CHEST

Reduced Cardiovascular Morbidity in Obesity-Hypoventilation Syndrome

An Ischemic Preconditioning Protective Effect?

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The resemblance between obese sleepy patients and Joe, the sleepy character in Dickens's book *The Pickwickian Papers* was first alluded to in the medical literature toward the end of the 19th century. Monitoring respiration in Pickwickian patients during sleep uncovered repeated apneic episodes causing intermittent hypoxia and sleep fragmentation which led to the description of OSA.[1] Since then, it has been established that despite similar presenting symptoms and patterns of sleep-disordered breathing, some Pickwickian patients also have chronic daytime hypoventilation. These patients are designated as having obesity-hypoventilation syndrome (OHS) that is distinctly different than OSA. OHS is defined by the presence of daytime hypercapnia ($PA_{CO_2} \geq 45$ mm Hg), sleep-disordered breathing, and obesity (BMI ≥ 30 kg/m^2), after exclusion of all other possible causes of chronic hypercapnia.[2] However, the diagnostic criteria of OHS, particularly with respect to the necessity of sleep-disordered breathing and hypercapnia, are still controversial.[3]

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In comparison with eucapnic obese, OHS is associated with impaired endothelial function and inflammation[4] and a high rate of morbidities and mortality.[5,6] Because it is well-documented that OSA by itself is also associated with significant endothelial dysfunction, cardiovascular morbidity (CVM), and increased mortality, particularly in relatively younger patients,[7] it could be assumed that OHS patients who also suffer from severe OSA would be at a higher risk of CVM than OHS patients with no or milder forms of OSA.

In this issue of *CHEST*, Masa et al[8] examine this hypothesis by investigating the association between the severity of OSA and CVM in patients with OHS by performing a cross-sectional analysis of baseline data of 302 patients with OHS participating in a multicenter study that compared the efficacy of three types of OHS treatments. CVM was defined as the presence of any of the following: ischemic cardiomyopathy, chronic heart failure, stroke, pulmonary hypertension, cardiac arrhythmia, and leg arteriopathy. Based on 3% oxygen desaturation index (ODI) tertiles, patients were divided into three OSA severity groups, and the prevalence of a single CVM and groups of CVM were compared between groups.

Surprisingly, the results did not support a worsening effect of OSA on OHS. On the contrary, there was an inverse relationship between the prevalence of CVM and OSA severity. With the exception of ischemic heart disease, the most severe ODI tertile had the lowest prevalence of pulmonary hypertension, stroke, arrhythmia, chronic heart failure, and leg arteriopathy. Of note, chronic heart failure had the strongest inverse relationship with ODI (23.5% vs 8.1%, in the lowest and highest ODI tertiles, respectively) and was the only single variable that reached statistical significance. Patients in the most severe ODI group and the least CVM were younger, predominantly male, more obese, sleepier, and had worse nocturnal and daytime gas exchange. But they had a lower prevalence of hypertension, better exercise tolerance, and fewer hospitalization days than the lowest OSA severity group. Logistic regression analysis performed with three adjustment models revealed significant differences

between the most severe and the least severe ODI groups. Adjusting for age and medical treatment did not affect the results. However, significance was lost in all three models once chronic heart failure was removed from the analysis. Similar results were obtained when analysis was repeated using ODI and apnea-hypopnea index as continuous variables.

Even assuming that the pathophysiology of the OHS-related hypoventilation is distinctly different than in the pure OSA, it is difficult to explain why the added burden of severe intermittent hypoxia in OHS was associated with reduced CVM. Of note, the most severe ODI group had a mean ODI of 95.8 and spent 72.7% of total sleep time with an oxygen saturation < 90% and had a mean oxygen saturation of 83.3% compared with 18.2, 58.9%, and 87.7%, respectively, in the least severe group. After excluding the possibility that the results could be accounted for by the younger age of the most severe patients, which could imply early diagnosis and treatment, the authors suggest that the inverse relationship between OSA severity and CVM in OHS might be explained by the protective effect of "ischemic preconditioning." This adaptive mechanism, in which brief repeated sublethal ischemia and reperfusion episodes confer profound protection from the occurrences of an acute lethal ischemia/reperfusion episode such as in acute myocardial infarction (AMI), was first demonstrated in the cardiovascular system,[9] and then was shown to occur in other organs including skeletal muscles, gut, brain, and the liver.[10] In 2006, Lavie and Lavie[11] hypothesized that the cycles of apneic events in OSA that resemble cycles of ischemia/reperfusion could exert protective effects from more severe ischemic events similar to ischemic preconditioning. Currently, accumulated evidence supports the Lavies' ischemic preconditioning hypothesis in OSA. For instance, patients with sleep apnea were shown to have age decline mortality rates,[12] and paradoxically increased longevity of elderly patients was documented in comparison with mortality rates in the general population.[13] Additionally, lower postoperative mortality rates and less recurrent CVD events were reported in comparison with those without apnea, suggesting again that OSA may confer some protection against CVM.[14] Moreover, evidence that patients with OSA and total coronary occlusion have more coronary collaterals than patients with similar occlusions but without OSA,[15] and that OSA patients after an AMI have more functional endothelial progenitors cells than patients with AMI without OSA,[16] may provide clues to some of the underlying mechanisms responsible for this protection. The Spanish results should be replicated in a well-planned study, preferably with age-matched groups, before accepting the conclusion that OSA may exert some protective effects in OHS. However, in view of the potentially important clinical implications of the present results regarding treatment and treatment prioritizing in OHS as well as in OSA patients, further research is urgently needed.

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Protective Cardiovascular Effect of Sleep Apnea Severity in Obesity Hypoventilation Syndrome

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BACKGROUND: Obesity hypoventilation syndrome (OHS) is associated with a high burden of cardiovascular morbidity (CVM) and mortality. The majority of patients with OHS have concomitant OSA, but there is a paucity of data on the association between CVM and OSA severity in patients with OHS. The objective of our study was to assess the association between CVM and OSA severity in a large cohort of patients with OHS.

METHODS: In a cross-sectional analysis, we examined the association between OSA severity based on tertiles of oxygen desaturation index (ODI) and CVM in 302 patients with OHS. Logistic regression models were constructed to quantify the independent association between OSA severity and prevalent CVM after adjusting for various important confounders.

RESULTS: The prevalence of CVM decreased significantly with increasing severity of OSA based on ODI as a continuous variable or ODI tertiles. This inverse relationship between OSA severity and prevalence of CVM was seen in the highest ODI tertile and it persisted despite adjustment for multiple confounders. Chronic heart failure had the strongest negative association with the highest ODI tertile. No significant CVM risk change was observed between the first and second ODI tertiles. Patients in the highest ODI tertile were younger, predominantly male, more obese, more hypersomnolent, had worse nocturnal and daytime gas exchange, lower prevalence of hypertension, better exercise tolerance, and fewer days hospitalized than patients in the lowest ODI tertile.

CONCLUSIONS: In patients with OHS, the highest OSA severity phenotype was associated with reduced risk of CVM. This finding should guide the design of future clinical trials assessing the impact of interventions aimed at decreasing cardiovascular morbidity and mortality in patients with OHS.

TRIAL REGISTRY: Clinicaltrial.gov; No.: NCT01405976; URL: www.clinicaltrials.gov

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ABBREVIATIONS: 6-MWD = 6-min walk distance; AHI = apnea hypopnea index; CVM = cardiovascular morbidity; EPAP = expiratory positive airway pressure; NIV = noninvasive ventilation; ODI = oxygen desaturation index; OHS = obesity hypoventilation syndrome; SpO_2 = oxygen saturation by pulse oximetry

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Nowadays, obesity affects more than one-third of the adult population, with an increase in the prevalence of severe obesity (BMI $\geq$ 40 kg/m^2). Obesity hypoventilation syndrome (OHS) is characterized by obesity and chronic hypercapnic respiratory insufficiency in the absence of other causes of hypoventilation, such as neuromuscular, metabolic, lung, or chest wall diseases.[1] The majority of patients with OHS (90%) have concomitant OSA.[2] However, in approximately 10% of patients with OHS, nocturnal alveolar hypoventilation may be the only respiratory sleep disorder.

The prevalence of OHS in the general population is unknown, although it has been estimated to be 0.3% to 0.4%.[3] Cardiovascular morbidity (CVM) is more prevalent in OHS than in patients with eucapnic OSA[4,5] and in eucapnic obese.[6,7] In addition, patients with OHS are at greater risk of hospitalization and death,[6-11] likely as a result of CVM.[4,12]

The association between eucapnic OSA and CVM has been well established.[13-15] Surges in sympathetic activity and intermittent hypoxemia associated with repetitive obstructive events during sleep have been postulated in the pathogenesis of CVM in patients with OSA.[16] Patients with OHS are also exposed to surges in sympathetic activity and intermittent hypoxemia by virtue of having OSA. However, in contrast to OSA, which is characterized by intermittent hypoxemia during sleep, patients with OHS also experience chronic sustained hypoxemia and hypercapnia during wakefulness, which may further increase the risk of CVM.[11,17]

Because the prevalence of CVM is increased in both OSA and OHS, it is clinically relevant to assess whether the risk of CVM is similar in the two main phenotypes of OHS: those with predominantly nocturnal hypoventilation vs patients with OHS who have nocturnal hypoventilation and significant OSA. Surprisingly, there is a paucity of studies assessing the association between CVM and OSA severity in OHS; we therefore sought to characterize the risk of CVM in a large cohort of patients with OHS according to the severity of OSA.[18]

Methods

Patients

From May 2009 to March 2013, we screened consecutive patients between 15 and 80 years of age who were referred for pulmonary consultation for suspected OHS or OSA at 16 tertiary care hospitals in Spain with the main objective to assess, in a randomized controlled trial, the comparative efficacy of noninvasive ventilation (NIV), CPAP, and lifestyle modification[18] (e-Appendix 1, e-Fig 1). OHS was defined as obesity with BMI $\geq$ 30 kg/m^2 plus stable hypercapnic respiratory failure during wakefulness ($PaCO_2$ $\geq$ 45 mm Hg, pH $\geq$ 7.35, and no clinical worsening during the previous 2 months) and no evidence of COPD (FEV_1 > 70% of predicted combined with FEV_1/FVC > 70), neuromuscular, chest wall, or metabolic disease. Other inclusion criteria were an absence of narcolepsy or restless legs syndrome, and a correctly executed 30-min CPAP/NIV treatment test (e-Appendix 1). The exclusion criteria were: (1) a psycho-physical inability to complete questionnaires, (2) severe chronic debilitating illness, (3) severe chronic nasal obstruction, and (4) lack of informed consent. The study was approved by the ethics committees of the 16 centers (e-Table 1) and written informed consent was obtained from all patients.

In the present cross-sectional analysis, we used data obtained during the baseline evaluation of 302 patients enrolled in the randomized controlled trial.

Outcomes

At baseline, we assessed arterial blood gases while breathing room air (e-Appendix 1), anthropometric data, comorbidities obtained from medical records performed by specialist, Framingham's risk score, dyspnea based on the Medical Research Council scale,[19] sleepiness on the Epworth sleepiness scale, all causes of hospital admissions and days in hospital in the previous year (obtained from patient's interview and from official database of the health system using the electronic medical record system), polysomnography, spirometry, and 6-min walk distance (6-MWD) test following standard recommendations.[20]

CVM: The primary outcome of the study was to estimate the independent risk of prevalent CVM in patients with OHS. CVM was defined as the presence of any of the following comorbidities: ischemic cardiomyopathy, chronic heart failure, stroke, pulmonary hypertension, cardiac arrhythmia, and leg arteriopathy.

Polysomnography: We used standard protocols to perform the polysomnography and analyze the results (e-Appendix 1).

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Statistical Analysis

Data management and statistical analyses were performed using SPSS software (IBM SPSS Statistics, version 22.0). Missing data imputation was not carried out because less than 5% of missing data was observed in each variable.

We first examined the prevalence of CVM in patients with OHS based on the severity of OSA. We chose 3% oxygen desaturation index (ODI) over apnea hypopnea index (AHI) and arousal index as marker of OSA severity because this variable is a reliable and a reproducible marker of intermittent hypoxemia and it was the most strongly associated with CVM. To better characterize subgroups of OHS, we chose to use tertiles of ODI based on its distribution. If there was a significant unadjusted association between ODI tertiles and CVM risk using an unadjusted logistic regression, we constructed logistic regression models to estimate adjusted risk of all CVM as well as any single CVM. To demonstrate that ODI is a reasonable metric of OSA severity in our cohort of patients with OHS, we repeated the previously mentioned analysis using both ODI and AHI as continuous variables.

Recognizing that certain independent variables of interest can be highly correlated with each other, we used data from the literature as well as biologic plausibility to identify the variables best suited for the adjusted logistic regression model. Using Pearson correlation analysis, we examined the correlation between variables related to acid-base balance and CVM. Bicarbonate was more strongly associated with CVM than pH and $PaCO_2$ and therefore bicarbonate were entered as a covariate in the model. For anthropometric variables, we chose waist-to-hip ratio over BMI and neck circumference given that it is a well-recognized marker of abdominal obesity and abdominal obesity has been strongly associated with CVM.[21] In addition to ODI tertiles, bicarbonate, and waist-to-hip ratio, the model 1 also adjusted for age, sex, alcohol and tobacco consumption, presence of hypertension, diabetes, and dyslipidemia, Epworth sleepiness scale, PaO_2, and duration of sleep time below oxygen saturation by pulse oximetry (SpO_2) of 90%. Model 2 included all variables in model 1 plus 6-MWD. Model 3 included all variables in model 1 plus whether the patient was receiving pharmacotherapy for hypertension, diabetes, and dyslipidemia.

Using tertiles of ODI distribution, we also examined the prevalence of all and any CVM as well as groups of CVM. We performed group comparisons of baseline characteristics of patients based on the tertiles of ODI (t test for continuous or χ^2 test for categorical variables). To better characterize the third tertile of ODI, we identified variables associated with this tertile and the association degree among these same variables by Pearson correlation.

Results

Figure 1 shows the flowchart and Table 1 the characteristics of 302 patients included in the analysis. The mean age was 61 years with a female predominance. Most patients were morbidly obese with a high prevalence of CVM as well as hypertension, diabetes, and dyslipidemia. Most patients with OHS (73.2%) had severe OSA and significant hypoxemia.

With the exception of ischemic heart disease, the highest ODI tertile (third tertile) had the lowest prevalence of pulmonary hypertension, stroke, arrhythmia, chronic heart failure, and leg arteriopathy, although it reached statistical significance only in chronic heart failure (Table 2). Chronic heart failure had the strongest negative association with the highest ODI tertile (ie, the prevalence of heart failure was lowest in patients in the highest ODI tertile) (Fig 2A). When CVMs were analyzed as a group, the three models of adjusted analysis were statistically significant for at least one CVM group, after including or excluding pulmonary hypertension, stroke, ischemic heart disease, arrhythmias, and leg arteriopathy (Table 2 and Fig 2B). However, when we excluded chronic heart failure the statistical significance of at least one CVM was lost in all three models (Table 2). No statistical significance was found for any analysis between the first (reference) and second ODI tertiles.

Figure 3 shows the association between CVM risk and OSA severity based on AHI and ODI as continuous variables. Although ODI showed slightly stronger association than AHI, both variables had statistically significant associations with CVM risk for unadjusted and adjusted analysis.

Table 3 summarizes patient characteristics grouped by ODI tertiles. Patients in the highest ODI tertile were

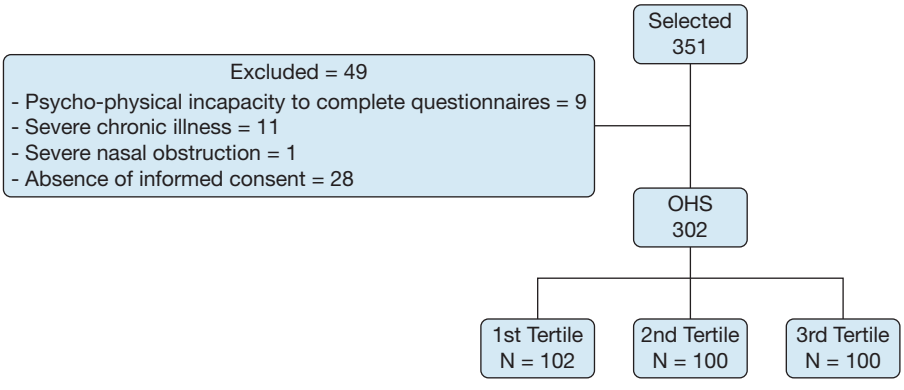

Figure 1 – *Flow chart of the study. The first tertile had a mean oxygen desaturation index (ODI) of 18 ± 8.2 and a range of 0.3-32; the second tertile had a mean ODI of 53 ± 12.0 and a range of 33-73; and the third tertile had a mean ODI of 96 ± 15 and a range of 73-140. OHS = obesity hypoventilation syndrome.*

TABLE 1] Baseline Characteristics and Polysomnographic Parameters of Patients With OHS

	N = 302
Age, y, mean (SD)	61.7 (12.3)
Sex, female, %	61.9
Smokers, %	26.5
Smoking, pack/y, mean (SD)[a]	34.7 (24.8)
Drinkers, %	16.9
Alcohol, g, mean (SD)[a]	38.4 (31.0)
BMI, kg/m^2 mean (SD)	42.8 (7.0)
Neck circumference, cm, mean (SD)	44.1 (4.6)
Waist-to-hip ratio, mean (SD)	0.982 (0.100)
ESS, mean (SD)	10.2 (5.1)
Dyspnea MRC scale, ≥ 2,%	50.5
Hypertension, %	71.1
Antihypertensive drugs, number, mean (SD)[a]	1.7 (0.9)
Systolic BP, mm Hg, mean (SD)	137.3 (16.2)
Diastolic BP, mm Hg, mean (SD)	78.9 (12.2)
Diabetes, %	37.4
Antidiabetes medications, %	36.1
Dyslipidemia, %	43.9
Pharmacologic treatment of dyslipidemia, %	35.1
Stroke, %	8.4
Ischemic heart disease, %	10.0
Arrhythmia, %	8.7
Chronic heart failure, %	17.3
Leg arteriopathy, %	8.7
Pulmonary hypertension, %	10.4
At least 1 CVM, %	39.7
CVM, mean (SD)	0.6 (0.9)
Framingham risk, mean (SD)	11.9 (9.2)
pH, mean (SD)	7.401 (0.034)
PaO_2, mm Hg, mean (SD)	62.9 (9.5)
$PaCO_2$, mm Hg, mean (SD)	50.5 (4.3)
Bicarbonate, mmol/L, mean (SD)	30.1 (3.3)
FEV_1, %, mean (SD)	77.5 (19.6)
FVC, %, mean (SD)	78.8 (20.6)
6-MWD, m, mean (SD)	347.7 (121.4)
Hospital admission in the previous y, %	47
Days in hospital in the previous y, mean (SD)	5.8 (8.9)
Polysomnographic parameters	
TST, h, mean (SD)	5.4 (1.3)
Sleep efficiency, %, mean (SD)	71.5 (16.3)
Light sleep, %, mean (SD)	79.5 (14.9)
Deep sleep, %, mean (SD)	10.9 (12.3)
REM sleep, %, mean (SD)	9.7 (9.4)
Arousal index, mean (SD)	49.8 (31.8)
Apnea index, mean (SD)	30.7 (32.1)
Hypopnea index, mean (SD)	24.9 (25.0)
AHI, mean (SD)	55.5 (35.0)
AHI < 30, %	26.8
AHI 30-64.9, %	31.8
AHI > 65, %	41.4
ODI, mean (SD)	55.5 (34.0)
Mean SpO_2, %, mean (SD)	85.2 (6.1)
Percent of TST with SpO_2 < 90%, mean (SD)	66.9 (30.9)

6-MWD = 6-min walk distance; 6-SpO_2 = oxygen saturation by pulse oximetry; AHI = apnea hypopnea index; CVM = cardiovascular morbidity; EES = Epworth sleepiness scale; MRC = Medical Research Council; ODI = 3% oxygen desaturation index; TST = total sleep time.
[a]Includes only patients who reported to be active smokers or drinkers or patients with hypertension.

younger, predominantly male, more obese, had higher levels of sleepiness and OSA severity, worse gas exchange, lower prevalence of hypertension, better exercise tolerance and fewer days hospitalized than patients in the lowest ODI tertiles (Fig 4 and e-Fig 2). Similar differences were found between second and third ODI tertiles except for hypertension prevalence and daytime PaO_2. The third ODI tertile had lower hospital admission than the second tertile (Fig 3). First and second ODI tertiles were only dissimilar in variables related to OSA severity. Figure 5 illustrates variables that are either negatively or positively associated with the highest tertile (third tertile) as well as the degree and direction of the association.

e-Figure 3 illustrates the population pyramid in each of the three tertiles. The patients in the highest tertile of ODI had a more uniform distribution of age with younger patients in comparison with patients in the lower tertiles of ODI.

Discussion

This is the first and the largest study examining the association between OSA severity and CVM in a cohort of patients with OHS. Our main findings were: (1) OSA severity was associated with a lower risk of CVM; (2) this association was statistically significant between the first and third ODI tertiles but not between

TABLE 2] Adjusted and Unadjusted Association of Cardiovascular Morbidity With Tertiles of Oxygen Desaturation Index for Each CVM and Several Groups

	ODI		OR (95% CI) Model 1	OR (95% CI) Model 2	OR (95% CI) Model 3
	Tertiles First Second Third	Unadjusted *P* Value	Tertiles Reference Second Third	Tertiles Reference Second Third	Tertiles Reference Second Third
PH, %	12.2 13.3 6.1	.218	…	…	…
Stroke, %	11.5 9.1 5.1	.282	…	…	…
IHD, %	7.1 16.3 7.1	.055	…	…	…
Arrhythmia %	11.2 12.1 3.0	.069	…	…	…
CHF, %	23.5 21.2 8.1	.013	1 0.723 (0.333-1.566) **0.286 (0.106-0.769)**[a]	1 0.823 (0.342-1.982) **0.335 (0.115-0.979)**[a]	1 0.713 (0.328-1.546) **0.293 (0.109-0.787)**[a]
LA, %	14.4 7.1 5.1	.062	…	…	…
At least one heart disease, %	32.7 36.7 14.1	.001	1 1.169 (0.596-2.290) **0.348 (0.153-0.792)**[b]	1 1.022 (0.480-2.178) **0.344 (0.142-0.833)**[a]	1 1.164 (0.593-2.283) **0.352 (0.154-0.802)**[b]
Classical CVM, %	38 44 18	.002	1 2.093 (0.924-4.741) **2.627 (1.200-5.754)**	1 2.108 (0.873-5.092) **2.529 (1.093-5.848)**	1 2.041 (0.900-4.628) **2.547 (1.159-5.593)**
CVM, %	47.4 44.9 24.2	.002	1 0.863 (0.452-1.644) **0.383 (0.185-0.794)**[b]	1 0.763 (0.368-1.582) **0.388 (0.175-0.861)**[a]	1 0.855 (0.447-1.636) **0.387 (0.186-0.805)**[a]
CVM without PH, %	43.2 41.8 19.2	.001	1 0.969 (0.507-1.854) **0.345 (0.162-0.735)**[b]	1 0.918 (0.442-1.908) **0.352 (0.155-0.797)**[a]	1 0.968 (0.503-1.862) **0.351 (0.164-0.752)**[b]
CVM without stroke, %	46.4 40.8 22.2	.001	1 0.739 (0.386-1.417) **0.333 (0.158-0.699)**[b]	1 0.647 (0.309-1.355) **0.342 (0.152-0.771)**[b]	1 0.733 (0.381-1.408) **0.336 (0.160-0.706)**[c]
CVM without IHD, %	47.4 37.8 20.2	.000	1 0.612 (0.322-1.165) **0.273 (0.129-0.577)**[c]	1 0.552 (0.266-1.144) **0.276 (0.123-0.624)**[c]	1 0.604 (0.316-1.155) **0.276 (0.130-0.585)**[c]
CVM without Arrhyth., %	46.3 42.9 23.2	.002	1 0.804 (0.420-1.540) **0.370 (0.177-0.775)**[b]	1 0.720 (0.346-1.500) **0.374 (0.166-0.832)**[a]	1 0.794 (0.413-1.528) **0.373 (0.178-0.785)**[b]
CVM without CHF, %	37.9 38.8 21.2	.014	1 1.114 (0.578-2.147) 0.565 (0.267-1.193)	1 1.023 (0.491-2.131) 0.583 (0.261-1.301)	1 1.104 (0.572-2.131) 0.570 (0.270-1.203)
CVM without LA, %	34.7 39.4 19.2	.007	1 1.104 (0.565-2.159) **0.449 (0.205-0.983)**[a]	1 1.008 (0.477-2.129) **0.423 (0.182-0.997)**[a]	1 1.101 (0.562-2.153) **0.452 (0.206-0.990)**[a]

P values of reference vs tertile 3 are in bold. Model 1 = covariates included age, sex, hypertension, diabetes, dyslipidemia, alcohol, tobacco, waist-to-hip ratio, Epworth sleepiness scale, PaO_2, bicarbonate and sleep time with $SpO_2 < 90\%$. Model 2 included all covariates in model 1 plus 6-min walk distance. Model 3 included all covariates in model 1 plus treatment (yes or no) for hypertension, diabetes, and dyslipidemia. CHF = chronic heart failure; classical CVM = stroke or ischemic heart disease or chronic heart failure; IHD = ischemic heart disease; LA = leg arteriopathy; PH = pulmonary hypertension. See Table 1 legend for expansion of other abbreviations.

[a] < .05.

[b] < .01.

[c] < .001.

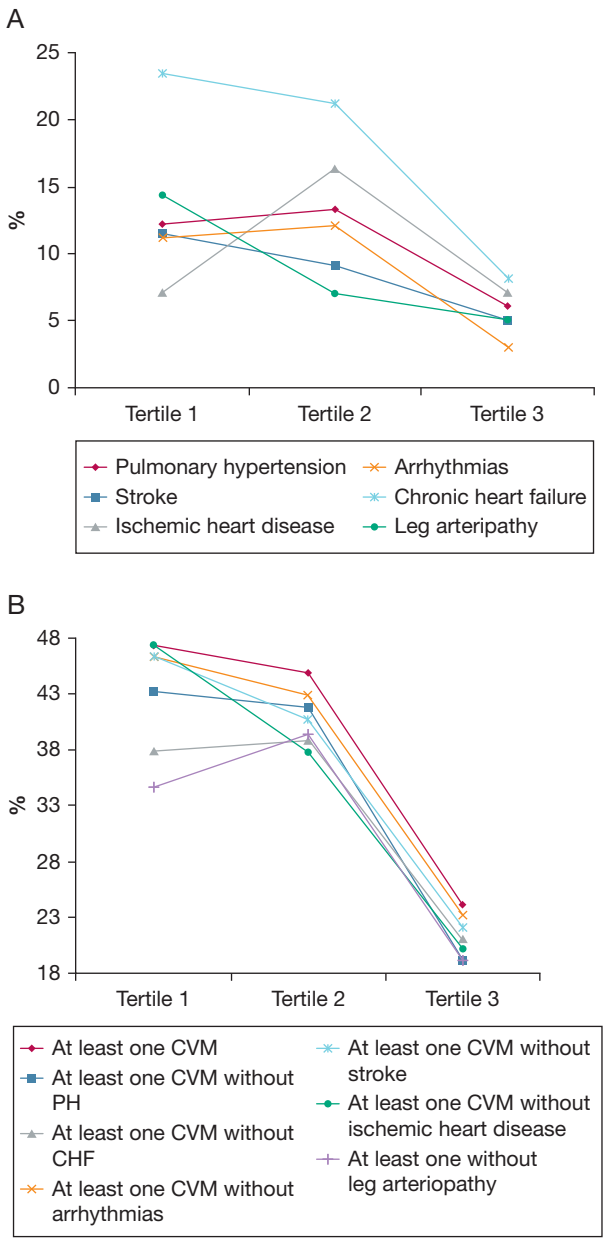

Figure 2 – *Prevalence of CVM according to tertiles of oxygen desaturation index. (A) Disease-specific analysis. (B) Analysis according to clusters of CVM. CVM = cardiovascular morbidity.*

the first and second ODI tertiles; and (3) the largest difference between the lowest and highest tertile of ODI was observed in the prevalence of chronic heart failure (23.5% vs 8.1%, respectively).

Several studies have reported that compared with the general population or patients with eucapnic OSA, patients with OHS have a higher prevalence of CVM, hypertension, diabetes, and dyslipidemia.[4-7] Moreover, the high mortality observed in patients with untreated OHS has been partly attributed to CVM.[9,11] Although we found the strongest negative association to be between highest ODI tertile and chronic heart failure, a negative association was also present with all CVM except ischemic heart disease. Chronic heart failure may have had the strongest negative association with ODI in part because it was the most frequent CVM in our cohort and in other OHS cohorts.[7,22,23]

Our data suggest that in patients with OHS, different phenotypes according to OSA severity (Table 3) result in different CVM risk. Patients in the highest ODI tertile were younger, predominantly male, more obese, had higher levels of sleepiness and OSA severity, worse nocturnal and daytime gas exchange, lower prevalence of hypertension, better exercise tolerance, and had fewer days hospitalized than patients in the lowest ODI tertile (Table 3 and e-Fig 2). However, there were no clear phenotypic differences between the second and first ODI tertiles, and these groups had similar CVM risk. This difference in CVM risk may be pertinent because it can allow stratification of patients with OHS for future trial design and clinical practice. Our finding of reduced hospital resource utilization in the prior year for highest ODI tertile adds more credence to this argument.

Although the first and second tertiles have similar phenotypic characteristics and CVM risk, the importance of the first ODI tertile (OHS without severe OSA) in our results cannot be undervalued. If we restrict the analysis to patients with ODI $>$ 5, unadjusted and adjusted association between CVM risk and OSA severity persists. However, if we restrict the analysis to patients in the second and third ODI tertiles, the association is present in the unadjusted but not in the adjusted models, emphasizing the importance of this population in our results. In fact, this last result did not occur if we only analyzed the first and third tertiles. Because our analysis using ODI and AHI as continuous variables suggests that there is a dose-response relationship, the second ODI tertile group may be considered as an intermediate CVM risk group between patients without severe OSA and extreme severity of OSA.

The protective effect of OSA severity on prevalent CVM is clearly surprising. From a pathophysiologic perspective, OSA increases arteriosclerotic diseases[24,25] and the association between untreated severe OSA and increased cardiovascular morbidity and mortality, particularly in individuals younger than 50 years of age, has been well demonstrated in several observational cohorts.[13,14,26] Our subset of patients with OHS with

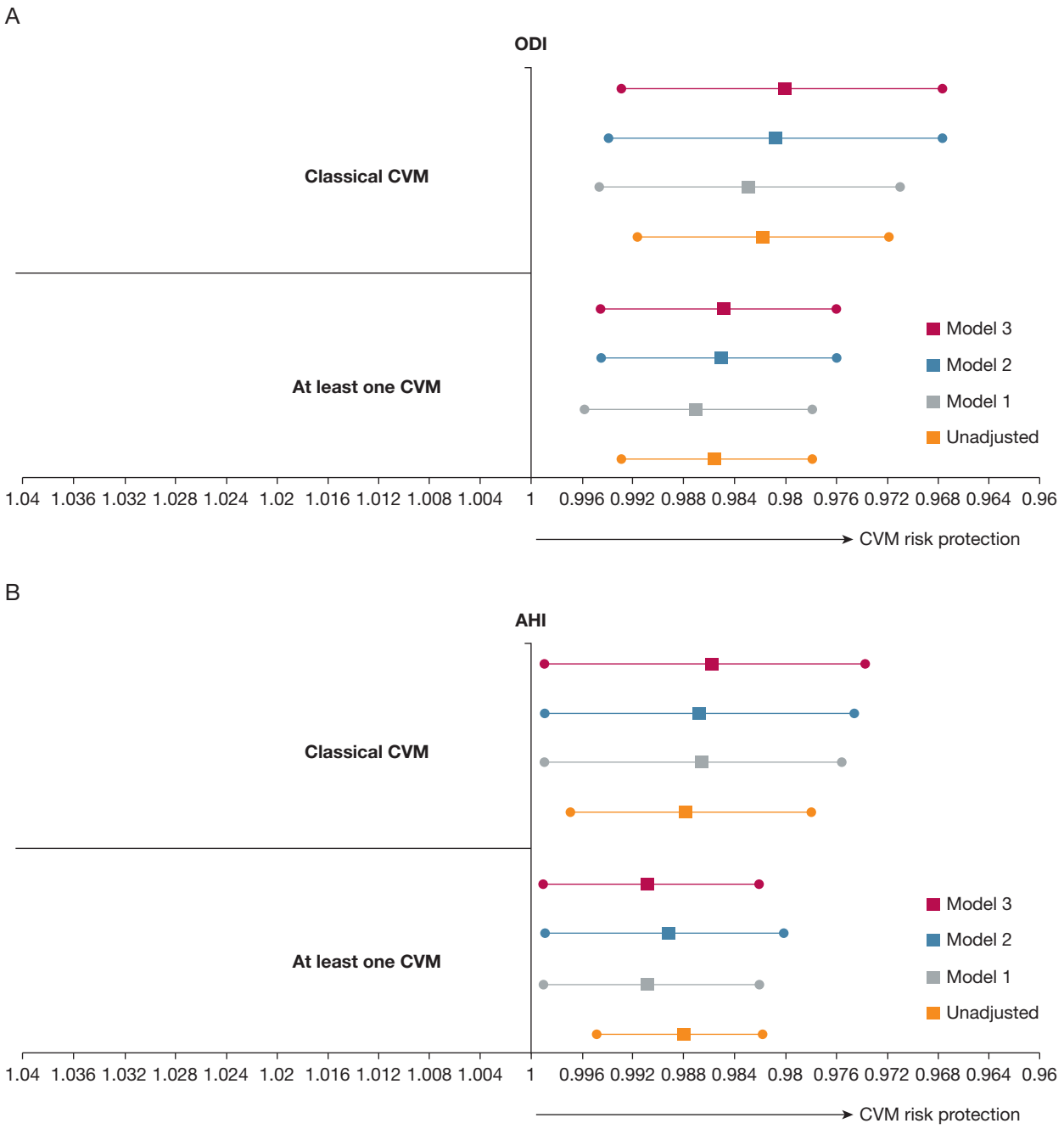

Figure 3 – *OR and 95% CI of CVM risk according to (A) ODI and (B) AHI, as continuous variables, for unadjusted and three adjusted analysis (model 1 included the following covariates: age, sex, hypertension, diabetes, dyslipidemia, alcohol, tobacco, waist-to-hip ratio, Epworth sleepiness scale, PaO_2, bicarbonate, and sleep time with SpO_2 lower than 90%; model 2 included all covariates in model 1 plus 6-min walk distance; model 3 included all covariates in model 1 plus treatment [yes or no] for hypertension, diabetes, and dyslipidemia). The analysis was carried out for "classical" CVM (stroke or ischemic heart disease or chronic heart failure) and at least one CVM. AHI = apnea hypopnea index. See Figure 1 and 2 legends for expansion of other abbreviations.*

more severe OSA (third ODI tertile) had several characteristics that would predispose them to increased risk of CVM such as male predominance, higher obesity, higher level of subjective sleepiness, and worse degrees of hypercapnia and hypoxemia. On the other hand, this highest tertile had several characteristics that could reduce the prevalence of CVM such as younger age, lower prevalence of hypertension, and higher 6-MWD. However, in the regression models, none of these variables fully explained the protective effect of the highest level of OSA severity. High 6-MWD has been associated with reduced CVM[27] and, although it was an independent protective factor for CVM, its inclusion or exclusion in the models did not mediate the protective

TABLE 3] Patient Characteristics According to Tertiles of ODI

	First Tertile N = 102	Second Tertile N = 100	Third Tertile N = 100	*P* Value
Age, y, mean (SD)	64.1 (11.3)	63.9 (10.8)	56.6 (13.2)	.000[a,b]
Sex, female, %	72.0	66.7	47.5	.001[a] .010[b]
Smoking, pack/y, mean (SD)	17.3 (27.0)	16.5 (21.6)	15.9 (21.2)	NS
Alcohol, g, mean (SD)	4.4 (12.9)	8.0 (19.9)	6.39 (22.5)	NS
BMI, kg/m^2, mean (SD)	41.1 (6.0)	42.1 (7.0)	45.4 (7.3)	.000[a] .001[b]
Neck circumference, cm, mean (SD)	43.0 (4.6)	43.8 (3.9)	45.7 (4.9)	.000[a] .003[b]
Waist-to-hip ratio, mean (SD)	0.980 (0.102)	0.975 (0.200)	0.987 (0.097)	NS
ESS, mean (SD)	9.8 (5.0)	9.4 (5.1)	11.3 (5.0)	.038[a] .009[b]
Dyspnea MRC scale ≥ 2,%	58.2	48.9	44.2	NS
Hypertension, %	77.8	72.7	63.6	.042[a]
Systolic BP, mm Hg, mean (SD)	135.9 (16.9)	139.1 (15.6)	136.9 (15.9)	NS
Diastolic BP, mm Hg, mean (SD)	78.8 (12.3)	78.2 (12.0)	79.6 (12.4)	NS
Diabetes, %	41.0	40.4	31.3	NS
Dyslipidemia, %	43.0	41.8	47.5	NS
CVM, mean (SD)	0.8 (0.9)	0.9 (1.1)	0.3 (0.7)	.001[a,b]
Framingham risk score, mean (SD)	10.8 (6.3)	13.5 (10.7)	11.2 (9.6)	NS
FEV_1, %, mean (SD)	77.7 (17.3)	75.3 (22.4)	79.4 (19.0)	NS
FVC, %, mean (SD)	80.3 (19.4)	76.3 (23.8)	79.9 (19.0)	NS
pH, mean (SD)	7.400 (0.282)	7.405 (0.038)	7.398 (0.0350)	NS
PaO_2, mm Hg, mean (SD)	65.1 (9.9)	62.7 (9.1)	61.1 (9.3)	.003[a]
$PaCO_2$, mm Hg, mean (SD)	49.8 (3.7)	51.1 (4.8)	50.7 (4.2)	.040[c]
Bicarbonate, mmol/L, mean (SD)	29.5 (2.7)	30.7 (3.5)	29.9 (3.7)	.008[c]
6-MWD, m, mean (SD)	335.6 (104.2)	328.8 (127.3)	376.3 (126.1)	.028[a] .008[b]
Hospital admission in the previous y, %	50	54	38	.032[b]
Days in hospital in the previous y, mean (SD)	6.4 (11)	6.5 (8.6)	3.6 (6.2)	.032[a] .020[b]
AHI, mean (SD)	25.1 (21.2)	51.8 (24.0)	89.9 (23.0)	.000[a,b,c]
Arousal index, mean (SD)	29.5 (22.4)	45.3 (23.3)	74.8 (30.6)	.000[a,b,c]
ODI, mean (SD)	18.2 (8.2)	52.9 (12.0)	95.8 (14.7)	.000[a,b,c]
Mean SpO_2, %, mean (SD)	87.7 (5.2)	84.7 (6.2)	83.3 (6.2)	.000[a,b]
Percent of TST with $SpO_2 < 90\%$, mean (SD)	58.9 (35.2)	69.1 (29.3)	72.7 (26.0)	.019[a] .002[b]

See Table 1 legend for expansion of abbreviations.
[a]*P* value comparison between tertiles 1 and 3
[b]*P* value comparison between tertiles 2 and 3.
[c]*P* value comparison between tertiles 1 and 2.

effect of OSA severity as measured by ODI tertiles. On the other hand, high 6-MWD may be simply more prevalent in patients with lower prevalence of CVM as opposed to conferring a real protective effect.

There are several alternative explanations for our findings. That patients in the highest severity of ODI tertiles were younger raises the possibility of survival bias. It is plausible that patients with OHS with very severe OSA died prematurely from fatal cardiovascular events.[28] However, in examining the age distributions of the tertiles (e-Fig 3), it becomes evident that the main difference between the third tertile of ODI and the two other tertiles was not a lower number of older patients, but an increase

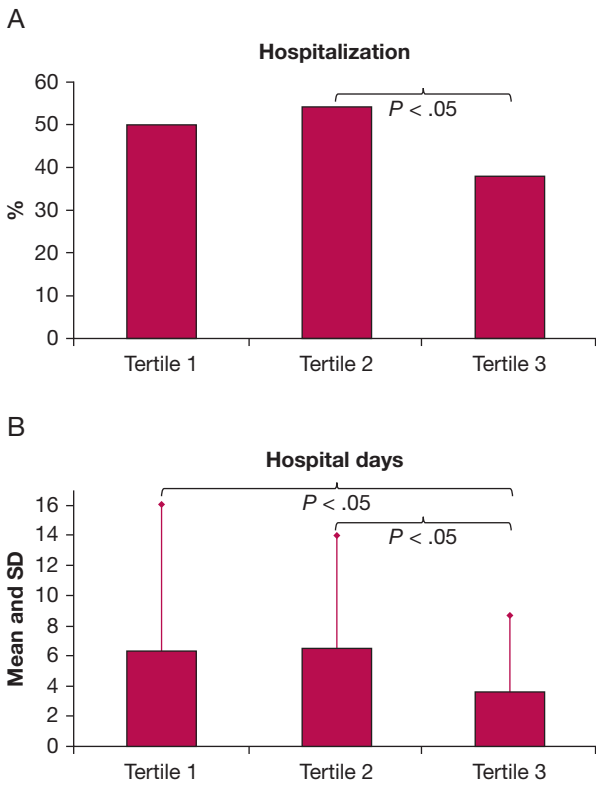

Figure 4 – *Percentage of patients with at least one (A) hospital admission in the previous year and mean and standard deviation of (B) hospital days in the same period according to ODI tertiles. See Figure 1 legend for expansion of abbreviation.*

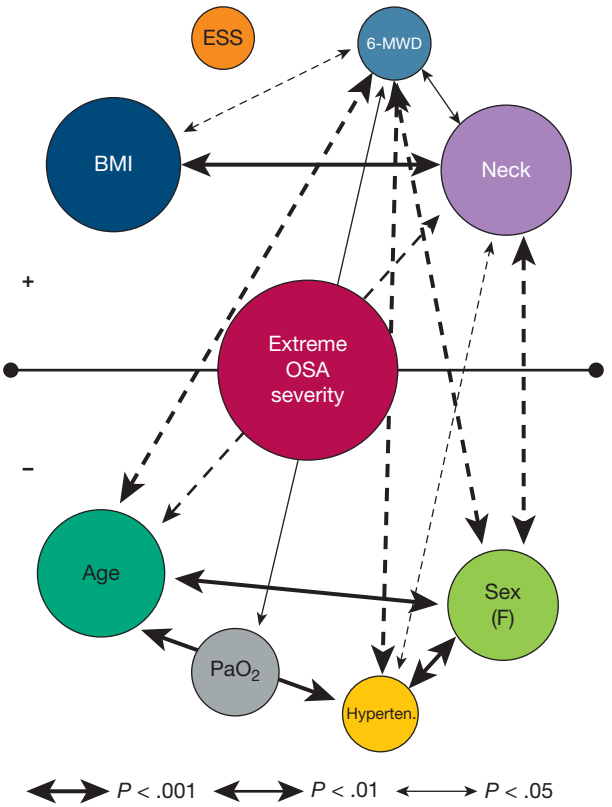

Figure 5 – *Extreme OSA severity phenotype network. The figure includes variables that were significantly associated with the highest tertile of ODI (extreme OSA severity phenotype). The size of the circles represents the degree of the association. Circles located below the dark line are negatively associated with super-Pickwick group. In contrast, circles above the line are positively associated with super-Pickwick group. The size of the line represents the statistical significance of the correlation amongst the variables that are associated with the highest ODI tertile (ie, P < .001 between BMI and neck circumference); solid and broken lines represent the positive or negative association, respectively. 6-MWD = 6-min walking distance test; ESS = Epworth sleepiness scale; F = female; hyperten = hypertension; neck = neck circumference. See Figure 1 legend for expansion of other abbreviations.*

in younger patients with OHS. This is probably the cause of the lower age in the third tertile. On the other hand, the same fact raises the possibility that patients in the highest ODI tertile came to medical attention at an earlier age, perhaps because of the more severe obesity and higher levels of snoring and sleepiness observed in this group. If patients in the third tertile of ODI sought medical attention earlier in the course of their disease and were started on medications for common comorbidities observed in obese patients with severe OSA (eg, hypertension, diabetes, dyslipidemia), it may have led to a reduction in their overall prevalence of CVM. However, adjusting for pharmacologic treatment of hypertension, diabetes, and dyslipidemia in the models did not modify the protective effect of OSA severity (Table 2).

Another invoked putative mechanism by which OSA could decrease mortality is by ischemia preconditioning. Lavie and colleagues[26] have reported lower rates of mortality in patients with OSA older than 50 years of age compared with younger patients and general population[29] with similar OSA severity, which led them to hypothesize that ischemic preconditioning phenomenon with repeated sublethal ischemia leads to angiogenic stimulation.[26,30-35] Studies have reported that in patients with acute myocardial infarction, those with OSA and intermittent hypoxemia during sleep have less severe cardiac injury, better coronary collateral circulation, and better angiogenic promotion.[36-38] Ischemic preconditioning seems to occur more readily with sustained hypoxemia than intermittent hypoxemia.[39] Patients with OHS included in the highest tertile of ODI had the combination of highest intermittent and sustained hypoxemia, which may have resulted in a more robust protective mechanism achieving better tissue perfusion vis-à-vis increasing collateral circulation. Our findings are in line with recent report from the Sleep Heart Health Study, which demonstrated a reduction in recurrent coronary heart events with increasing OSA severity[37] and from Aronson et al,[40] showing a lack of detrimental long

term effect of OSA in patients with acute myocardial infarction.

The overall pattern of CVM observed in our cohort is that the prevalence was similar between first and second ODI tertiles and a significant reduction of CVM prevalence in the third tertile of ODI. The only exception was ischemic heart disease (Table 2). Relative to the first tertile of ODI, the prevalence of ischemic heart disease doubled in the second tertile of ODI. However, in the third tertile of ODI the prevalence of CVM was similar to the first tertile. The lack of a clear dose response relationship between ODI and ischemic heart disease remains unclear. However, our findings are consistent with several studies reporting a lack of association between severity of OSA (measured either by AHI or ODI) and adverse outcomes after ischemic cardiac events.[30,36,37,40]

Although obesity, increased sympathetic activity, and chronic hypoxemia and hypercapnia can increase the risk of left and right ventricular dysfunction,[41,42] it is plausible that improved myocardial perfusion as a result of ischemic preconditioning could be the reason behind lower CVM prevalence and reduced risk of chronic heart failure observed in our cohort.

ODI has been shown to be a sensitive marker of OSA in eucapnic populations. In the patients in our study with OHS, the level of hypoxemia can cause a shift in the oxyhemoglobin dissociation curve and the 3% ODI could be produced by much more subtle changes in ventilation rendering it an inadequate marker of OSA severity. However, ODI and AHI had similar association with CVM risk. Therefore, ODI was a reasonable marker of OSA severity in our OHS population.

Our study has several limitations. First, the present analysis was performed in a cohort of patients with OHS enrolled in a randomized controlled trial designed to determine the efficacy of different treatment alternatives in patients with OHS. Although we enrolled consecutive patients across several participating centers, our inclusion and exclusion criteria may have led to some selection bias and may therefore not be reflective of "real-life" patients with OHS seen in clinical practice; nevertheless, it should affect similarly to the three tertiles. Second, the diagnosis of CVM was performed by clinical specialists and extracted from medical records in the health system databases. Although we did not adjudicate every single diagnoses of CVM, it is unlikely that there was a systematic bias because it would have similarly affected all three groups of ODI. Third, although the vast majority of enrolled patients had severe OSA leading to a high ODI, patients in our study were sequentially screened; therefore, we believe our sample is representative of patients with OHS. Finally, the current analysis is cross-sectional in nature and precludes any inferences on the direction of causality. Nonetheless, it provides the opportunity to generate important hypotheses to test in future longitudinal studies. Specifically, further research is needed to understand whether the impact of CPAP or NIV therapy on cardiovascular risk reduction in patients with OHS is similar regardless of the severity of OSA.

A recent study found lower unadjusted survival in patients with OHS without significant OSA in comparison with patients with OHS who also had significant OSA.[10] A longitudinal study of patients with OHS identified low levels of expiratory positive airway pressure (EPAP) during NIV (EPAP < 7 cm H_2O) as a significant and independent risk factor for cardiovascular mortality. Although the reason for low EPAP level remains unclear, we speculate that it was because OSA was less severe in patients with OHS requiring lower levels of EPAP.[4] Our finding is in line with these two studies and suggests that patients with OHS with less severe OSA are at increased risk of cardiovascular morbidity and mortality. These findings raise the question as to whether patients with OHS without extreme forms of OSA and lower daytime hypoxemia should be prioritized for treatment.

In summary, the risk of CVM in patients with OHS is distributed unequally according to OSA severity. In our cohort, CVM risk was significantly lower in the OHS phenotype with extreme OSA severity and worse nocturnal and daytime oxygenation level. This group was in general younger, predominantly male, more obese, with higher levels of daytime sleepiness, lower prevalence of hypertension better exercise tolerance, and fewer days hospitalized in the previous year. In contrast, in the OHS phenotype with less severe OSA, the degree of intermittent hypoxemia was not significantly associated with CVM risk. This finding should guide the design of future clinical trials assessing the impact of interventions aimed at decreasing cardiovascular morbidity and mortality in patients with OHS.

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Additional information: The e-Appendix, e-Figures, and e-Table can be found in the Supplemental Materials section of the online article.

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