# Depressive symptoms in patients with obstructive sleep apnea: biological mechanistic pathways.

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# Depressive symptoms in patients with obstructive sleep apnea: biological mechanistic pathways

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**Abstract** This study examined the association between depressive symptoms, as well as depressive symptom dimensions, and three candidate biological pathways linking them to Obstructive sleep apnea (OSA): (1) inflammation; (2) circulating leptin; and (3) intermittent hypoxemia. Participants included 181 obese adults with moderate-to-severe OSA enrolled in the Cardiovascular Consequences of Sleep Apnea (COSA) trial. Depressive symptoms were measured using the Beck Depression Inventory-II (BDI-II). We assessed inflammation using C-reactive protein levels (CRP), circulating leptin by radioimmunoassay using a double antibody/PEG assay, and intermittent hypoxemia by the percentage of sleep time each patient had below 90% oxyhemoglobin saturation. We found no significant associations between BDI-II total or cognitive scores and CRP, leptin, or percentage of sleep time below 90% oxyhemoglobin saturation after controlling for relevant confounding factors. Somatic symptoms, however, were positively associated with percentage of sleep time below 90% saturation ($\beta = 0.202$, $P = 0.032$), but not with CRP or circulating leptin in adjusted models. Another significant predictor of depressive symptoms included sleep efficiency ($\beta_{BDI\ Total} = -0.230$, $P = 0.003$; $\beta_{cognitive} = -0.173$, $P = 0.030$ ($\beta_{somatic} = -0.255$, $P = 0.001$). In patients with moderate-to-severe OSA, intermittent hypoxia may play a role in somatic rather than cognitive or total depressive symptoms.

**Keywords** Obstructive sleep apnea · Depression · Inflammation · Insomnia · C-reactive protein · Leptin

## Introduction

Obstructive sleep apnea (OSA) is a highly prevalent chronic condition characterized by episodes of partial or complete upper airway collapse during sleep that lead to intermittent hypoxemia and sleep fragmentation (Punjabi 2008). OSA has been linked to increased risk of cardiovascular disease (CVD) (Ozeke et al. 2011), type 2 diabetes mellitus (DM) (Pamidi et al. 2010) and all-cause mortality (Marshall et al. 2008).

Depressive symptoms are common among patients diagnosed with OSA, with up to 17% presenting with major depressive disorder (Benton et al. 2007). Co-morbid depressive symptoms, even at subclinical levels, have detrimental effects on self-management and functioning in chronic medical illness (Katon 2003), and among OSA patients have been shown to adversely affect adherence to positive airway pressure therapy, daytime symptoms and health-related quality of life (Kjelsberg et al. 2005; Santamaria et al. 2007). Among patients with coronary heart

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disease, co-morbid depression and OSA were shown to result in higher morbidity and mortality associated with myocardial infarction than either condition alone (Hayano et al. 2012). Therefore, in addition to their impact on OSA-related symptoms and quality of life, the presence of depressive symptoms in OSA patients, particularly among those at high risk for heart disease, confer additional and dangerous risk for cardiovascular complications.

In spite of the importance of depressive symptoms in OSA, the pathways linking these two conditions remain unknown. Inflammation has been proposed as an important biological mediator linking these two conditions as it is a common pathway of disease for both OSA and depression. An increased production of inflammatory markers has been reported among OSA patients (Shamsuzzaman et al. 2002). Similarly, depressive symptoms have been linked to elevations of inflammatory markers, particularly C-reactive protein (CRP) and interleukin-6 (IL-6) (Suarez 2004). Two recent studies among high-risk OSA patients (Einvik et al. 2011, 2013), showed a positive association between CRP and depressive symptoms. However, few studies have examined these associations among patients with a confirmed diagnosis of OSA.

Another novel hypothesis has been recently proposed and suggests that leptin, a peptide secreted by adipocytes, may play a mechanistic role in the link between depression and obesity-related conditions (Lu 2007), such as OSA. This hypothesis proposes that adipose tissue is not directly implicated in the elevations of inflammatory markers, but rather it is leptin that has a role in the up-regulation of immune response (Miller et al. 2003; Wozniak et al. 2009) that may later lead to depressive symptoms. Interestingly, in addition to its impact on inflammation, leptin has also been shown to have an independent association with depressive symptoms, particularly those in the somatic domain, among patients with obesity-related conditions such as metabolic syndrome (Chirinos et al. 2013a) and type 2 diabetes (Labad et al. 2012). Importantly, these associations remained significant after controlling for relevant confounding factors including inflammation and body adiposity (Arnardottir et al. 2013; Chirinos et al. 2013a; Labad et al. 2012). In spite of these provocative findings, no study to date has examined the association between leptin levels and depressive symptoms among adults with OSA.

A third mechanistic hypothesis suggest that the hypoxemia experienced during episodes of airway collapse in patients with OSA may contribute to depressive symptoms. Specifically, the degree of oxygen desaturation has been shown to be positively associated with depression in a sample of predominantly male subjects with OSA (Means et al. 2003). This association, however, has only been studies in the context of small convenient samples that have not included relevant confounding factors such as day-time symptoms of sleep apnea, adiposity or inflammation.

In this study, we aimed to address the gap in the literature by examining the three candidate biological pathways which may play a role in the association between depressive symptoms and OSA: (1) inflammation, measured by CRP levels; (2) circulating leptin; and (3) intermittent hypoxia, measured by the percentage of sleep time the patient had below 90% oxyhemoglobin saturation. Additionally, given the high overlap between daytime symptoms of OSA and somatic depressive symptoms, we examined the association between these biological pathways and depressive symptom domains (somatic vs. cognitive), and included relevant confounding factors such as OSA daytime symptoms, sleep efficiency, body adiposity and cardiovascular risk factors.

## Methods

### Study sample

The sample was comprised of 181 obese adults with moderate-to-severe OSA (apnea hypopnea index [AHI] $\geq$15 events/hour) enrolled in the Cardiovascular Consequences of Sleep Apnea trial (COSA) (Chirinos et al. 2014). Participants were diagnosed with OSA with a 12-channel diagnostic polysomnogram (PSG). All participants had serum CRP >1.0 mg/L, which was an inclusion criterion for the parent trial (Chirinos et al. 2014). Reasons for exclusion based on social and psychiatric factors include: severe depression, defined by a score $\geq$29 on the Beck Depression Inventory-II (BDI-II); suicidal ideation; high-risk occupation or motor vehicle driving record, as defined by a score of 10 points or higher on an Occupational and Driving Habits Questionnaire (Owsley et al. 1999); current illicit drug use; or alcohol use of >14 drinks per week. Sleep-related exclusions included: use of continuous positive airway pressure (CPAP) less than 8 weeks before screening; predominant central sleep apnea; sustained ventricular or supraventricular tachycardia $\geq$30 s during diagnostic sleep study; restless legs syndrome and/or chronic pain syndrome. Medical exclusions from the trial included: a blood pressure measurement >160/95 mmHg; acute coronary syndrome or stroke within 3 months of screening; required use of supplemental oxygen; erythrocytosis; any active infection, malignancy, or chronic inflammatory disorders; left ventricular ejection fraction <30%; decompensated congestive heart failure or respiratory function that required hospitalization within 1 year of screening; surgery within 3 months of screening; women who were pregnant or likely to become pregnant;

and Type 1 or uncontrolled Type 2 DM, demonstrated by either (1) an HbA1c >7%, (2) unstable anti-diabetic therapy, (3) or an inability to perform home blood glucose monitoring. Participants were also excluded due to systemic steroid use, an unstable dose of statin therapy, or any concomitant use of peroxisome proliferator-activated receptor gamma (PPAR-γ) or peroxisome proliferator-activated alpha (PPAR-α). The study protocol was approved by both the University of Pennsylvania and the Philadelphia VAMC Institutional Review Boards. All subjects provided written informed consent.

## Measures

Demographic data were collected on the subjects' screening visits. During the baseline visit, anthropometric measurements such as height, weight, and blood pressure were collected to assure eligibility. Following those measurements, fasting blood samples were drawn prior to an intravenous glucose tolerance test (IVGTT) in which 24 samples of blood were drawn over 195 min. During the IVGTT, each subject was asked to fill out a series of questionnaires.

### *Depression*

Depressive symptoms were assessed with the BDI-II (Dozois et al 1998). High scores on the BDI-II indicate the presence of depressive symptoms. The BDI-II may be scored to yield two subscale scores, measuring cognitive and somatic depressive symptoms. Subscale scores were calculated for all participants. Based on BDI-II scores, and for descriptive purposes participants were classified within a minimal (0–13), mild (14–19), moderate (20–28) or severe (29–63) depression category.

### *Sleepiness*

The self-administered Epworth Sleepiness Scale (ESS) (Johns 1991) was used to assess subjective daytime sleepiness at the time of the baseline visit. Scores range from 0–24, and ESS score >10 indicated clinically-significant sleepiness.

### *Biochemical markers*

All biomarkers were measured in serum or plasma obtained by participants after a 12 h fasting blood draw. Each draw occurred between 8:00 and 10:00am from a peripheral vein. CRP samples were measured using human serum with the Siemens CardioPhase® hsCRP BNII/BN ProSpec® system. Leptin was measured by radioimmunoassay using a double antibody/PEG assay. The kit was obtained from EMD Millipore (Billerica MA) and is specific for human leptin. All of the manufacturers' protocols were followed without modification for these analyses.

### *PSG parameters*

Prior to enrollment, subjects were required to undergo a full-night in-lab diagnostic PSG in order to determine eligibility for the trial. Measures that were collected during the PSG included variables for total AHI, oxygen desaturation, and sleep efficiency. All data were output using the Sandman PSG Software. Trained technicians scored the polysomnographic recordings and computed the AHI as (apneas + hypopneas)/hours of sleep time. An apnea was defined as ≥10 s of airflow cessation. A hypopnea required ≥10 s of reduction in airflow: (1) either ≥50%, or (2) ≥30% with >3% fall in SaO2 or an arousal. Oxyhemoglobin saturation data were reviewed and artifact was excluded by a trained PSG technologist. Using the remaining (valid) oxyhemoglobin saturation data, we computed percent time below 90% (%time <90%) as minutes with saturation value <90% divided by total sleep time. The oxygen desaturation index-3 was calculated as the hourly rate of desaturations of at least 3% magnitude, compared against the immediately preceding baseline, during sleep. Arousals were scored using criteria defined by the American Sleep Disorders Association (Arousals 1992). Sleep efficiency was computed as hours of sleep time/time in bed.

*Statistical analysis* Preliminary analyses included descriptive statistics, outlier detection, and assessment of normality. Non-normal variables including CRP and circulating leptin were log-transformed. Descriptive statistics were stratified by gender as literature shows significant differences in key variables by gender. The t-student test and Mann–Whitney test were used to compare men and women on continuous variables, as necessary, and the Chi square test of independence was used to test differences in categorical variables. SPSS version 19.0 was used for data preparation and descriptive analyses. Multiple regression models were used to examine associations among variables of interest. Demographic characteristics (age, gender, race and ethnicity), daytime sleepiness, BMI, systolic blood pressure, AHI, sleep efficiency and antidepressant use were included in multivariate regression models as control variables. Separate multiple regression models were fitted using BDI-II total scores, BDI-II cognitive and BDI-II somatic scores as dependent variables. Regression assumptions were examined and satisfied. Circulating leptin missing values were available for a subsample of 133

subjects. Full information likelihood was used for the estimation of parameters in the presence of missing data. This method has been shown to perform better than older missing data procedures, including listwise deletion, and produces efficient and accurate measures of statistical uncertainty (Collins et al. 2001). Mplus version 6.0 was used for multiple regression analyses and full information maximum likelihood estimation. Statistical significance was taken at the 0.05 level.

## Results

### Sample characteristics

The sample included 181 participants (104 men and 77 women) diagnosed with OSA. Mean age was 48.9 years and mean AHI was 42.0 Participants had a mean BDI-II total, cognitive and somatic score of 6.9, 3.1 and 3.8, respectively. When using BDI-II cut-off scores to categorize participants according to symptom severity, 88.30% of participants fell within the minimal depression category (BDI scores 0–13), 8.90% within the mild depression category (14–19), 2.20% fell within the moderate category (20–28) and 0.60% within the severe depression category (29–63).

In this sample, men had significantly higher diastolic blood pressures and lower levels of CRP and circulating leptin compared to women. Similarly, men had significantly higher AHI, oxygen desaturation index (number of oxyhemoglobin desaturations of $\geq$3% magnitude, per hour of sleep), and percentage of sleep time below 90% saturation than women. Descriptive characteristics of the sample are presented in Table 1.

### Correlates of depressive symptoms

We fitted multiple regression models to examine associations between BDI-II total score and variables of interest. Multivariate models included as independent variables demographic characteristics (age, gender, race and ethnicity), sleepiness, BMI, systolic blood pressure, AHI, sleep efficiency, antidepressant use, percentage of sleep time below 90% saturation, CRP and circulating leptin levels. No significant associations were found between BDI-II total score and CRP ($\beta = 0.050$, $P = 0.591$), cir-

**Table 1** Descriptive statistics of the study sample

| | All ($n = 181$) M (SD)/Median (IQR) | Men ($n = 104$) M (SD)/Median (IQR) | Women ($n = 77$) M (SD)/Median (IQR) | $P$ value |
|---|---|---|---|---|
| *Demographic characteristics* | | | | |
| Gender, male % | 57.2 | – | – | – |
| Age, years | 48.9 (11.2) | 47.5 (10.5) | 50.7 (11.8) | 0.062 |
| Race, African American % | 41.5 | 40.2 | 43.2 | 0.757 |
| Ethnicity, hispanic % | 2.9 | 3.1 | 2.7 | 0.872 |
| *Biological characteristics* | | | | |
| BMI, kg/m$^2$ | 38.7 (6.5) | 37. 9 (6.3) | 39.7 (6.8) | 0.075 |
| Waist circumference, cm | 121.1 (14.6) | 122.3 (14.5) | 118.9 (14.5) | 0.150 |
| Systolic blood pressure, mmHg | 127.9 (11.1) | 127.2 (10.8) | 128.9 (11.6) | 0.317 |
| Diastolic blood pressure, mmHg | 79.3 (7.5) | 80.6 (6.9) | 77.3 (8.0) | **0.005** |
| C-Reactive protein, mg/L | 4.0 (2.2-8.5) | 3.2 (1.8-6.8) | 7.0 (3.2-10.1) | **<0.001** |
| Leptin, ng/mL | 28.9 (15.8-44.2) | 17.9 (13.0-31.5) | 43.6 (30.7-61.3) | **<0.001** |
| *PSG Parameters* | | | | |
| AHI, events/hr | 42.0 (22.7) | 48.3 (21.7) | 33.4 (21.3) | **<0.001** |
| Oxygen desaturation index, events/hrs | 25.27 (22.4) | 30.4 (23.6) | 18.3 (18.8) | **<0.001** |
| Oxygen saturation below 90%, sleep time % | 6.9 (13.0) | 9.9 (15.9) | 2.8 (6.1) | **<0.001** |
| Sleep efficiency % | 81.6 (11.5) | 81.9 (11.9) | 81.0 (10.8) | 0.623 |
| *Psychometric scales* | | | | |
| BDI-II, total score | 6.8 (5.8) | 6.7 (6.0) | 7.1 (5.6) | 0.625 |
| BDI-II, cognitive score | 3.1 (3.6) | 3.1 (3.7) | 3.1 (3.4) | 0.995 |
| BDI-II, somatic score | 3.8 (2.8) | 3.6 (2.9) | 4.1 (2.7) | 0.339 |
| Epworth Sleepiness scale, score | 9.3 (4.5) | 9.3 (4.5) | 9.3 (3.6) | 0.930 |

Bold values indicate statistical significance ($p < 0.05$)

*M* mean, SD standard deviation, *BMI* body mass index, *AHI* apnea hypopnea index, *BDI* beck depression inventory

**Table 2** Predictors of BDI-II total, cognitive and somatic score

| | BDI-II Total | | BDI Cognitive | | BDI Somatic | |
|---|---|---|---|---|---|---|
| | β (95% CI) | *P* value | β (95% CI) | *P*-value | β (95% CI) | *P*-value |
| *Multivariate model*[¥] | | | | | | |
| Epworth sleepiness scale | 0.094 (−0.037–0.225) | 0.238 | 0.089 (−0.046–0.224) | 0.280 | 0.084 (−0.043–0.211) | 0.274 |
| Body mass index | −0.109 (−0.276–0.057) | 0.280 | −0.07 (−0.241–0.101) | 0.499 | −0.124 (−0.287–0.039) | 0.212 |
| Systolic blood pressure | −0.009 (−0.145–0.126) | 0.911 | 0.026 (−0.114–0.165) | 0.760 | −0.061 (−0.193–0.071) | 0.447 |
| AHI | −0.161 (−0.323–0.000) | 0.100 | −0.116 (−0.282–0.051) | 0.253 | −0.184 (−0.34–0.028) | 0.052 |
| SAT90 | 0.154 (−0.006–0.314) | 0.113 | 0.089 (−0.076–0.254) | 0.376 | 0.201 (0.047–0.355) | **0.032** |
| Sleep efficiency | −0.23 (−0.355–0.104) | **0.003** | −0.173 (−0.303–0.042) | **0.030** | −0.255 (−0.376–0.134) | **0.001** |
| Antidepressant use | 0.032 (−0.097–0.16) | 0.684 | −0.019 (−0.151–0.113) | 0.814 | 0.092 (−0.031–0.216) | 0.219 |
| C-reactive protein | 0.05 (−0.103–0.202) | 0.591 | 0.02 (−0.137–0.177) | 0.833 | 0.077 (−0.07–0.224) | 0.291 |
| Leptin | −0.112 (−0.283–0.059) | 0.279 | −0.08 (−0.258–0.097) | 0.455 | −0.162 (−0.337–0.013) | 0.128 |
| *R squared* | 0.122 | | 0.078 | | 0.181 | |

Bold values indicate statistical significance ($p < 0.05$)

*AHI* apnea hypopnea index, $O_2$ oxygen

[¥] Models controlled for age, gender, race, ethnicity

**Table 3** Estimated marginal means for candidate biological pathways by BDI category

| | Minimal Depression | | Mild Depression | | Moderate Depression | | Severe Depression | |
|---|---|---|---|---|---|---|---|---|
| | EMM | 95% CI | EMM | 95% CI | EMM | 95% CI | EMM | 95% CI |
| *Biological pathways* | | | | | | | | |
| CRP | 4.315 | 3.742–4.970 | 3.770 | 2.409–5.900 | 4.150 | 1.993–8.646 | 2.440 | 0.569–10.459 |
| Leptin | 26.870 | 24.375–29.646 | 20.267 | 14.943–27.508 | 31.375 | 18.927–52.012 | 38.283 | 14.012–104.587 |
| SAT90 | 8.145 | 5.833–10.457 | 6.945 | −0.359–14.249 | 21.097 | 9.403–32.790 | 7.105 | −16.688–30.898 |

*EMM* estimated marginal mean, *CI* confidence interval, *CRP* C-reactive protein, *SAT90* percentage of sleep time below 90% saturation

culating leptin ($\beta = -0.112$, $P = 0.279$), or percentage of sleep time below 90% saturation ($\beta = 0.154$, $P = 0.113$). Sleep efficiency was the only significant predictor of BDI-II total scores ($\beta = -0.230$, $P = 0.003$). The final model accounted for 12% of variance in depression scores (See Table 2, Column 1). For descriptive purposes, estimated marginal means (EMM) by depression category were calculated for each biological pathway (CRP, leptin and percentage of sleep time below 90% saturation) after adjusting for all other control variables in regression models. These are presented in Table 3.

### Depressive symptom dimensions

Multivariate models were fitted separately for BDI-II cognitive and somatic scores In line with the findings on BDI-II total scores, cognitive depressive symptoms were significantly and negatively associated with sleep efficiency ($\beta = -0.173$, $P = 0.030$), but not with CRP ($\beta = 0.020$, $P = 0.833$), circulating leptin levels ($\beta = -0.080$, $P = 0.455$), or percentage of sleep time below 90% saturation ($\beta = 0.089$, $P = 0.376$). Similarly, somatic depressive symptoms were not found to be significantly associated with CRP ($\beta = 0.077$, $P = 0.291$) or circulating leptin levels ($\beta = -0.162$, $P = 0.128$). However, results showed somatic depressive symptoms were positively associated with percentage of sleep time below 90% saturation ($\beta = 0.201$, $P = 0.032$), and negatively associated with sleep efficiency ($\beta = -0.255$, $P = 0.001$), after adjusting for confounding variables.

The final models explained 7 and 18% of the variance in cognitive and somatic depressive symptoms, respectively. Multivariate models are presented in Table 2 (See Columns 2 and 3).

## Discussion

This study examined the association between total depressive symptoms, as well as depressive symptom domains (cognitive vs. somatic), and three candidate mechanistic pathways linking them to OSA: (1) inflam-

mation; (2) leptin; and (3) intermittent hypoxia. We found no association between these three candidate pathways and total depressive symptoms or cognitive depressive symptoms in obese adults with moderate-to-severe OSA. However, although no significant association was observed with CRP or leptin levels, somatic depressive symptoms were significantly associated with the percentage of sleep time patient had below 90% saturation, suggesting that intermittent hypoxia may play a role in somatic depression. This association was independent of important confounding demographic characteristics (age, gender, race and ethnicity), sleepiness measured by the ESS, sleep efficiency, BMI, systolic blood pressure, AHI and antidepressant use.

In contrast to other studies reporting significant associations between inflammation and depressive symptoms in high-risk OSA patients (Einvik et al. 2011, 2013), our study found no association between CRP levels, depressive symptoms or symptom dimensions. Given that both participants with CRP scores lower than 1 mg/L and those with BDI-II scores higher than 29 at the screening visit were excluded from the study, our results are only generalizable to participants with moderately elevated CRP levels and mild to moderate depressive symptoms. It is worth noting, however, that only 10.2 and 3.6% of patients screened were excluded due to out-of-range CRP and depression scores, respectively. Furthermore, our sample contained sufficient variability in CRP and depressive scores to allow statistical analyses. Another possible explanation for the null findings in regards to CRP and depressive symptoms is the fact that our measure of depressive symptoms, the BDI-II, only measures symptoms present in the past 2 weeks. It is possible that symptoms of depression among our participants may not have been longstanding, and therefore, may not have yet impacted CRP levels.

Other studies have found conflicting results, which may be due to differences in the characteristics of the samples studied. While Einvik and colleagues (Einvik et al. 2011, 2013) examined a sample of high-risk OSA as indicated by the Berlin index, our study sample was comprised of patients with moderate-to-severe OSA diagnosed with PSG. Of note, questionnaires such as the Berlin have been shown to have only 60% sensitivity in detecting OSA (Young et al. 2002). Additionally, participants enrolled in our study were obese, with BMI $\geq$30 kg/m$^2$. Therefore, the health status and the severity of OSA symptoms among our participants were likely different than those of subjects from previous studies (Einvik et al. 2011, 2013). Finally, as noted by (Harris et al. 2009) in a recent review, conflicting findings might be a result of differences in the assessment of depression/depressive symptoms. While some studies used clinical interviews to diagnose major depressive disorder (Einvik et al. 2011), others, including our group, used self-report instruments such as BDI (Einvik et al. 2013), which assess both clinical and subclinical depressive symptomatology.

We found no association between circulating leptin levels and total depressive symptoms or depressive symptom dimensions. To our knowledge, ours is the first study to examine these associations in a sample of patients with OSA. Previous studies have reported significant positive associations between depressive, particular those in the somatic domain, and circulating leptin independent of body adiposity and inflammatory markers among patients with other obesity-related conditions (Chirinos et al. 2013b; Labad et al. 2012; Lutter and Elmquist 2009; Milaneschi et al. 2012), including the metabolic syndrome (Chirinos et al. 2013b) and type 2 DM (Labad et al. 2012). Differences in the pathophysiology of each condition may explain these conflicting results.

Our results suggest a significant association between the percentage of sleep time the patient had below 90% oxyhemoglobin saturation, a marker of intermittent hypoxia, and the BDI-II somatic domain. In line with our findings are previous reports on the link between depression and hypoxemia (Means et al. 2003), as well as a recent case–control study which showed that oxygen therapy resulted in a significant reduction in depressive symptoms (Yue et al. 2003). Our study extends the findings of previous reports by elucidating the nature of depressive symptoms most likely to be associated with oxyhemoglobin desaturation. Somatic depressive symptoms include loss of energy, changes in sleeping pattern and/or appetite, tiredness and fatigue and loss of interest in sex (Dozois et al. 1998). Although there is high overlap between somatic depressive symptoms and OSA daytime symptoms, we showed this association is independent of symptoms of daytime sleepiness measured by the ESS and other potential confounding factors disease severity (AHI), BMI, or antidepressant use. Somatic depressive symptoms have also been shown to bear stronger associations with other chronic medical conditions, such as cardiovascular disease (Jonge et al. 2006; Doyle et al. 2010; Hoen et al. 2010; Linke et al. 2009; Martens et al. 2010; Roest et al. 2011; Schiffer et al. 2009; Smolderen et al. 2009), than cognitive symptoms.

The mechanisms relating intermittent hypoxia to depression are unclear, but some studies suggest common neurobiological pathways. Previous studies have shown that chronic intermittent hypoxia may lead to cell injury and adversely affect functions in the prefrontal cortex as well as hippocampal neurogenesis (Buckley and Schatzberg 2005; Nestler et al. 2002; Peterson and Benca 2006), contributing to the development of mood disorders. Interestingly, a previous study that used functional neuroimaging showed abnormalities in the activation of the

prefrontal cortex among patients with OSA and major depressive disorder (Germain et al. 2004).

Another important predictor of depressive symptoms, as well as both depressive symptom domains (cognitive and somatic) in this study was sleep efficiency. Sleep efficiency (ratio of sleep time measured by PSG/amount of time spent in bed (sleep opportunity) correlates strongly with self-report insomnia scales (Bastien et al. 2001), and measures of sleep quality (Buysse et al. 2008). These findings are consistent with other studies showing insomnia is associated with increased risk of depression (Pigeon 2010; Staner 2010), and those highlighting is a well-known feature of major depression (Sunderajan et al. 2010).

Further research is also needed to elucidate the mechanistic pathways linking depressive symptoms and OSA parameters, in particular oxygen desaturation, with the use of a longitudinal design. This may be of great importance, given that interventions targeting hypoxemia may have an impact on somatic depressive symptoms among men and women with OSA. Although, as we noted earlier, some studies have found a reduction of depressive symptoms after oxygen (Yue et al. 2003) and CPAP therapy (Means et al. 2003), these studies have used small, convenience samples. A randomized, controlled, adequately-powered trial is needed to assess the impact of CPAP therapy on depressive symptoms. Similarly, changes in depressive symptoms may result in improvements in OSA parameters such at intermittent hypoxia. Although these issues are important for future investigation, we believe our findings highlight the importance of considering depressive symptoms in the design of OSA prevention strategies.

A strength of this study is the inclusion of relevant confounding factors that impact the association between these potential mechanistic pathways and depressive symptoms. In particular, adiposity and hypertension have been highlighted as important confounders in these relationships, given that their associations with depressive symptoms are well established (Faith et al. 2011; Scuteri et al. 2009). However, few studies to date have previously assessed all of these parameters in the same study sample.

One limitation of this study is its relatively small sample size. Furthermore, given the exclusion criteria, these findings are not generalizable to larger groups with moderate-to-severe OSA who may have comorbid illnesses, such as uncontrolled hypertension and diabetes. An epidemiological study that includes a population-based sample of participants would provide informative data regarding the generalizability of these results. Similarly, studies including individuals with comorbid illness such as diabetes are needed. Given the high rates of depression among patients with type 2 diabetes, these individuals may be most likely to benefit from treatment. Finally, our study is limited by its cross-sectional design, therefore, the directionality of the association between somatic depressive symptoms and oxyhemoglobin desaturation cannot be determined. However, pending prospective data, our findings provide important insights into the relationship between OSA and depression and the possible underlying mechanistic pathways linking these conditions.

## Conclusion

In summary, we found no evidence of an association between inflammation or circulating leptin and total depressive symptoms or depressive symptom dimensions in moderate-to-severe OSA. Oxyhemoglobin desaturation, however, was associated with somatic depressive symptoms but not with cognitive or total depressive symptoms, suggesting that intermittent hypoxia may play a role in somatic depression. Future research is needed to elucidate the mechanistic pathways linking depressive symptoms and OSA parameters, in particular oxygen desaturation, with the use of longitudinal designs.

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**Compliance with ethical standards**

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**Human and animal rights and Informed consent** All procedures followed were in accordance with ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study.

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