of depressive mood in coronary artery disease patients with obstructive sleep apnea and response to continuous positive airway pressure treatment in non-sleepy and sleepy phenotypes in the RICCADSA cohort

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Abstract

We explored determinants of depressive mood in adults with coronary artery disease and obstructive sleep apnea and response to positive airway pressure treatment in sleepy and non-sleepy phenotypes. In this secondary analysis of the RICCADSA trial conducted in Sweden, 493 cardiac patients with obstructive sleep apnea (n = 386) or no obstructive sleep apnea (n = 107) with complete Epworth Sleepiness Scale and Zung Self-rating Depression Scale questionnaires were included. Sleepy (Epworth Sleepiness Scale ≥10) versus non-sleepy (Epworth Sleepiness Scale <10) patients with depressive mood (Zung Self-rating Depression Scale score ≥50) were evaluated after 3 and 12 months of positive airway pressure treatment. In all, 133 patients (27.0%) had depressive mood (29.3% of obstructive sleep apnea versus 18.7% of no obstructive sleep apnea; p = 0.029), with a higher percentage among the sleepy phenotype (36.9% versus 24.5%; p = 0.009). In multivariate analysis, depressive mood was significantly associated with female sex, body mass index and Epworth Sleepiness Scale. Among 97 obstructive sleep apnea patients with depressive mood at baseline, there was a significant reduction in the scores at follow-up both in the sleepy and non-sleepy patients allocated to positive airway pressure treatment, whereas no significant changes were observed in the untreated group (p = 0.033). The device use (hr/night) predicted improvement in mood (odds ratio, 1.33; 95% confidence interval, 1.10–1.61; p = 0.003) adjusted for age, female sex, body mass index, left ventricular ejection fraction, apnea–hypopnea index and delta Epworth Sleepiness Scale score. We conclude that obstructive sleep apnea was associated with depressive mood in adults with coronary artery disease. Treatment with positive airway pressure improved mood in both phenotypes, independent of the confounding factors.

KEYWORDS

coronary artery disease, daytime sleepiness, depression, obstructive sleep apnea, positive airway pressure

1 | INTRODUCTION

Obstructive sleep apnea (OSA) is a common condition characterized by repeated cessation of breathing during sleep as a result of complete or partial pharyngeal obstruction and is associated with increased cardiovascular and neurocognitive morbidity (Banno & Kryger, 2007). OSA may cause excessive daytime sleepiness (EDS) and fatigue (Stoohs, Guilleminault, Itoi, & Dement, 1994) and it has been associated with anxiety and depression (Ohayon, 2003). Similarly, OSA has been reported to be more common in patients with depression (Gupta, Simpson, & Lyons, 2016).

It has also been suggested that depression may be an independent risk factor for incident coronary artery disease (CAD), as well as for increased mortality in CAD (Barth, Schumacher, & Herrmann-Lingen, 2004). Increased plasma levels of inflammatory markers have been demonstrated in conditions with increased stress activity exacerbated by depression (Frisbee et al., 2015). Moreover, coexisting depression has been associated with increased risk of mortality in patients with CAD adjusted for the other independent predictors (Bush et al., 2001).

Continuous positive airway pressure (CPAP) is the first-line treatment for patients with OSA with EDS (Loube et al., 1999). Randomized controlled trials (RCTs) have demonstrated favourable effects of CPAP on quality of life in addition to improvement in EDS in sleep-clinic cohorts (Celik et al., 2016; Jenkinson, Davies, Mullins, & Stradling, 1999). Less is known regarding the contribution of OSA to depression in CAD patients and impact of CPAP treatment in the sleepy and non-sleepy phenotypes. In the SAVE trial, comprising a large number of patients with CAD and cerebrovascular disease, CPAP treatment improved mood in the intention-to-treat (ITT) population (McEvoy et al., 2016).

The Randomized Intervention with CPAP in CAD and OSA (RICCADSA) trial primarily aimed to explore the impact of CPAP on the composite of repeat revascularization, myocardial infarction, stroke and cardiovascular mortality in patients with CAD and OSA (Peker et al., 2016). The current subprotocol evaluated the determinants of depressive mood at baseline and additionally addressed response to 3 and 12 months of CPAP treatment in sleepy versus non-sleepy OSA phenotypes.

2 | METHODS

As previously described (Peker et al., 2009), CAD patients with a history of percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) within 6 months prior to recruitment in the Skaraborg County of West Götaland, Sweden, were invited to participate. The patient enrollment was conducted between 2005 and 2010 and the follow-up for the primary outcomes was ended in May 2013 (Peker et al., 2016). As shown in Figure 1a, the CAD patients were classified as OSA (apnea–hypopnea index [AHI] ≥15/h) and no-OSA (AHI <15/h) based on the baseline cardiorespiratory polygraphy. The non-sleepy OSA patients (Epworth Sleepiness Scale [ESS] <10) were randomized to CPAP or no-CPAP and the sleepy OSA patients (ESS ≥10) were offered CPAP (Figure 1b). For the first part of the current protocol, all patients who completed Zung Self-rating Depression Scale (SDS) questionnaires at baseline (n = 493) were included for evaluation of variables associated with depressive mood at baseline and 107 no-OSA patients were chosen as controls (Figure 1a). Additional baseline comparisons were performed within the OSA group (n = 386) between the sleepy (n = 123) and non-sleepy (n = 203) phenotypes. For the second part, the OSA patients with sleepy versus non-sleepy phenotype, who started CPAP treatment and who had completed Zung SDS questionnaires at baseline and after 3 and 12 months (n = 123 sleepy OSA versus 99 non-sleepy OSA), were further evaluated with regard to response to CPAP treatment (Figure 1b). The non-sleepy OSA arm randomized to no-CPAP (n = 104) served as an additional control group. The Ethics Committee of the Medical Faculty of the University of Gothenburg approved the study protocol (approval nr 207-05; 09.13.2005; amendment T744-10; 11.26.2010; amendment T512-11; 06.16.2011) and written informed consent was provided by all patients. The trial was registered (ClinicalTrials.gov; NCT 00519597).

2.1 | Cardiorespiratory polygraphy

Overnight sleep studies at baseline were conducted by using the Embletta® Portable Digital System device (Embla, Broomfield, CO, USA). As previously described in detail (Peker et al., 2009), the Chicago criteria were used for apnea and hypopnea definitions (American Academy of Sleep Medicine Task Force, 1999).

2.2 | Epworth Sleepiness Scale

Daytime sleepiness was assessed by the ESS questionnaire (Johns, 1991) containing eight questions regarding the chance of dozing off under eight different scenarios in the past month. The total score ranges between 0 and 24 and a cut-off value of 10 for the ESS score was used for categorizing the patients with excessive daytime sleepiness in this protocol.

2.3 | Zung Self-rating Depression Scale

All participants were requested to complete Zung SDS questionnaire at baseline and at follow-ups. The Zung SDS is a widely accepted questionnaire, that provides both a total score and a categorical rate of depression (Zung et al., 1965). In summary, 20 items are included and the rating scale is scored from 1 to 4 points, resulting in a real total score from 20 to 80. The real score is multiplied by 1.25, resulting in a total range of 25–100 (Zung et al., 1965). The individuals with SDS score <50 were categorized as normal, the ones with scores between 50 and 59 as having mild depressive mood, those with scores between 60 and 69 as moderate depressive mood and those with scores ≥70 as severe depressive mood (the details of the questionnaire as well as the scoring manual are provided in Supporting Information Table S1). As answers to question number 2 ("Morning is when I feel the best") and question number 4 ("I have trouble

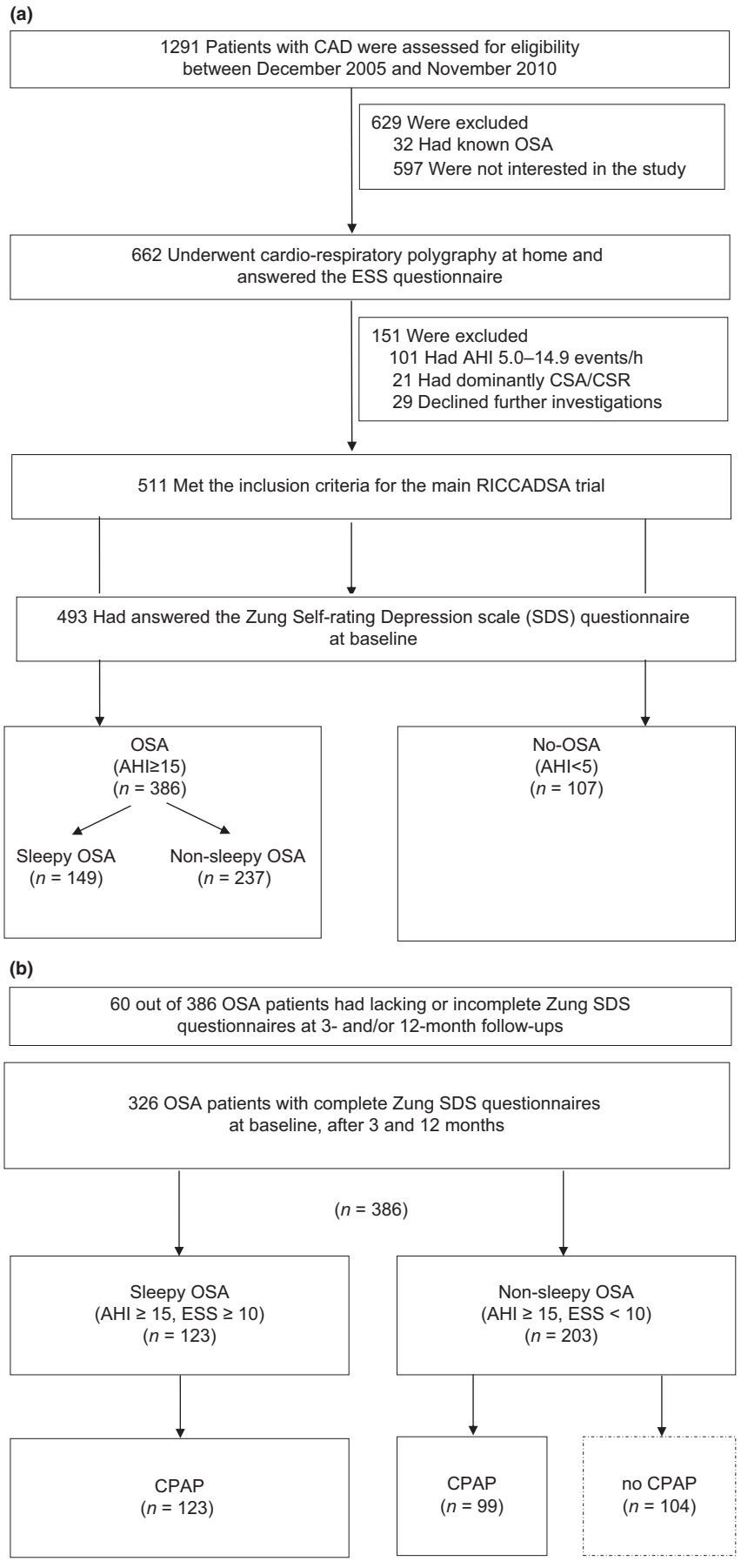

FIGURE 1 Flow of patients through the study. (a) Baseline study cohort. (b) Follow-up population. AHI, apnea–hypopnea index; CAD; coronary artery disease; CPAP, continuous positive airway pressure; CSA-CSR, central sleep apnea–Cheyne Stokes respiration; ESS, Epworth Sleepiness Scale; OSA, obstructive sleep apnea; RICCADSA, Randomized Intervention with CPAP in Coronary Artery Disease and Sleep Apnea; SDS, Self-rating Depression Scale

sleeping at night") may overlap, a separate calculation was performed excluding these items from the total scores. All answers were entered into the database by a research nurse blinded to the group allocation and clinical data.

2.4 | Comorbidities

Baseline anthropometrics, smoking habits and medical histories of the entire study population were obtained from the medical records (Peker et al., 2009). Obesity was defined as a body mass index (BMI) $\geq$30 kg/m^2 (World Health Organization, 2000).

2.5 | Group assignment, randomization, interventions and follow-up

The group assignment was based on the baseline polygraphy results and the ESS scores (Figure 1). Non-sleepy OSA patients randomized to CPAP were provided with a self-titrating CPAP device (S8® or S9®; San Diego, CA, USA) with a nasal or full-face mask and humidifier. All patients receiving CPAP were contacted by telephone after 1 week and all patients were followed after 1 month, 3 months, 6 months and 1 year, and then yearly to the end of the main study (Peker et al., 2009).

2.6 | Adherence to CPAP

All patients receiving CPAP brought their devices to the clinic at each scheduled follow-up visit and CPAP hr/night and CPAP days/period were downloaded from the device and accumulated CPAP hr/night/all nights was calculated. All technical adjustments were carried out according to the clinical routines by the Sleep Medicine Unit staff. Patients who were not using the devices were followed as part of the treatment arm as defined in the intention-to-treat (ITT) analysis (Peker et al., 2009).

2.7 | Outcomes and the sample size

The main outcomes of the current protocol were the occurrence and determinants of depressive mood at baseline in the entire RICCADSA cohort in the first part of the study and the absolute change in the Zung SDS scores in response to CPAP treatment in sleepy versus non-sleepy OSA phenotypes in the second part of the study. In addition, a categorical variable, "improvement in mood", was defined for the depressive mood group in terms of change into a better SDS category (no or milder depressive mood) versus worsening/no change (mild or moderate-to-severe depressive mood) at 1-year follow-up. No specific power estimate was made for the current study, as the sample size estimation for the RICCADSA trial was based on the calculations for the primary endpoints.

2.8 | Statistical analysis

Data are given as mean ± standard deviation or standard error of mean for continuous variables and categorical variables are represented as numbers and percentages. An independent sample *t* test was used for between-group differences in means and the chi-squared test (or when appropriate, Fisher's exact test) was used to compare categorical variables. Only patients who had answered all 20 SDS items were included in the study. Repeated measures of SDS scores were analysed using a two-way analysis of covariance (ANCOVA). A logistic regression analysis was applied for the patients with depressive mood at baseline to determine the variables associated with improvement in mood and odds ratios (ORs) with 95% confidence intervals (CIs) were reported. All statistical tests were two-sided and $p < 0.05$ was considered statistically significant. Statistical analysis was performed using the Statistical Package for Social Sciences, version 22.0 for Windows® system (SPSS® Inc., Chicago, Illinois, USA).

3 | RESULTS

3.1 | Patient characteristics and variables associated with depressive mood at baseline

As illustrated in Figure 1, a total of 511 patients were included in the main study. After exclusion of 18 patients with missing SDS questionnaires at baseline, 493 (mean age 63.9 ± 8.6 years; female, 16.8%) remained for the current protocol. As shown in Table 1, OSA patients were slightly older and had higher BMI, AHI and ESS score values compared to those in the no-OSA group. Hypertension, diabetes mellitus, CABG at baseline and history of atrial fibrillation were significantly more common in the OSA group, whereas the percentage of current smokers was higher in the no-OSA group. In the entire study cohort, 133 (27.0%) had depressive mood (29.3% of OSA versus 18.7% of no-OSA; $p = 0.029$). As shown in Table 2, depressive mood was associated with OSA and AHI, as well as with female sex, obesity, BMI, ESS and EDS, in the univariate analysis. In the multivariate model, female sex (OR, 2.50), BMI (OR, 1.01) and ESS (OR, 1.10) remained significant. When excluding the two items overlapping regarding sleep, raw total scores decreased from 34.8 ± 7.7 to 30.5 ± 7.2 in the OSA group and from 32.6 ± 8.6 to 28.6 ± 7.8 in the no-OSA group without any meaningful between-group difference. In total, 17.6% in the OSA group and 13.1% in the no-OSA group had answered "little of the time" to the item "morning is when I feel the best" with no between-group difference regarding the sleepy and non-sleepy phenotypes (16.1% versus 18.6%). Regarding the item "I have trouble sleeping at night", 4.9% in the OSA group and 0.9% in the no-OSA group had replied "most of the time" with no significant between-group difference in the sleepy and non-sleepy OSA phenotypes (5.4% versus 4.6%, respectively). A detailed distribution of the items within the groups as well as within the OSA phenotypes is provided in Supporting Information Tables S2 and S3, respectively.

As shown in Table 3, the non-sleepy patients were older and had slightly lower BMI and AHI. Zung SDS scores, as well as the percentage of patients with depressive mood, were significantly higher in the sleepy group. Other comorbidities and use of antidepressive

TABLE 1 Baseline clinical characteristics of the study population with coronary artery disease (n = 493)

	OSA (n = 386)	No-OSA (n = 107)	p value
Age, years	64.6 ± 8.2	61.4 ± 9.6	**0.001**
Age ≥ 65 years, %	48.7	38.3	0.057
Female, %	14.2	26.2	**0.004**
AHI, events/hr	30.0 ± 14.5	3.0 ± 1.3	**<0.001**
ESS score	8.1 ± 4.1	5.5 ± 2.9	**<0.001**
EDS (ESS ≥ 10), %	38.6	6.5	**<0.001**
BMI, kg/m^2	28.9 ± 4.0	25.5 ± 3.0	**<0.001**
Obesity, %	33.2	6.5	**<0.001**
Current smoker, %	16.3	26.2	**0.020**
Pulmonary disease, %	8.0	14.0	0.060
Hypertension, %	61.4	45.8	**0.004**
Diabetes mellitus, %	24.9	13.1	**0.010**
Acute MI at baseline, %	50.3	59.8	0.080
History of atrial fibrillation, %	18.9	8.4	**0.010**
Stroke, %	7.3	3.8	0.267
CABG at baseline, %	26.7	15.9	**0.021**
Former revascularization, %	19.7	16.8	0.504
Antidepressive medication, %	5.3	3.9	0.798
Zung SDS score	42.8 ± 9.8	40.7 ± 10.7	0.058
Depression (Zung SDS score ≥ 50), %	29.3	18.7	**0.029**

Bold indicate significance values.
AHI, apnea–hypopnea index; BMI, body mass index; CABG, coronary artery bypass grafting; EDS, excessive daytime sleepiness; ESS, Epworth Sleepiness Scale; MI, myocardial infarction; OSA, obstructive sleep apnea; SDS, Self-rating Depression Scale.

medication did not differ significantly between the groups at baseline (Table 3). Demographic and clinical characteristics at baseline did not differ significantly between the excluded patients with incomplete data (n = 60) and the ones remaining in the study (Zung SDS scores 44.2 ± 12.2 versus 43.2 ± 9.3).

3.2 | Adherence to CPAP treatment

Among patients with depressive mood at baseline, 19 out of the 29 non-sleepy patients (65.5%) and 43 out of the 46 with a sleepy phenotype (93.5%) were remaining on CPAP at 1-year follow-up (p = 0.002). CPAP usage in hr/night was lower in the non-sleepy phenotype but the difference was not statistically significant (3.5 ± 3.1 in non-sleepy OSA versus 4.4 ± 2.4 hr/night in sleepy OSA, p = 0.173).

3.3 | Response to CPAP treatment

3.3.1 | Intention to treat population

Among 97 OSA patients with depressive mood at baseline, there was a significant decline in the scores in both phenotypes allocated to CPAP (Figure 2a). SDS scores decreased from 54.6 to 46.9 after 3 months and to 45.0 after 1 year in the sleepy group and from 55.1 to 46.9 after 3 months and to 44.2 after 1 year in the non-sleepy group. The corresponding values were 53.9 at baseline, 53.7 after 3 months and 53.9 at 1-year follow-up in the non-sleepy OSA group allocated to no-CPAP (p = 0.033 for the between-group difference in ANCOVA, adjusted for age, sex, BMI, AHI and ESS at baseline). CPAP prescription, regardless of usage, was significantly associated with improvement in mood at 1-year (OR, 6.86; 95% CI, 2.36–19.09; p < 0.001) (Table 4). No changes were observed regarding the antidepressive medications during the follow-up period and none of the patients was hospitalized because of depression.

TABLE 2 Logistic regression analysis of covariables associated with depression at baseline (n = 493)

	Odds ratio	95% CI	p value
Univariate			
Age	0.99	0.96–1.01	0.295
Age ≥ 65 years	0.93	0.62–1.39	0.717
Female sex	**2.05**	**1.25–3.35**	**0.005**
OSA	**1.80**	**1.06–3.07**	**0.031**
BMI	**1.12**	**1.06–1.18**	**<0.001**
Obesity	**2.14**	**1.40–3.28**	**<0.001**
Current smoking	1.03	0.62–1.72	0.906
Hypertension	0.72	0.43–1.22	0.231
Diabetes mellitus	1.28	0.81–2.04	0.293
AMI at baseline	1.15	0.77–1.72	0.490
CABG at baseline, %	0.82	0.51–1.33	0.426
Former revascularization	1.19	0.72–1.95	0.495
Pulmonary disease	1.21	0.62–2.34	0.579
Stroke	0.61	0.24–1.51	0.285
AHI	**1.01**	**1.00–1.03**	**0.026**
ESS	**1.10**	**1.04–1.15**	**<0.001**
EDS (ESS score ≥10)	**1.98**	**1.31–2.99**	**0.001**
Multivariate (Model 1)			
AHI	1.00	0.99–1.02	0.654
Age	1.01	0.98–1.03	0.629
Female sex	**2.45**	**1.44–4.17**	**0.001**
BMI	**1.10**	**1.04–1.16**	**0.001**
ESS	**1.09**	**1.04–1.15**	**0.001**
Multivariate (Model 2)			
OSA	1.16	0.63–2.16	0.601
Age	1.01	0.98–1.03	0.674
Female sex	**2.48**	**1.45–4.24**	**0.001**
BMI	**1.10**	**1.04–1.16**	**0.001**
ESS	**1.09**	**1.03–1.15**	**0.002**

Bold indicate significance values.
AHI, apnea–hypopnea index; AMI, acute myocardial infarction; BMI, body mass index; CABG, coronary artery bypass grafting; EDS, excessive daytime sleepiness; ESS, Epworth Sleepiness Scale; OSA, obstructive sleep apnea; SDS, Self-rating Depression Scale.

TABLE 3 Clinical characteristics of the coronary artery disease patients with OSA phenotypes (n = 386)

	Non-sleepy OSA (n = 237)	Sleepy OSA (n = 149)	p value
Age, years	**65.9 ± 8.4**	**62.5 ± 7.3**	**<0.001**
Age ≥ 65 years, %	**54.9**	**38.9**	**0.002**
Female, %	16.5	10.7	0.118
AHI, events/hr	**28.8 ± 13.5**	**31.9 ± 15.9**	**0.040**
ESS score at baseline	**5.5 ± 2.3**	**12.2 ± 2.6**	**<0.001**
BMI, kg/m^2	**28.4 ± 3.7**	**29.8 ± 4.3**	**0.001**
Obesity, %	**27.8**	**41.6**	**0.005**
Current smoker, %	15.6	17.4	0.634
Pulmonary disease, %	6.8	10.1	0.243
Hypertension, %	64.1	57.0	0.164
Atrial fibrillation, %	19.0	18.8	0.962
AMI at baseline, %	50.6	49.7	0.853
Former revascularization, %	20.3	18.8	0.725
Stroke, %	9.3	4.1	0.053
CABG at baseline, %	26.6	26.8	0.955
Diabetes mellitus, %	24.5	25.5	0.820
Antidepressive medication, %	3.9	7.4	0.133
Zung SDS score	**41.7 ± 9.7**	**44.7 ± 9.8**	**0.003**
Depression (Zung SDS score ≥50), %	**24.5**	**36.9**	**0.009**

Bold indicate significance values.

AHI, apnea–hypopnea index; AMI, acute myocardial infarction; BMI, body mass index; CABG, coronary artery bypass grafting; EDS, excessive daytime sleepiness; ESS, Epworth Sleepiness Scale; OSA, obstructive sleep apnea; SDS, Self-rating Depression Scale.

3.3.2 | On treatment population

In post hoc analysis of the patients with depressive mood at baseline, there was a decline from 54.5 to 45.3 after 3 months and to 43.3 after 1 year among 40 patients using the CPAP device ≥4 hr/night, whereas the corresponding values were 54.6, 50.8 and 49.5, respectively, among 57 patients with CPAP use <4 hr/night or no-CPAP allocation (p = 0.002) (Figure 2b). As shown in Table 4, pulmonary disease (asthma or chronic obstructive pulmonary disease) at baseline was negatively correlated with improvement in mood, whereas CPAP hr/night and ESS score change from baseline were significant predictors of improvement at 1-year follow-up. Other comorbidities as well as drugs were not related to change in depressive mood (data not shown). In multivariate analysis, CPAP hr/night (OR, 1.33) as well as CPAP usage cut-off categories (3, 4, 5 hr/night, respectively) remained as significant predictors of improvement in mood (ORs, 2.96, 3.77 and 3.72, respectively), adjusted for age, female sex, BMI, left ventricular ejection fraction, AHI and ESS score change from baseline (Table 4). Pulmonary disease remained inversely correlated with improvement in all models tested and delta ESS score predicted improvement in mood first in the model with CPAP use at least 4 hr/night (Table 4).

4 | DISCUSSION

In the current study, 27% of the revascularized CAD patients demonstrated depressive mood at baseline with a higher percentage among the OSA patients with a sleepy phenotype. Female sex, BMI and ESS score were significant determinants of depressive mood at baseline. CPAP treatment improved mood in both phenotypes independent of the confounding factors and ESS change from baseline.

To our best knowledge, this is the first study addressing the occurrence of depressive mood in revascularized CAD patients with OSA and response to CPAP treatment in sleepy and non-sleepy phenotypes. We observed depressive mood among approximately one-fourth of the entire population and the vast majority of those patients had minor depressive scores. In a systemic meta-analysis of CAD patients, including 22 studies, major depression was found among 20% and the prevalence was even higher (30%) among the hospitalized patients with CAD (Thombs et al., 2006). Persisting depression after acute myocardial infarction was also defined (Lesperance, Frasure-Smith, & Talajic, 1996) and increased risk of cardiac mortality in such cases has been reported (Frasure-Smith et al., 2000).

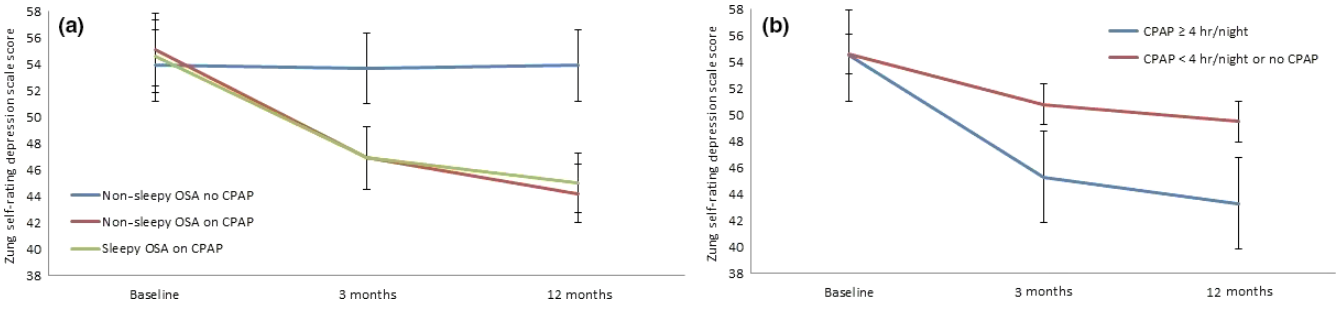

FIGURE 2 Mean values with standard error of means at baseline and after 3 and 12 months. (a) Among the sleepy and non-sleepy OSA patients with depressive mood at baseline allocated to continuous positive airway pressure (CPAP) and no-CPAP (control) groups in intention-to-treat population. (b) Among the patients using CPAP ≥4 hr/night/all nights versus CPAP <4 hr/night or no-CPAP in the on-treatment population who had depressive mood at baseline (p-values were calculated using ANCOVA analysis)

TABLE 4 Significant predictors of improvement in mood after 12 months in the sleepy and non-sleepy OSA patients with Zung SDS score ≥50 at baseline (n = 97)

	Odds ratio	95% CI	p value
Univariate			
Age	1.01	0.96–1.06	0.612
Age ≥ 65 years	0.86	0.38–1.96	0.726
Female sex	1.38	0.49–3.89	0.543
BMI	0.97	0.88–1.07	0.533
Obesity	0.63	0.28–1.44	0.276
LVEF, %	1.00	0.96–1.05	0.866
Pulmonary disease	**0.09**	**0.01–0.76**	**0.027**
AHI	0.99	0.97–1.01	0.439
ESS	1.07	0.98–1.18	0.148
ESS score change from baseline	**1.15**	**1.02–1.30**	**0.026**
CPAP prescription	**6.86**	**2.36–19.09**	**<0.001**
CPAP hr/night/all nights	**1.34**	**1.14–1.59**	**<0.001**
CPAP 3 hr/night	**3.43**	**1.45–8.09**	**0.005**
CPAP 4 hr/night	**4.14**	**1.63–10.53**	**0.003**
CPAP 5 hr/night	**4.52**	**1.65–12.42**	**0.003**
Multivariate model 1[a]			
CPAP hr/night/all nights	**1.33**	**1.10–1.61**	**0.003**
CPAP 3 hr/night/all nights	**2.96**	**1.13–7.72**	**0.027**
CPAP 4 hr/night/all nights	**3.77**	**1.36–10.49**	**0.011**
CPAP 5 hr/night/all nights	**3.72**	**1.25–11.13**	**0.019**
Multivariate model 2[b]			
CPAP hr/night/all nights	**1.36**	**1.10–1.68**	**0.005**
ESS score change from baseline	1.12	0.96–1.02	0.139
Pulmonary disease	**0.03**	**0.00–0.37**	**0.006**
Multivariate model 3[b]			
CPAP 4 hr/night/all nights	**3.59**	**1.22–10.56**	**0.020**
ESS score change from baseline	**1.17**	**1.02–1.35**	**0.025**
Pulmonary disease	**0.04**	**0.00–0.45**	**0.009**

Bold indicate significance values.

AHI, apnea–hypopnea index; BMI, body mass index; EDS, excessive daytime sleepiness; ESS, Epworth Sleepiness Scale; LVEF, left ventricular ejection fraction; OSA, obstructive sleep apnea; SDS, Self-rating Depression Scale.

[a]Adjusted for age, female sex, BMI, AHI at baseline, LVEF and ESS score change from baseline.

[b]Adjusted for age, female sex, BMI and AHI at baseline.

4.1 | Determinants of depressive mood at baseline in a revascularized CAD cohort

In the current study, the percentage of CAD patients with depressive mood was significantly higher among the OSA patients compared with no-OSA. Previous studies suggesting an association between OSA and depression were conducted mainly in sleep clinics or community-based cohorts. Edwards et al. used the patient health questionnaire (PHQ)-9 in a sleep-clinic cohort and reported a significant relationship between severity of depression (PHQ-9 scores) and AHI (Edwards et al., 2015). In the APPLES study, impact of CPAP on neurocognitive function as well as on EDS was evaluated (Kushida et al., 2012) and the baseline report from a subgroup of the same cohort showed no relationship between mild OSA and worse mood (Quan et al., 2014). Chen et al. compared 2,818 OSA and 14,090 non-OSA patients using a longitudinal health-insurance database in Thailand and observed an increased incident depression rate in the OSA group, which was more common in women (Chen, Keller, Kang, Hsieh, & Lin, 2013). In our cohort, the association between OSA and depressive mood was dependent on sex, BMI and EDS. The presented relationship between female sex and depressive mood is in line with a few previous studies in this context. Strik et al. reported that incident depression was more common in women than in men in patients with myocardial infarction, but there was no impact of sex on cardiac events (Strik, Lousberg, Cheriex, & Honig, 2004). In a multicentre study, the relationship between anxiety/depression and all-cause mortality in 1,125 CABG patients was addressed and although female sex was associated with preoperative depression (OR, 1.43; 95% CI, 1.06–1.92), this was not predictive for all-cause mortality (Geulayov, Novikov, Dankner, & Dankner, 2018). The relationship between BMI and depression has also been shown previously (Dragan & Akhtar-Danesh, 2007). The other significant determinant of depressive mood in our cohort was ESS score, which is also in line with the previous reports. In one study, 50 patients who were referred to the sleep clinic for sleep disturbances and EDS were evaluated based on the Hospital Anxiety and Depression Scale questionnaires and a significant association between EDS and depression was demonstrated (Smith et al., 2018). In a large cross-sectional survey of 8,937 adults, sleepiness was associated with an increased risk of major depression (Ohayon, 2012).

4.2 | Impact of CPAP on depressive mood in sleepy versus non-sleepy OSA patients

In the RCT arm of the RICCADSA trial, we have recently demonstrated significant reductions in the SDS scores in non-sleepy OSA patients randomized to CPAP compared with those in the no-CPAP group in the ITT population (Balcan, Thunström, Strollo, & Peker, 2019). In the SAVE trial comprising 2,410 patients with CAD and cerebrovascular disease, CPAP treatment was related to improvement in mood in the ITT population after 2 years (McEvoy et al., 2016). Of note, approximately 20% of the entire population had mild sleepiness (ESS 10-15) and no distinction was made between the participants with regard to ESS levels when evaluating the impact of CPAP on mood in that trial (McEvoy et al., 2016).

As previously summarized, CPAP was effective in some studies (Campos-Rodriguez et al., 2016; Diamanti et al., 2013) and not in some others (Barnes et al., 2004; Gagnadoux et al., 2014). CPAP treatment did not resolve depressive symptoms in many OSA patients and persistent depressive symptoms were strongly associated with EDS (Gagnadoux et al., 2014). On the other hand, beneficial effects of CPAP on mood based on the Zung SDS scores were reported in a 2-year follow-up study of 47 patients with OSA

(Yamamoto, Akashiba, Kosaka, Ito, & Horie, 2000), as well as in another sleep-clinic cohort of 132 patients after 8 weeks of CPAP treatment (Kawahara, Akashiba, Akahoshi, & Horie, 2005). In a recent RCT, with 307 female patients with moderate to severe OSA, Campos-Rodriguez et al. showed significant improvement in depression after 3 months of CPAP therapy compared to conservative treatment (Campos-Rodriguez et al., 2016). In a meta-analysis, including 19 trials, CPAP treatment was shown to be effective in improving depression and a greater benefit of treatment was observed especially in patients with higher depression scores at baseline (Povitz et al., 2014).

As described above, EDS is one of the most critical symptoms of OSA and it is very likely that there exists an interaction between EDS and depression in OSA patients. The benefits of CPAP treatment for EDS are already recognized (Pecotic et al., 2018). We observed improvement in both SDS and ESS scores following 1 year of CPAP treatment in both phenotypes. The between-group differences regarding the improvement in depressive mood in response to CPAP treatment in both sleepy and non-sleepy patients versus untreated OSA are indeed important. In on-treatment analysis, there was a significant association between CPAP use in hr/night and improvement in mood in multivariate analysis adjusted for the confounding factors. The cut-off value of CPAP usage for improvement in mood was 4 hr/night when ESS score change from baseline was entered into the model, suggesting that improvement in depression is strongly dependent on the improvement in EDS in such cases. In other words, the required "dose effect" of CPAP seems to be higher in sleepy apneic patients with a history of heart disease.

Our study has a number of limitations. First, the power estimate for the entire RICCADSA cohort was conducted for the primary outcome (i.e. reduction in composite of repeat revascularization, myocardial infarction, stroke and cardiovascular mortality) for the RCT arm and not for the secondary outcomes assessed in this study for comparison of the sleepy and non-sleepy phenotypes. Second, the diagnostic procedure at baseline was based on the cardiorespiratory sleep studies in comparison to polysomnography and consequently, the total sleep time could not be given exactly. However, the cut-off value for AHI (15/h) chosen for OSA diagnosis was previously shown to be reliable (Dingli et al., 2003). Third, the distinction between "non-sleepy" and "sleepy" OSA in this cohort was based on an ESS threshold, which may not reflect an objective sleepiness. However, the ESS questionnaire is a generally accepted tool for subjective daytime sleepiness and other methods, such as the Multiple Sleep Latency Test (Wise, 2006), which is suggested as an objective tool, are time consuming and not reasonable to run for large-scale intervention studies in cardiac populations. Likewise, it may also be argued that the Zung SDS questionnaire is a subjective tool and may not necessarily reflect a real depression state. Nevertheless, the survey is a largely accepted tool to assess depressive mood in clinical cohorts.

5 | CONCLUSIONS

In this revascularized CAD cohort, OSA was associated with depressive mood but this was dependent on sex, BMI and ESS. CPAP treatment improved mood in both sleepy and non-sleepy OSA phenotypes after 3 months in patients who had depressive scores at baseline. The improvement in mood remained significant at the 12-month follow-up and was predicted by CPAP hr/night independent of sex, BMI and improvement in daytime sleepiness.

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AUTHORS' CONTRIBUTIONS

YP, conception and design; BB, ET, PS and YP, analysis and interpretation; BB, ET, PS and YP, drafting the manuscript for important intellectual content. All authors approved this manuscript in its final form.

CONFLICT OF INTEREST

BB reports no conflicts of interest. ET received consultant fees from ResMed and Pfizer. PS received institutional grants from Philips-Respironics, ResMed, Inspire Medical Systems and National Football League PinMed, and advisory fees from ResMed, Emmi Solutions, Jazz Pharmaceuticals, Itamar Medical, Inspire Medical Systems and Seperation Design Group (all outside the current work). YP received institutional grants from ResMed for the current work and consultant fees from BresoTec and lecture fees from ResMed and Philips-Respironics outside the current work.

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