Hyperlipidaemia prevalence and cholesterol control in obstructive sleep apnoea: Data from the European sleep apnea database (ESADA)

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Hyperlipidemia Prevalence and Cholesterol Control in Obstructive Sleep Apnea: Data from the European Sleep Apnea Database (ESADA)

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Running headline: Hyperlipidemia in sleep apnea

Abstract

Background and objective: Obstructive sleep apnea (OSA) and hyperlipidemia are independent risk factors for cardiovascular disease. This study investigates the association between OSA and prevalence of hyperlipidemia in patients of the European Sleep Apnea Database (ESADA) cohort.

Methods: The cross-sectional analysis included 11,892 patients (age 51.9±12.5 years, 70% male, body mass index (BMI) 31.3±6.6 kg/m^2, mean Oxygen Desaturation Index (ODI) 23.7±25.5 events/h) investigated for OSA. The independent odds ratio (OR) for hyperlipidemia in relation to measures of OSA (ODI, Apnea Hypopnea Index, mean and lowest oxygen saturation) was determined by means of General Linear Model analysis with adjustment for important confounders like age, BMI, comorbidities, and study site.

Results: Hyperlipidemia prevalence increased from 15.1% in subjects without OSA to 26.1% in those with severe OSA, p<0.001. Corresponding numbers in diabetic patients were 8.5% and 41.5%, p<0.001. Compared with ODI quartile I, patients in ODI quartiles II-IV had an adjusted OR (95% CI) of 1.33 (1.15-1.55), 1.37 (1.17-1.61), and 1.33 (1.12-1.58) (p <0.001), respectively, for hyperlipidemia. Obesity was defined as a significant risk factor for hyperlipidemia. Subgroups of OSA patients with cardio-metabolic comorbidities demonstrated higher prevalence of HL. In addition, differences in hyperlipidemia prevalence was reported in European geographical regions with the highest prevalence in central Europe.

Conclusion: OSA, in particular intermittent hypoxia, was independently associated with the prevalence of hyperlipidemia diagnosis.

Key words: cholesterol— hyperlipidemia—hypoxia—obesity—sleep apnea

Introduction

Obstructive sleep apnea (OSA) is a common disorder characterized by repeated episodes of apneas and hypopneas during sleep affecting at least 20% of male and 10% of female adults in the general population.[1,2] OSA is an independent risk factor for the incidence of cardiovascular disease.[1,3,4] Metabolic dysfunction also increases the risk for cardiovascular morbidities. Likewise, independent associations between OSA and impaired glycemic health and insulin resistance have also been reported [5–8] However, both the underlying mechanisms as well as the existence of an independent relationship between OSA and hyperlipidemia remains unclear.[9–11]

Experimental data suggested a potential causal role of OSA for the incidence of hyperlipidemia through pathophysiological mechanisms such as intermittent hypoxia (IH) together with elevated sympathetic activity, oxidative stress, systemic inflammation, and sleep fragmentation in patients with OSA.[8,12,13] Indeed, in the current study cohort we identified an independent correlation between cholesterol levels and OSA severity indices in individuals without a known history of hyperlipidemia.[14] However, systematic reviews summarizing the current epidemiological evidence came up with inconclusive results for an independent association between OSA and a hyperlipidemia diagnosis. [11,15]

The European Sleep Apnea Cohort (ESADA) study is a multicentre, multinational study which prospectively recruits patients investigated for suspected OSA in European sleep laboratories. The aim of the current analysis was to examine the relationship between the prevalance of diagnosed hyperlipidemia and the severity of OSA. It was hypothesized that OSA is associated with the diagnosis of hyperlipidemia; and that control of cholestrol in these patients despite pharmacological treatment is worse in patients with concomitant OSA. We addressed measures of central obesity and the ESADA study design allowed us to study potential geographical influences on the prevalence of hyperlipidemia in OSA patients.

Methods

The European Sleep Apnea Database (ESADA)

The ESADA has been described elsewhere in detail.[16] Shortly, the ESADA is comprised of data provided by predominantely academic sleep centers distributed across Europe. Data from 24 centers in 18 countries contributed to the current analysis. Patients eligible for inclusion in the cohort were aged between 18 and 80 years and underwent a sleep study for suspected OSA. Data collected in the ESADA include anthropometrics, daytime symptoms, smoking, alcohol consumption, blood tests data, medical history and medication. Patient and physician-reported comorbiditis like cardiovascular disease, metabolic disease like diabetes mellitus, hyperlipidemia and hyperuricemia are captured in detail. Daytime sleepiness is quantified by the Epworth sleepiness scale (ESS) score [17]. Coded data are entered, reported via a web-based system and stored in a central database. The ESADA protocol was approved by the local research ethics committee at each of the participating center and informed consent is obtained from all included patients**.**

Definition of hyperlipidemia

The diagnosis of hyperlipidemia is based on the sleep physicians' decision at the time of the diagnostic work up. The information is based on different sources including patients self report, information about concomitant medication, the referral letter and/or the hospital charts. In addition, cholesterol levels are assessed in conjunction with the sleep apnea evaluation visit. The lipid analysis was performed at each study center. Patients using lipid modifying agents were identified when concomittant medication with ATC code C10 ("lipid modifying agents") was reported. Control of hyperlipidemia was defined using the National Cholesterol Education Program Adult Treatment Panel III criteria [18]: Total cholesterol (TC) < 200 mg/dl.

Sleep study

A total of 5996 subjects (50.4%) underwent polysomnography (PSG) and the remainder cardiorespiratory polygraphy (n=5896) sleep studies for the diagnosis of OSA in accordance with local practice at each participating center. Data were edited manually before entry according to protocol definitions. Scoring of PG and PSG studies in the ESADA were

performed according to AASM criteria [19] and the procedures are described in detail. [20] Severity of sleep-disordered breathing (SDB) was assessed by calculation of the apnea-hypopnea index (AHI) and the oxygen desaturation index (ODI). AHI was defined as the mean number of apneas/hypopneas and ODI as the number of transient desaturations (≥4%) per hour of sleep (PSG) or per hour of analyzed time (PG) recordings. [19]

Diagnosis of obstructive sleep apnea

Diagnosis and severity of OSA was established according to the AHI cut off values of ≥5, 5-<15, 15-<30, and ≥30 events/hour. In accordance with previous clinical and population based studies (ref Kent study and SHHS), , quartiles of sleep disordered breathing (AHI, ODI, mean and lowest SpO_2) were calculated for regression analysis where the first quartiles were representative of subjects without sleep apnea. Thus, predictors of HL were aimed to be identified in subjects with increasing burden of sleep disordered breathing compared to subjects without OSA.

Assessment of anthropometric measures

Weight and height were measured with light clothing and without shoes. BMI was defined as the body mass (kilograms) divided by the square of the body height (meters), expressed in units of kg/m^2. Neck, waist and hip circumferences were measured and the waist-to-hip ratio (WHR) was calculated.

Statistics

Statistical analyses were performed using IBM SPSS Statistics 22.0 (Armonk, NY, USA: IBM Corp.). In order to minimize incompatibilites due to the use of different sleep methodologies as well as variabilities in ESADA centers, ODI data were used to characterize the severity of OSA in the present study. ODI quartiles were built for each analysis separately with subjects in the first quartile having the lowest ODI and serving as a reference category in the analysis. Baseline patient characteristics across quartiles were compared using ANOVA with post hoc Bonferroni analysis, Kruskal–Wallis and Mann–Whitney U-tests, and Chi-squared tests for parametric, nonparametric, and categorical variables, respectively. Factorial ANCOVA was performed to generate adjusted mean lipid value for each ODI classes. Adjusted means were compared following Bonferroni's post-hoc correction. Generalized Linear Regression

Models (GLM) were used to identify independent predictors and odd ratios for hyperlipidemia diagnosis. Adjustments for age, sex, BMI, waist/hip circumference ratio, comorbidities (hypertension, ischemic heart disease, stroke/transient ischemic attack, diabetes) and European study sites were performed in the analyses described above. All tests were two-tailed and statistical significance was taken at $p < 0.05$.

Results

Anthropometric data

Among 18,542 subjects enrolled in ESADA, 11,892 subjects were included in the current study. Reasons for study exclusion were lack of information on cholesterol levels (n=5062), sleep study results (n=979) and hyperlipidemia diagnosis (n=470). There were no clinically meaningful differences between included and excluded patients (age 51.9±12.5 vs 52.7±13.2, BMI 31.3±6.6 vs 31.5±6.7, male gender 69.9% vs 72.1%, ODI 23.7±25.5 vs 22.9±24.8, respectively). Descriptive characteristics of the final study population, stratified according to ODI quartiles, are shown in **table 1**. Subjects with severe OSA were more likely to be male, more obese, and to have comorbidities.

Prevalence of hyperlipidemia in the ESADA Cohort

The prevalence of hyperlipidemia increased significantly along with different measures of OSA severity. In the entire cohort, 21.7% (n=2657) had reported hyperlidemia and the prevalence increased from 12.2% in subjects without OSA (AHI<5) to 19.3%, 23.2%, and 27.5% in patients with mild (AHI 5-<15), moderate (AHI 15-<30), and severe OSA (AHI≥30), respectively, p<0.001. The corresponding numbers for ODI quartiles (95% CI), ranged from 15.1% (13.9-16.4) in ODI quartile I to 26.1% (24.6-27.7) in ODI quartile IV, p<0.001 (**table 1, figure 1**). Between group comparison demonstrated a significant difference in the prevalence rates of HL in ODI quartile I vs quartiles II- IV **(figure 1)**. Lipid lowering medication usage among subjects with hyperlipidemia diagnosis increased across ODI classes. Patients with diabetes mellitus, hypertension and ischemic heart disease had higher prevalence of hyperlipidemia and the prevalence increased significantly with OSA severity (**table 1**). Prevalence of hyperlipidemia also increased across BMI classes (13.8%, 20.1%, 24.9%, 27.3%; BMI classes I-IV respectively, p<0.001).

Measures of sleep apnea event frequency (AHI and ODI) as well as of nocturnal oxygenation independently predicted the likelihood of a reported hyperlipidemia diagnosis. In the unadjusted model, all measures of sleep disordered breathing predicted HL significantly and the ORs increased linearly across the quartiles of OSA severity (**table 2a**). In the adjusted model, in comparison with subjects in ODI quartile I, patients in ODI quartiles II-IV had an OR (95% CI) of 1.33 (1.15-1.55), 1.37 (1.17-1.61), and 1.33 (1.12-1.58) (p <0.001), respectively, for a hyperlipidemia diagnosis. The fourth quartile of AHI and second and third quartiles of mean and lowest SpO_2 significantly predicted hyperlipidemia diagnosis after adjustment for confounders (**table 2b**). Hyperlipidemia prevalence was also significantly predicted by cardiovascular comorbidities. There was an inverse U-shaped relationship between BMI and hyperlipidemia prevalence. Obese and overweight patients were associated with higher hyperlipidemia prevalence than patients with morbid obesity or normal weight in the GLM model. Hyperlipidemia prevalence was significantly influenced by study sites and geographical regions with the highest prevalence in the Central region and the lowest in Northern Europe (**figure 2**). Finally, when using the clinical AHI cut off for OSA severity (5-<15, 15-<30, ≥30), adjusted OR´s for hyperlipidemia diagnosis were 1.16 (0.98-1.38), 1.28 (1.08-1.52), and 1.37 (1.16-1.63), p=0.078, 0.006, and <0.001, respectively.

Control of cholesterol levels in treated and untreated hyperlipidemia

The adjusted mean cholesterol concentrations in subjects without hyperlipidemia and in hyperlipidemia with and without lipid lowering treatment (ATC code C 10) were 172.9 ± 2.1 mg/dl, 179.4 ± 4.1 and 207.5 ± 7.17 mg/dl respectively (p<0.001) **(figure 3)**. In patients with a known hyperlipidemia diagnosis (with and without lipid lowering treatment) we could not identify a dose response relationship between lipid level (TC, HDL- and LDL-cholesterol or triglycerids) and the degree of sleep apnea severity classified as AHI or ODI quartile (data not shown).

Discussion

This cross-sectional study, including the largest patient sample on this topic to date, demonstrated that intermittent hypoxia during sleep is an independent predictor of hyperlipidemia diagnosis. Hyperlipidemia prevalence increased from 15.1% in subjects without OSA to 26.1% in those with severe OSA. Hyperlipidemia prevelance was higher in subgroups of OSA subjects with co-existing cardiovascular comorbidities, particularly in severe OSA subjects. Obesity was identified as a significant predictor of hyperlipidemia. Differences in prevalence rates of hyperlipidemia were recorded among geographical European regions.

Hyperlipidemia in OSA – epidemiological evidence

The influence of OSA on hyperlipidemia has been examined predominantly through lipid concentrations rather than reported hyperlipidemia diagnosis. In the large Sleep Heart Health Study cohort [10], OSA severity was associated with TC concentration in younger males and with HDL-C and triglyceride concentrations in women. In a meta-analysis of 13 cross-sectional studies, OSA severity demonstrated a significant relationship with lipid concentrations in only 3 studies. Additionally, several studies either reported a weak association or no relationship at all. [11,21–23] Chou et al. [24] reported a very high hypercholesterolemia prevalence of 61.1% in 236 male, mostly obese OSA subjects. Kono et al. [25] demonstrated an association between OSA and components of metabolic syndrome including hypertension, dyslipidemia, and hyperglycemia in a non-obese male population. In the study of Guan et al. [26] a nonlinear dose-effect relationship between dyslipidemia and OSA severity has been reported. In the Hypnolaus study investigating the prevalence of OSA in general population having a mean 25.6 kg/m^2 BMI, 30% (n=641) prevalence of metabolic syndrome as well as independent association between OSA and metabolic syndrome have been reported. [1] In our previous study from the ESADA cohort, we determined a strong linear association between OSA severity and several lipid concentration (total cholesterol, HDL and LDL cholesterol, and triglycerides) in OSA patients without a reported diagnosis of hyperlipidemia or use of lipid lowering medication. [14] In the current study, these findings were substantially confirmed by the identification of an association of OSA with a reported hyperlipidemia diagnosis. On the other hand, although the prevalence of elevated cholesterol blood levels in our previous study was 51%, the prevalence for reported

hyperlipidemia in the current study was 21.9%. Despite differences in the populations actually studied, the low prevalence of a recognized hyperlipidemia diagnosis reported in the current study suggest a significant underrecognition of hyperlipidemia in OSA subjects. This finding is supported by data from the Hypnolaus study. Despite a lower BMI compared to our subjects, the rate of metabolic syndrome was higher (30%) in this population based cohort supporting a potential underrecognition of HL in our OSA patient population [1]. In the present study, we analysed several measures of OSA severity in predicting hyperlipidemia in the adjusted model. Measures of intermittent and sustained hypoxia, like all ODI quartiles II-IV, mean and lowest saturation quartiles II and III, were defined as significant predictors of HL, but only the fourth quartile of AHI demonstrated an independent association with HL. Differences in sleep study methodology (PG/PSG) may partially explain these findings since ODI is less sensitive to the between center variability in recording and analysis method used. Thereby our data suggest that ODI as a measure of intermittent hypoxia is a stronger predictor of HL in OSA subjects when compared with AHI as a measure of OSA event frequency.

Studies examining the relationship of OSA and dyslipidemia have also investigated the influence of obesity. As some studies claim that there is not a true relationship beyond the effects of obesity [27], some suggest the existence of a strong association between OSA and hyperlipidemia even independent of BMI. [10,21] [25] [28] Despite obesity being a strong risk factor for cardiovascular diseases, a phenomenon called obesity paradox, in which overweight or obese people with cardiovascular diseases have a better prognosis than lean subjects, has been described. [29] Recently, the term “adiposopathy”, described as the primary cause of adiposity-related metabolic disease and elevated risk for cardiovascular diseases, is being referred for elucidating the obesity paradox. [30] These findings are in line with the data in our study showing that morbid obesity did not have an influence on the association of OSA and hyperlipidemia whereas an independent risk for hyperlipidemia has been established for overweight and obese patients (BMI categories 25-<30 kg/m^2 and 30-<35 kg/m^2, respectively). In this context, the effects of central obesity and peripheral subcutaneous fat on the development of manifest hyperlipidemia may be different.[31] However, a specific focus on diet and increases in physical activity in the morbid obesity group may also be a potential reason for the non-linear association seen between body

weight and hyperlipidemia diagnosis, often referred to as “reversed causality” in j-or u-shaped cross sectional association studies.

While we observed a cross-sectional association between OSA and hyperlipidemia prevalence, a potential causative role for OSA in driving the development of hyperlipidemia is suggested by clinical trials of continuous positive airway pressure (CPAP) therapy. In the meta-analysis of Li et al., 6 RCTs with 348 patients and 351 controls were analyzed and a modest but significant effect of CPAP on the decrease of total cholesterol levels was reported.[32] A further study examining the effect of CPAP on lipid profiles in ESADA cohort is warranted.

There are consistent reports suggesting considerable regional differences in lipid control. In particular, elevated cholesterol was more prevalent in Northern European countries and less prevalent in the Southern regions. [33,34] In a recent study from the Multi-Ethnic Study of Atherosclerosis (MESA) cohort, race/ethnicity has been demonstrated as a risk factor for cardiovascular disease and increased OSA severity among four different race groups in Unites States of America.[35] The reflections of regional varieties such as different body fat distribution patterns, previously identified genetic and dietary factors may account for the differences in hyperlipidemia prevalence among study sites. [18] Our data confirm those previously mentioned interactions by demonstrating a strong influence of different European sites on the hyperlipidemia prevalence. Nonetheless, certain disparities regarding prevalence of impaired lipid metabolism in our dataset were noted. For instance, patients in Northern region, where highest cholesterol concentrations were reported in our previous study, demonstrated lowest prevalence of a hyperlipidemia diagnosis in the current study.[14] Potential explanantions of this finding include regional differences in genetic predisposition to hyperlipidemia, diet, and awareness of the medical profession to lipid status. Thus, further studies providing insight regarding regional/ethnical disparities as well as treatment strategies in the lipid metabolisms of European OSA populations are needed.

Strengths and limitations

There are several strengths and limitations of our study. The generalizability of the results originating from the multinational and multicentre study design as well as the large cohort constitutes a major strength. On the other hand, a trend for clinical referral bias is present in the current cohort which constitutes data from academic sleep centers. Since ESADA collaborator institutions are mostly tertiary hospitals, patient referrals from primary and secondary hospitals generate a potential clinical referral bias for the studies. Thus, the present results may be representative for European OSA patients but not for the general population. Our study results may be also affected by clinical referral bias. In fact, the design of our study does not allow us to identify the actual cause of referral for each individual patient. However, according to clinical guidelines, nocturnal symptoms, excessive daytime sleepiness or the existence of comorbid diseases like hypertension, ischemic heart disease, diabetes or stroke are the most common reasons for an evaluation of suspected sleep apnea. The latter named comorbidities are likely to be associated with an elevated prevalence of a HL diagnosis and may constitute a referral bias which may affect the association between OSA severity and the prevalence of a HL diagnosis in our study. Indeed, our data clearly showed stronger associations between OSA severity and HL in the subgroups with comorbidities (table 1, lower part). Our study evaluated the influence of OSA on hyperlipidemia as a clinical diagnosis but controlled also for actual drug treatment on cholesterol levels in hyperlipidemia. However, the cross-sectional design of our study does not allow to determine any causal relationship between OSA and hyperipidemia. Besides, we could not evaluate the precise effect of OSA on the control of HL since treatment of HL varies depending on the risk assessment of the physician and is not limited to medication. In addition, patient adherence to prescribed lipid-lowering medication was not monitored in our study. Some important confounders that could influence the association between OSA and HL like family history of lipid disorders, diet and exercise could not be controlled in the present study. Sleep test methodology was either PG or PSG, which influences AHI and ODI values substantially, a detailed analysis of the sleep analysis performed in the ESADA study can be found elsewhere. [20] In the current analysis, we therefore focused on ODI quartiles as a measure for OSA severity as this parameter has been demonstrated to be less sensitive to methodological differences when compared with the AHI. [20] Lastly, despite studies report that patients with OSA tend to be sedentary [36],

we could not examine the potential influence of physical exercise in our study cohort. The prospective evaluation of CPAP therapy on lipid status in the ESADA cohort may overcome at least some of the study limitations.

Conclusion

OSA was independently associated with the diagnosis of hyperlipidemia and the link was particulary strong with intermittent hypoxia. Meanwhile, hyperlipidemia was notably underrecognized in OSA subjects. The geographical impact of different European sites was identified and defined as a new confounder. Further studies elucidating the effect of CPAP therapy on lipid status in the ESADA cohort are of importance.

Conflict of interest statement

Among the authors of the present manuscript, Dr. Pepin reports grants from Air Liquide Foundation, grants and personal fees from Agiradom, grants and personal fees from AstraZeneca, grants from Fisher and Paykel, grants from Mutualia, grants and personal fees from Philips, grants and personal fees from Resmed, grants from Vitalaire, personal fees from Boehringer Ingelheim, personal fees from Jazz pharmaceutical, personal fees from Night Balance, personal fees from Sefam, outside the submitted work.

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Dr. Hedner reports grants from ResMed, and Philips Respironics during the conduct of the study; personal fees from ResMed, Philips, Itamar Medical, Astra Zeneca, Bayer, Takeda, p Bresotec and Desitin, outside the submitted work.

The remaining authors has no conflict of interest to declare.

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Figure legends

Figure 1. Hyperlipidemia prevalence rates(95% CI) in OSA increases across quartiles of ODI (15.1%, 21.7%, 24.4% and 26.1%, respectively; p<0.001, between groups). Significant differences in HL prevalences between groups were reported for quartile I vs II-IV and for quartile II vs IV (p<0.05 both, within groups). 95% confidence intervals were demonstrated by bars.

Figure 2. Reported hyperlipidemia prevalence (95% CI) differed among five ESADA study geographical regions (p<0.001, between groups). Lowest prevalence was demonstrated in North (14.1%) and highest in Central (36.4%) regions. 95% confidence intervals were demonstrated by bars.

Figure 3. Adjusted means of cholesterol (95% CI) in subjects without HL diagnosis and in treated and untreated patients with a HL diagnosis demonstrated a significant difference between groups (p<0.001). Subjects without HL diagnosis had the lowest cholesterol level (172.9 mg/dl) and untreated HL subjects had the highest (207.5 mg/dl). 95% confidence intervals were demonstrated by bars.

Table 1. Patient characteristics (n=11892) according to ODI quartiles

	ODI quartiles					
	Total n=11892	<4.50 n=2964	4.50-13.69 n=2966	13.70-35.89 n=2984	>35.89 n=2978	p-value
Anthropometric data						
Age	51.9±12.5	46.9±12.9	52.6±11.9	54.5±11.8	53.5±11.8	<0.001
Gender (female)	30.1%	41.0%	32.4%	26.0%	21.2%	<0.001
BMI (kg/cm^2)	31.3±6.6	27.6±4.8	30.2±5.5	31.7±5.8	35.6±7.2	<0.001
Systolic Blood Pressure (mmHg)	133.9±17.8	129.0±17.4	134.0±17.8	135.6±17.2	136.9±17.7	<0.001
Diastolic Blood Pressure (mmHg)	82.0±11.7	79.8±11.2	82.1±11.3	82.7±11.7	83.5±12.3	<0.001
Pulse pressure	51.8±13.9	49.1±12.9	52.0±14.0	52.9±13.9	53.3±14.3	<0.001
Waist (cm)	107.1±15.6	97.0±12.8	104.3±13.1	109.1±13.2	117.9±15.4	<0.001
Hip (cm)	110.2±12.7	104.7±9.9	108.2±10.7	110.9±12.0	117.0±14.5	<0.001
W/H Ratio	0.97±0.08	0.93±0.08	0.96±0.08	0.99±0.08	1.01±0.08	<0.001
Neck (cm)	41.2±4.3	38.6±3.7	40.4±3.8	41.8±3.8	43.9±4.3	<0.001
BMI categories						
Normal weight	14.2%	30.6%	15.1%	7.9%	3.2%	<0.001
Overweight	33.9%	44.1%	39.5%	35.2%	16.8%	
Obese	28.6%	17.9%	29.3%	33.3%	33.7%	
Morbid obese	23.3%	7.4%	16.0%	23.6%	46.3%	
Smoking	24.1%	25.9%	22.5%	22.4%	25.6%	<0.001
Comorbidities						
Hypertension	39.9%	21.8%	38.6%	45.6%	53.6%	<0.001
Ischemic heart disease	8.4%	4.6%	7.7%	10.2%	11.1%	<0.001
TIA/stroke	2.4%	1.2%	2.8%	3.0%	2.5%	<0.001
Diabetes	12.7%	4.8%	10.2%	15.4%	20.4%	<0.001
AHI	27.5±26.1	5.7±8.4	13.4±10.2	27.8±12.6	62.8±21.6	<0.001
Mean SpO_2 (%)	93.2±3.4	95.1±1.7	94.1±1.8	93.3±2.1	90.3±4.7	<0.001
Lowest SpO_2 (%)	80.8±9.8	88.2±4.9	84.0±5.2	80.0±6.7	70.5±10.8	<0.001
Hyperlipidemia diagnosis						
Hyperlipidemia	21.9%	15.1%	21.7%	24.4%	26.1%	<0.001
Treated hyperlipidemia	12.2%	7.3%	13.0%	14.5%	14.2%	<0.001
Hyperlipidemia in hypertension	4749	13.1%	23.7%	28.6%	34.5%	<0.001
Hyperlipidemia in ischemic heart diseae	997	11.7%	23.7%	31.2%	33.3%	0.005
Hyperlipidemia in diabetes mellitus	1511	8.5%	20.2%	29.9%	41.5%	<0.001

Abbreviations: ODI: oxygen desaturation index; BMI: body mass index classes; W/H: waist/hip; TIA: transient ischemic attack; SpO_2: arterial oxygen saturation measured by pulse oximetry

Table 2a. Predictors of hyperlipidemia diagnosis across quartiles of SDB severity measures

	ODI (n=11892)		Mean SpO_2 (n=11730)		Lowest SpO_2 (n=11859)		AHI (n=11892)	
	OR (95%CI)	P value	OR (95%CI)	P value	OR (95%CI)	P value	OR (95%CI)	P value
Quartile 2 vs 1	1.56 (1.36-1.78)	<0.001	1.41 (1.24-1.60)	<0.001	1.37 (1.24-1.56)	<0.001	1.64 (1.43-1.88)	<0.001
Quartile 3 vs 1	1.82 (1.59-2.07)	<0.001	1.60 (1.43-1.80)	<0.001	1.72 (1.51-1.96)	<0.001	2.05 (1.79-2.34)	<0.001
Quartile 4 vs 1	1.99 (1.12-1.58)	<0.001	1.79 (1.74-2.26)	<0.001	1.62 (1.42-1.84)	<0.001	2.45 (2.15-2.79)	<0.001

(unadjusted model)

Table 2b. Independent predictors of hyperlipidemia diagnosis across quartiles of SDB severity measures*

*The values were adjusted for age, gender, body mass index classes, waist/hip ratio, smoking,

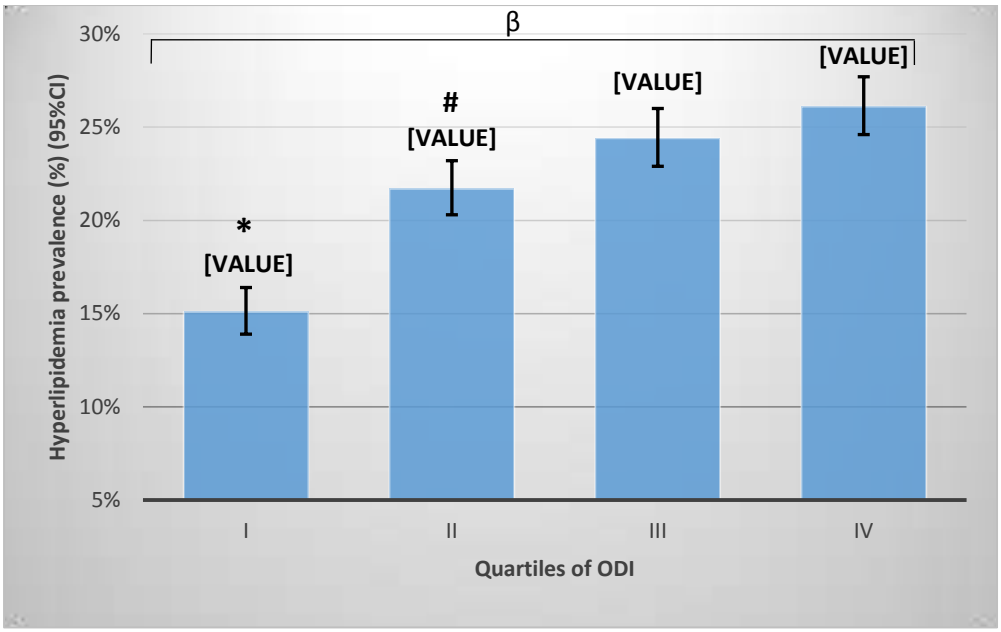
	ODI (n=11892)		Mean SpO_2 (n=11730)		Lowest SpO_2 (n=11859)		AHI (n=11892)	
	OR (95%CI)	P value	OR (95%CI)	P value	OR (95%CI)	P value	OR (95%CI)	P value
Quartile 2 vs 1	1.34 (1.15-1.56)	<0.001	1.28 (1.11-1.48)	0.001	1.22 (1.05-1.41)	0.008	1.14 (0.98-1.33)	0.095
Quartile 3 vs 1	1.37 (1.17-1.61)	<0.001	1.27 (1.10-1.46)	0.001	1.29 (1.11-1.51)	0.001	1.15 (0.98-1.35)	0.083
Quartile 4 vs 1	1.33 (1.12-1.58)	0.001	1.12 (0.96-1.31)	0.147	1.09 (0.93-1.28)	0.298	1.28 (1.08-1.50)	0.004

hypertension, ischemic heart disease, transient ischemic attack/stroke, diabetes and study sites

Abbreviations: AHI: apnoea-hypopnoea index; ODI: oxygen desaturation index; SpO_2: arterial oxygen saturation measured by pulse oximetry; OR: odds ratio

ODI quartiles(n/h): *quartile 1: 0-4.49, quartile 2: 4.50-13.69, quartile 3: 13.70-35.89; quartile 4: >35.89;* ***Mean SpO_2 quartiles(%):*** *quartile 1: >94.99, quartile 2: 94-94.99, quartile 3: 92-93.99; quartile 4: <92;* ***Lowest SpO_2 quartiles(%):*** *quartile 1: >87.99, quartile 2: 83-87.99, quartile 3: 77-82.99; quartile 4: <77;* ***AHI quartiles(n/h):*** *quartile 1: 0-6.79, AHI quartile 2: 6.80-18.99, AHI quartile 3: 19.10-41.99; AHI quartile 4: >41.99*

Figure 1.



β p<0.001 between groups I-IV

* p<0.05 within groups I vs II, III and IV

# p<0.05 within groups II vs IV

Figure 2.

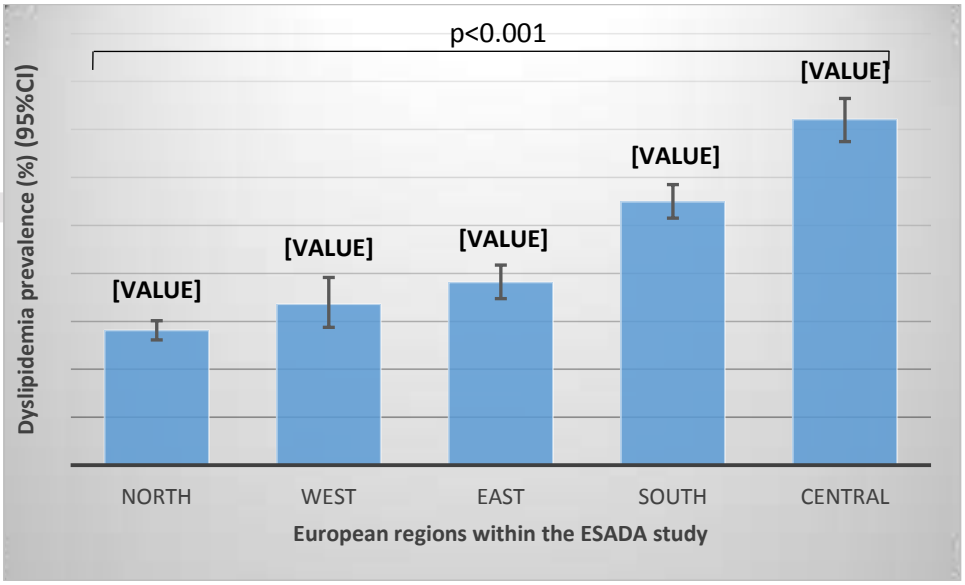


Figure 3.