Journal Pre-proof

Long-term positive airway pressure therapy is associated with reduced total cholesterol levels in patients with obstructive sleep apnea: Data from the European Sleep Apnea Database (ESADA)

Canan Gunduz, Ozen K. Basoglu, John Arthur Kvamme, Johan Verbraecken, Ulla Anttalainen, Oreste Marrone, Paschalis Steiropoulos, Gabriel Roisman, Pavol Joppa, Holger Hein, Georgia Trakada, Jan Hedner, Ludger Grote, on behalf of the European Sleep Apnea Database collaborators[1]

PII: S1389-9457(20)30103-9

DOI: https://doi.org/10.1016/j.sleep.2020.02.023

Reference: SLEEP 4342

To appear in: *Sleep Medicine*

Received Date: 7 October 2019

Revised Date: 2 February 2020

Accepted Date: 25 February 2020

Please cite this article as: Gunduz C, Basoglu OK, Kvamme JA, Verbraecken J, Anttalainen U, Marrone O, Steiropoulos P, Roisman G, Joppa P, Hein H, Trakada G, Hedner J, Grote L, on behalf of the European Sleep Apnea Database collaborators[1], Long-term positive airway pressure therapy is associated with reduced total cholesterol levels in patients with obstructive sleep apnea: Data from the European Sleep Apnea Database (ESADA), *Sleep Medicine*, https://doi.org/10.1016/j.sleep.2020.02.023.

Long-term positive airway pressure therapy is associated with reduced total cholesterol levels in patients with obstructive sleep apnea: Data from the European Sleep Apnea Database (ESADA)

Canan Gunduz[1,2], Ozen K Basoglu[2], John Arthur Kvamme[3], Johan Verbraecken[4], Ulla Anttalainen[5-6], Oreste Marrone[7], Paschalis Steiropoulos[8], Gabriel Roisman[9], Pavol Joppa[10], Holger Hein[11], Georgia Trakada[12], Jan Hedner[13,14], Ludger Grote[13,14], on behalf of the European Sleep Apnea Database collaborators[¶]

[1]Sureyyapasa Chest Diseases and Thoracic Surgery Training and Research Hospital, Istanbul, Turkey
[2]Ege University, Department of Chest Diseases, Izmir, Turkey
[3]Sleep Laboratory, ENT Department, Førde Central Hospital, Førde, Norway
[4]Multidisciplinary Sleep Disorders Centre, Antwerp University Hospital and University of Antwerp, Antwerp, Belgium
[5]Division of Medicine, Department of Pulmonary Diseases, Turku University Hospital, Turku, Finland
[6]Hospital and Sleep Research Centre, Department of Pulmonary Diseases and Clinical Allergology, University of Turku, Finland
[7]CNR, Istituto per la Ricerca e l'Innovazione Biomedica, Palermo, Italy
[8]Sleep Unit, Department of Pneumonology, Democritus University of Thrace, Alexandroupolis, Greece
[9]Sleep Disorders Center, Antoine-Beclere Hospital, Clamart, France
[10]Department of Respiratory Medicine and Tuberculosis, Faculty of Medicine, P.J.Safarik University and L. Pasteur University Hospital, Kosice, Slovakia
[11]Sleep Disorders Center, Johanniter-Krankenhaus, Geesthacht, Germany
[12]Division of Pulmonology, Department of Clinical Therapeutics, National and Kapodistrian University of Athens, School of Medicine, Alexandra Hospital, Athens, Greece
[13]Center for Sleep and Vigilance Disorders, Sahlgrenska Academy, Gothenburg University, Gothenburg, Sweden
[14]Sleep Disorders Center, Pulmonary Department, Sahlgrenska University Hospital, Gothenburg, Sweden
[¶]For a list of the ESADA collaborators and their affiliations see Acknowledgement

Content Abstract- 262 words, main text- 3262 words, 4 tables, 2 figures, 26 references

Corresponding author

Canan Gunduz

Sureyyapasa Chest Diseases and Thoracic Surgery Training and Research Hospital
Başıbüyük Mah. Hastane Yolu Cad, D: C Blok, 34844 Maltepe
Istanbul, Turkey

E-mail address: cananguduz@yahoo.com

Abstract:

Background and aim:

Obstructive sleep apnea (OSA) is an independent risk factor for dyslipidemia. The current study examined the effects of positive airway pressure (PAP) treatment on lipid status in the European Sleep Apnea Database (ESADA).

Methods:

The prospective cohort study enrolled 1564 OSA subjects (74% male, mean age 54±11y, body mass index (BMI) 32.7±6.6 kg/m^2 and apnea-hypopnea index (AHI) 40.3±24.4 n/h) undergoing PAP therapy for at least three months (mean 377.6 ± 419.5 days). Baseline and follow-up total cholesterol (TC) from nine centers were analyzed. Repeated measures and logistic regression tests (adjusted for age, sex, weight changes, lipid lowering medication, PAP compliance and treatment duration) were used to compare changes in TC concentration. Incident risk for a coronary heart disease event (CHD) was used to compute a Framingham CHD risk score (estimated from age, BMI, blood pressure, and TC).

Results:

Adjusted means of TC decreased from 194.2 mg/dl to 189.3 mg/dl during follow-up (p=0.019). A clinically significant (10%) reduction of TC at PAP follow-up was observed in 422 patients (27%). Duration of PAP therapy was identified as independent predictor for TC reduction, which implies an approximately 10% risk reduction for incident CHD events (from 26.7% to 24.1% in men and from 11.2% to 10.1% in women, p<0.001 respectively).

Conclusion:

This observational study demonstrates a reduction of TC after long-term PAP treatment. The close association between TC concentration and cardiovascular (CV) mortality suggests that identification and treatment of OSA may have a beneficial effect on overall CV risk due to this mechanism. This possibility needs to be evaluated in prospective randomized studies.

Keywords: Cholesterol, hypoxia, positive airway pressure, sleep apnea, cardiovascular risk.

Short title: PAP effects on lipids in obstructive sleep apnea

Background

Obstructive sleep apnea (OSA) is a common sleep disorder with a prevalence of 20% in male and 10% in female adults [1]. Repetitive episodes of partial or complete upper airway obstruction during sleep with this condition may result in intermittent hypoxia which promotes oxidative stress, systemic inflammation and endothelial dysfunction [2]. OSA is recognized for its association with metabolic dysfunction and increased cardiovascular (CV) mortality [3,4]. Treatment with positive airway pressure (PAP) may have beneficial effects on all-cause and CV mortality in clinical cohorts of patients with severe OSA [5].

In previous studies of the European Sleep Apnea Database (ESADA) cohort, we identified OSA as an independent predictor of dyslipidemia. Measures of nocturnal hypoxia like the oxygen desaturation index (ODI) demonstrated a strong linear relationship with elevated total- and LDL-cholesterol and reduced HDL-cholesterol concentrations as well as the diagnosis of hyperlipidemia [6,7]. However, previous studies examining the effect of PAP treatment on lipid status showed rather conflicting results. In a meta-regression analysis examining 1,958 OSA subjects from 29 observational studies, an improvement of lipid profile was reported for total-, LDL- and HDL-cholesterol [8]. In contrast, a recent review of randomized controlled PAP treatment trials in OSA reported no significant effects on lipid status. Most controlled studies were small and of short duration and potentially not fully controlling confounding factors on top of PAP treatment [9].

The ESADA is a multicenter, multinational cohort including patients with suspected OSA from sleep laboratories across Europe. The current analysis examined the relationship between lipid concentrations and hypoxia in OSA subjects undergoing PAP therapy. As lipid status is an important parameter for the different prediction models of coronary heart disease (CHD) risk, we aimed to investigate the effect of PAP treatment on such computed CHD risk estimates. It was hypothesized that OSA treatment reduces serum cholesterol and triglyceride concentrations, which subsequently modify the calculated incident risk for CHD.

Methods

Subjects and settings

The detailed description of the ESADA cohort has been published elsewhere [10]. In short, the ESADA gathers data from 30 sleep centers distributed across 20 countries in Europe and Israel. For the current analysis, which included only patients on PAP treatment for at least three months and with lipid samples at both baseline and at the PAP follow up visit. Data from 1,564 patients (aged 18 and 80 years inclusive) representing nine different centers in South, Central and North European regions were included. The analyzed data included anthropometrics, daytime symptoms, smoking, alcohol consumption, medical history and medication. Venous blood samples were collected at each center for assessment of lipid profile at baseline and follow-up [10]. Patient and physician-reported comorbidities including CV disease, metabolic disease including diabetes mellitus, hyperlipidemia and hyperuricemia were captured in detail. Daytime sleepiness was quantified by the Epworth sleepiness scale (ESS) score [11]. Lipid modifying agents were defined as those with the ATC code C10 ("lipid modifying agents"). Coded data were entered, reported via a web-based system and stored in a central database. The ESADA protocol has been reviewed and approved by the local research ethics committee at each participating center and written informed consent was obtained from all included patients**.** The current study analyzed data from the ESADA database sampled between 2007 and 2016.

Sleep study

A total of 854 patients (54.6%) were diagnosed with polysomnography (PSG) and the remainder with cardiorespiratory polygraphy (PG, n=710). The sleep studies were conducted in accordance with local practice at each center and manual edition of the data was applied. AASM criteria were used during the scoring of PG and PSG studies in the ESADA [12] with further details mentioned elsewhere [13]. Severity of sleep-disordered breathing (SDB) was assessed by computing the apnea-hypopnea index (AHI) and the oxygen desaturation index (ODI). AHI was presented by the mean number of apneas/hypopneas, whereas ODI was defined as the number of transient oxygen desaturations (≥4%) per hour of sleep (PSG) or per hour of analyzed time (PG). [12] A sensitivity analysis examining the potential effects of

the diagnostic method used (PG or PSG) showed no significant effect in line with our previous studies addressing dyslipidemia in OSA. [6,7]

Assessment of anthropometric measures

Weight and height were assessed with the patient wearing light clothing and no shoes. Body mass index (BMI) was calculated as the body mass (kilograms) divided by the square of the body height (meters) and presented in units of kg/m^2. Further calculations included the circumferences of neck, waist and hip, as well as the waist-to-hip ratio (WHR).

Calculation of Framingham 10-year Coronary Heart Disease risk score

A sex-specific point score based on categorical values of age, National Cholesterol Education Program (NCEP) [14] total cholesterol, HDL and LDL cholesterols, blood pressure, smoking, and comorbid diabetes was calculated. The scoring sheet is available in the study by Wilson et al., [15]. Separate scores were calculated before and during PAP intervention for each subject.

Statistical methods

Severity of OSA was measured categorically after arranging data into AHI and ODI quartiles. In the descriptive analysis, central tendency of continuous variables was expressed as means with standard deviations and frequencies of categorical variables were calculated. The unadjusted difference in lipid concentration between baseline and follow up was evaluated with in a paired t-test. In order to adjust for important confounders, repeated measures ANOVA test adjusted for age, sex, change in weight, lipid lowering medication use, PAP compliance and duration was used to compare changes in total-cholesterol, TG, LDL-cholesterol (Friedewald formula [16]), HDL-cholesterol and the Framingham risk score [15]. The proportion of patients with a clinical meaningful decrease of cholesterol were identified (cut off levels of ≥10% and ≥25%).

All tests were two-tailed and statistical significance was defined at $p \leq 0.05$. Statistical analyses were performed using IBM SPSS Statistics 22.0 (Armonk, NY, USA: IBM Corp.).

Results

Anthropometric data

Our prospective cohort study included 1,564 OSA subjects out of the 18,542 subjects registered in the ESADA database at the time of analysis. Patients had used PAP therapy for at least three months and information on total cholesterol concentration had been recorded (including 866 subjects for the fasting TG, 835 subjects for the HDL-C and 828 subjects for the LDL-C analysis). Compared to ESADA patients on PAP therapy, but without data on lipid status at follow up (n=1857), patients in the current analysis had similar anthropometric data (age 54 ± 11 vs. 54 ± 11 years, BMI 32.5 ± 6.8 vs. 32.7 ± 6.6 kg/m^2 and 73.5% vs. 74.4% males, all $p>0.05$) and more severe sleep apnea (AHI 36.1 ± 25.8 vs 40.3 ± 24.4, $p<0.001$). Cardiometabolic comorbidities were slightly more prevalent in the study population compared with the remaining ESADA cohort **(Table 1a)**. At baseline, 25.4% OSA subjects received lipid lowering medication. At follow-up, lipid lowering medication had been initiated in 38 patients and stopped in 11 patients (3.1%). Weight reduction at follow-up was observed in 37.8% and weight gain in 44.9% of subjects. A significant weight reduction of ≥ 10% was observed in 4% of patients. Continuous positive airway pressure (CPAP) therapy was the dominant PAP modality (n=1,016, 64.8%), followed by auto-titrating positive airway pressure (n=468, 29.9%) and Bi-level positive airway pressure (n=80, 5.1%) therapy. Mean treatment duration was 377.6 ± 419.5 days with a mean daily PAP use of 5.3 ± 2.0 hours. Characteristics of patients with (n= 397) or without lipid lowering therapy (n=1,167) is shown in **Table 1b**. Medication users were significantly older, had slightly more central obesity and showed higher rates of comorbidities compared with subjects without medication.

Table 1a. Comparison of baseline characteristics of the analysis population (n=1564) and excluded subjects from ESADA cohort on PAP treatment with missing lipid analysis (n=1587). Despite similar anthropometric and lipid profiles, the analysis population had higher rates of cardiometabolic comorbidities, more severe sleep apnea, higher degree of sleepiness and longer use of PAP treatment.

		Analysis population (n=1564)	ESADA patients on PAP treatment without lipid analysis (n=1587)	Between group statistics
Age (year)		53.9 ± 10.7	53.9 ± 11.9	0.87
Sex (males) %		74.4	73.5	0.31
BMI (kg/m^2)		32.7 ± 6.6	32.5 ± 6.8	0.72
Waist-to-hip ratio*		0.99 ± 0.08	0.98 ± 0.08	0.001
Diabetes mellitus, % *		20.9	14.1	<0.001
Arterial hypertension, % *		48.3	44.5	0.03
Lipid lowering medication, % *		25.4	21.9	0.006
Ischemic heart disease, % *		10.6	8.6	0.02
Transient ischemic attack, %		2.9	2.9	0.92
Smokers, %		23.3	20.7	0.09
Alcohol (units) *		3.5 ± 7.1	5.1 ± 8.6	0.001
Baseline total cholesterol (mg/dl)		200.1 ± 43.8	198.2 ± 41.6	0.254
Baseline HDL cholesterol (mg/dl)		45.1 ± 13.3	46.4 ± 14.5	0.162
Baseline LDL cholesterol (mg/dl)		122.3 ± 38.7	121.0 ± 37.2	0.659
Baseline triglycerides (mg/dl)		178.9 ± 104.0	174.4 ± 106.5	0.259
ESS score *		10.1 ± 5.1	11.2 ± 5.4	<0.001
AHI (n/h) *		40.3 ± 24.4	36.1 ± 25.8	<0.001
AHI classes, % *	Mild	13.3	19.0	<0.001
	Moderate	29.2	26.2	
	Severe	57.5	54.8	
ODI (n/h)		32.6 ± 25.0	30.7 ± 25.8	0.14
Mean SaO_2, n (%)*		92.3 ± 4.0	92.7 ± 3.0	0.005
Lowest SaO_2, n (%)		77.8 ± 10.1	78.5 ± 9.4	0.14
Time spent SaO_2< 90% (min) *		50.6 ± 79.0	61.5 ± 82.4	0.013
PAP adherence (>4 h/day) n (%)*		81.6	67.5	<0.001
PAP use/day (hours) *		5.31 ± 1.98	4.39 ± 2.52	<0.001
PAP duration (days) *		377.6 ± 419.5	250.8 ± 322.5	<0.001
Change in weight during follow-up (kg)		-0.2 ± 6.1	-0.3 ± 7.9	0.93

*Parameters with p value <0.05 **Variables expressed as percentage or mean ± standard deviation.

Abbreviations:

BMI: body mass index; HDL: high-density lipoprotein; LDL: low-density lipoprotein; ESS: Epworth sleepiness score; AHI: apnea-hypopnea index; ODI: oxygen desaturation index; SaO_2: arterial oxygen saturation; PAP: positive airway pressure.

Table 1b. The baseline characteristics of the study population under lipid lowering medication (n=297) compared with patients not using lipid lowering medication (n=1167). The subjects under lipid lowering medication were older, had higher rates of comorbidities, higher LDL-cholesterol CHD risk scores and lower cholesterol levels.

		Lipid lowering medication		P value
		Users (n=397)	Non-users (n=1167)	
Age (year) *		59.2 ± 9.3	52.2 ± 11.5	<0.001
Sex (males) %		74.7	74.2	0.78
BMI (kg/m2)		32.8 ± 6.4	32.5 ± 6.9	0.245
Waist-to-hip ratio *		1.00 ± 0.08	0.98 ± 0.08	<0.001
Diabetes mellitus, % *		33.2	12.0	<0.001
Arterial hypertension, % *		68.8	39.2	<0.001
Ischemic heart disease, % *		27.9	4.2	<0.001
Transient ischemic attack, % *		7.4	1.5	<0.001
Smokers, % *		10.8	15.7	0.004
Alcohol (units)		4.9 ± 8.3	4.4 ± 7.9	0.177
Baseline total cholesterol (mg/dl) *		177.6 ± 41.2	208.0 ± 41.9	<0.001
Baseline HDL cholesterol (mg/dl) *		43.5 ± 10.7	45.8 ± 13.2	0.011
Baseline LDL cholesterol (mg/dl) *		98.7 ± 34.8	130.7 ± 37.1	<0.001
Baseline triglycerides (mg/dl)		178.4 ± 102.5	178.2 ± 105.2	0.979
Baseline CHD risk score in males (cholesterol points)		25.7 ± 16.2	26.1 ± 16.5	0.641
Baseline CHD risk score in males (LDL-cholesterol points) *		27.8 ± 16.7	25.7 ± 16.9	0.029
Baseline CHD risk score in females (cholesterol points)		12.1 ± 8.2	11.2 ± 8.6	0.069
Baseline CHD risk score in females (LDL-cholesterol points) *		14.0 ± 9.7	12.5 ± 9.9	0.007
ESS score *		10.0 ± 5.0	11.0 ± 5.0	<0.001
AHI (n/h)		36.8 ± 24.4	38.3 ± 26.1	0.138
AHI classes	**mild**	17.7	14.9	0.092
	moderate	27.3	28.2	
	severe	55.0	56.9	
ODI (n/h)		31.6 ± 24.5	31.3 ± 26.1	0.787
Mean SaO_2, n (%)		92.4 ± 3.0	92.6 ± 3.6	0.277
Lowest SaO_2, n (%)		77.7 ± 9.4	78.4 ± 9.9	0.091
Time spent SaO_2< 90% (min)		58.4 ± 83.9	54.5 ± 79.7	0.436
PAP adherence (>4 h/day) n (%)		75.1%	74.5%	0.77
PAP use/day (hours)		4.9 ± 2.4	4.8 ± 2.3	0.277
PAP duration (days)		310 ± 357	303 ± 332	0.646

Change in weight during follow-up (kg)	0.2 ± 8.5	-0.4 ± 7.7	0.086

*Parameters with p-value<0.05 **Variables expressed as percentage or mean ± standard deviation.

Abbreviations:

BMI: body mass index; HDL: high-density lipoprotein; LDL: low-density lipoprotein; CHD: coronary heart disease; ESS: Epworth sleepiness score; AHI: apnea-hypopnea index; ODI: oxygen desaturation index; SaO_2: arterial oxygen saturation; PAP: positive airway pressure.

Lipid status at PAP follow up

In the unadjusted analysis, we observed a reduction of total- and LDL-cholesterol as well as triglycerides while HDL cholesterol increased following PAP treatment **(Table 2)**. In the repeated measures ANOVA, after adjustment for age, sex, lipid lowering medication, change in weight, PAP compliance and duration, total cholesterol concentration decreased by 4.9 mg/dl after PAP therapy (p=0.019) **(Figure 1)**. In the sub-cohort analysis, adjusted LDL cholesterol and HDL concentrations tended to improve, but the changes did not reach statistical significance after adjustment for confounding factors. Triglycerides remained unchanged after PAP treatment. A ≥10% reduction of total cholesterol concentration (applied as a clinically relevant modification), was found in 27% of the study population. In 5.5% of subjects there was a more pronounced reduction (>25%) of total cholesterol. OSA patients with profound reduction in cholesterol were under no or unchanged lipid lowering medication treatment. The change in cholesterol following PAP treatment was more pronounced in patients from the North compared with the South regions (-6.44 ± 33.05 versus -2.21 ± 32.63; p=0.028).

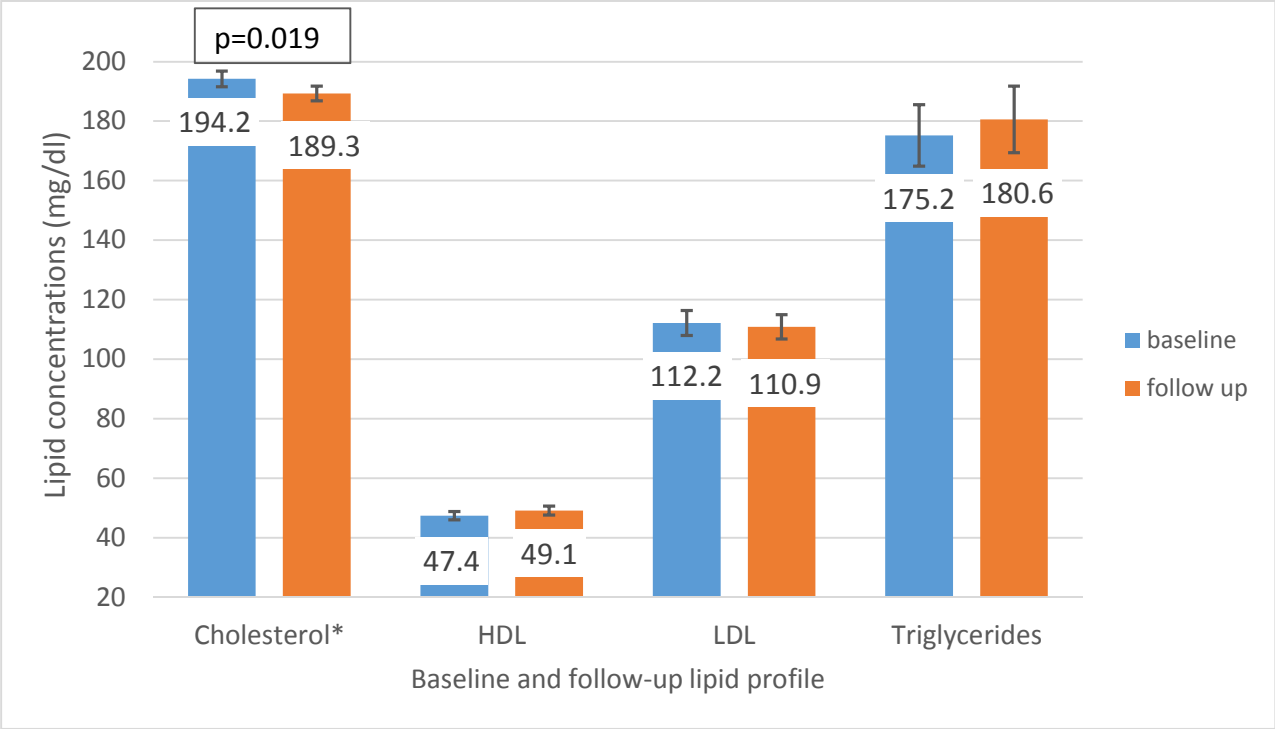
Table 2. The unadjusted pairwise comparison of lipid concentrations.

	N	Baseline Mean ± SD	Follow-up Mean ± SD	Mean Difference ± SD	95% CI	p-value
Total cholesterol *	1564	200.3 ± 43.8	195.7 ± 42.0	-4.58 ± 33.75	-6.26 ; -2.91	<0.001
HDL cholesterol *	835	45.3 ± 12.7	46.5 ± 13.7	1.30 ± 9.87	0.63 ; 1.97	<0.001
LDL cholesterol *	828	123.4 ± 39.0	122.0 ± 37.4	-3.57 ± 29.11	-5.55 ; -1.58	<0.001
Triglycerides	866	178.3 ± 104.5	173.7 ± 104.8	-4.28 ± 90.43	-8.78 ; 0.21	0.062

* Parameters with p value < 0.05,**All parameters expressed in mg/dl.

The subsequent sensitivity analysis addressed the adjusted mean for total cholesterol concentration in subgroups defined by sex, smoking status, concomitant lipid lowering medication, comorbidities, long-term PAP use and low versus high PAP compliance **(Table 3)**. The decrease in cholesterol was less pronounced in patients with comorbidities like diabetes ($p<0.001$) and ischemic heart disease ($p=0.057$). However, 47.5% subjects with diabetes and 65.9% subjects with ischemic heart disease had lipid lowering medication use. Although subjects without lipid lowering medication demonstrated a significant reduction in cholesterol, the mean follow-up cholesterol concentrations were higher than subjects using lipid lowering medication (202.1 ± 41.3 mg/dl vs 178.5 ± 39.6 mg/dl).

Figure 1. Pairwise comparisons in lipid profile in regression model adjusted for age, sex, lipid lowering medication, change in weight, PAP compliance and duration.



**Parameters with p<0.05, **all values expressed as mean ± SD (mg/dl).*

In univariate analysis, the change in total cholesterol correlated with age ($r=0.065$, $p=0.01$), duration of PAP treatment ($r= -0.071$, $p=0.005$) and there was a trend for mean overnight oxygen saturation ($r= -0.047$, $p=0.06$) but not with measures of obesity, weight change, sleep apnea intensity or the degree of intermittent nocturnal hypoxia. A multivariate linear regression model for defining independent predictors of change in total cholesterol

concentrations after PAP treatment was built and adjusted for the statistically significant parameters in univariate analysis and t-test. In the adjusted regression analysis, duration of PAP treatment was the only independent predictor for a reduced cholesterol concentration whereas comorbid diabetes and drug treated hyperlipidemia were associated with an increase in total cholesterol concentrations **(Table 4)**. Furthermore, duration of PAP treatment was the only variable associated with a pronounced reduction (≥25%) of total cholesterol (p=0.003). [17] Additionally, the change in total cholesterol correlated with change in LDL cholesterol (r=0.842, p<0.001) following PAP treatment.

Table 3. Independent t-test demonstrating the difference for the change in cholesterol by categorical variables. The decrease in cholesterol was smaller in patients with comorbidities including diabetes (p<0.001) and ischemic heart disease (p=0.057).

		N	Change in total cholesterol (mg/dl) (±SD)*	Mean difference (mg/dl) (95%CI)	P value
Sex	Male	1163	-4.46 ± 32.80	-0.48 (-4.31, 3.36)	0.81
	Female	401	-4.94 ± 36.41		
Smoking	Smokers	365	-5.46 ± 33.67	1.16 (-2.81, 5.10)	0.57
	Non-smokers	1199	-4.32 ± 33.78		
Lipid lowering medication use *	Users	397	0.47 ± 36.68	-6.77 (-10.84, -2.69)	0.001
	Non-users	1167	-6.30 ± 32.53		
PAP duration	≥365 days	590	-6.80 ± 36.70	3.56 (-0.02, 7.13)	0.051
	<365 days	974	-3.24 ± 31.77		
PAP compliance	≥ 6 hours/day	783	-4.67 ± 33.93	0.17 (-3.18, 3.52)	0.92
	<6 hours/day	781	-4.50 ± 33.59		
Arterial Hypertension (AHT)	AHT (+)	755	-3.61 ± 35.08	-1.84 (-5.21, 1.50)	0.27
	AHT (-)	804	-5.47 ± 32.50		
Ischemic heart disease (IHD)	IHD (+)	166	0.14 ± 37.84	-5.27 (-10.71, 0.16)	0.057
	IHD (-)	1393	-5.13 ± 33.23		
Transient ischemic attack (TIA)	TIA (+)	45	-0.13 ± 32.53	-4.57 (-14.59, 5.45)	0.37
	TIA (-)	1514	-4.70 ± 33.81		
Diabetes mellitus (DM) *	DM (+)	327	1.10 ± 35.94	-7.17 (-11.28, -3.07)	0.001
	DM (-)	1232	-6.07 ± 33.03		

* Parameters with p value < 0.05, **Change in total cholesterol was calculated as follow-up cholesterol-baseline cholesterol concentrations.

Abbreviations: PAP: positive airway pressure; AHT: arterial hypertension; IHD: ischemic heart disease; TIA: transient ischemic attack; DM: diabetes mellitus.

Table 4. Multivariate linear regression model with predictors of change in total cholesterol concentrations after PAP treatment (n=1559). The duration of PAP treatment was the only parameter significantly associated with a decrease in total cholesterol levels.

Predictors	β	Std. Error	CI (95%)	P value
Age (years)	0.12	0.08	-0.04, 0.28	0.135
Lipid lowering medication use (yes/no) *	4.82	2.08	0.74, 8.90	0.021
Diabetes mellitus (yes/no) *	4.67	2.20	0.36, 8.98	0.034
Duration of PAP treatment (months) *	-0.16	0.06	-0.28,- 0.04	0.011

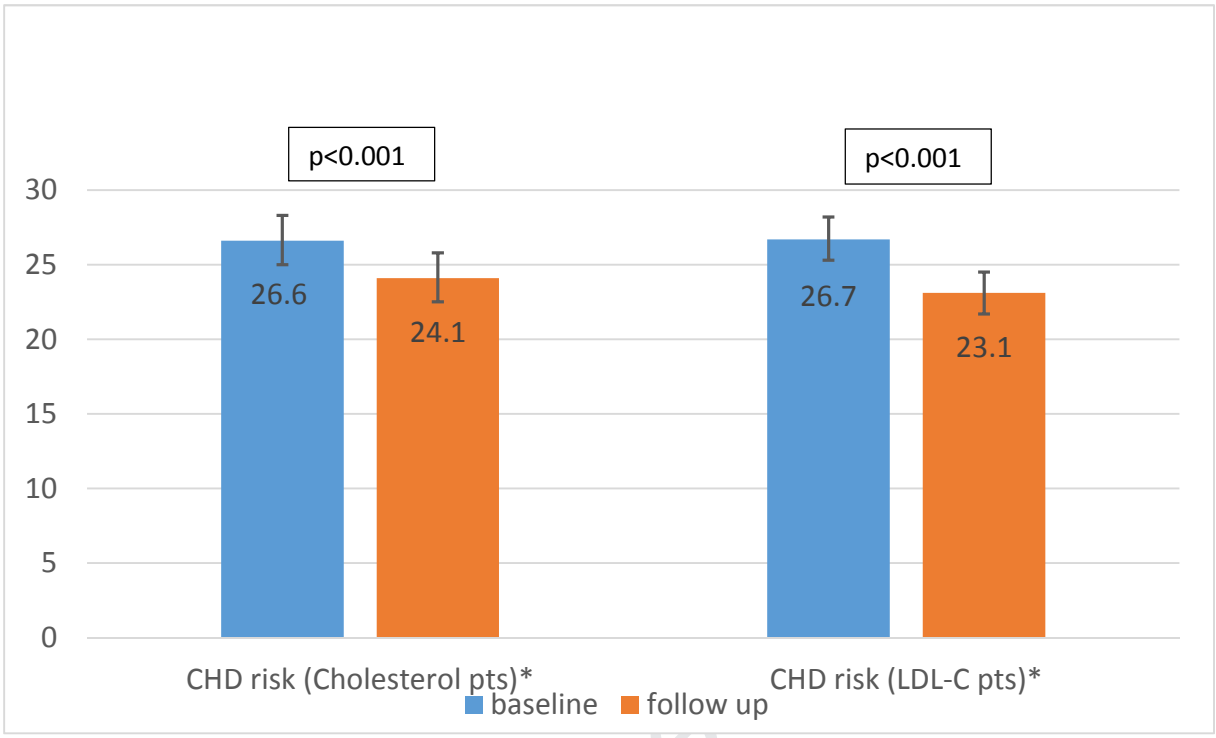
*Parameters with p value < 0.05 ** β value indicates the change in cholesterol in mg/dl for each predictor. The effect of age is calculated in terms of years and duration of PAP treatment is calculated in terms of months.
#The model was adjusted for age, lipid lowering medication use, diabetes mellitus and duration of PAP treatment.

Framingham risk score for coronary heart disease

The Framingham risk score for incident CHD was computed based on total cholesterol and LDL cholesterol decreased following PAP in both sexes in the regression analysis for repeated measures after adjustment for PAP duration, use of lipid lowering medication and change in weight **(Figure 2 a, b)**. Moreover, the duration of PAP treatment was associated with CHD risk reduction in both sexes (p<0.001).

Figure 2 a, b. Comparison of baseline and follow up CHD risk scores** in male (2a) and female (2b) patients adjusted for PAP duration, lipid lowering medication and change in weight.

Figure 2a.

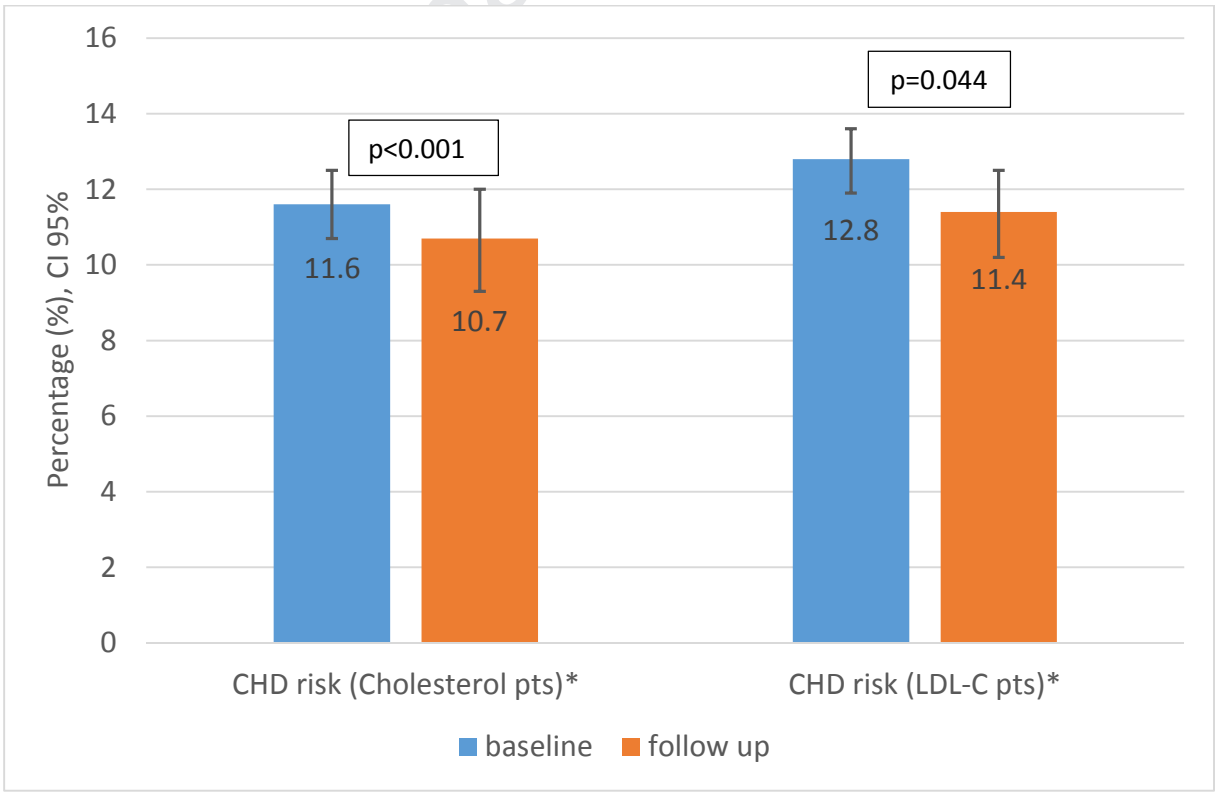


Baseline and follow up coronary heart disease risk scores in males.

*Parameters with p value<0.05.

**Framingham coronary heart disease risk has been calculated in terms of total cholesterol and LDL-C points.

Figure 2b.



Baseline and follow up coronary heart disease risk scores in females

*Parameters with p value <0.05.
**Framingham coronary heart disease risk has been calculated in terms of total cholesterol and LDL-C points.

Discussion

In this prospective study comprising a large multinational cohort, we observed a significant effect of PAP therapy on plasma lipid concentrations. The reduction in total cholesterol following PAP persisted after adjustment for important confounding factors and the change was predicted by the duration of PAP treatment. The reduction in cholesterol and LDL-cholesterol concentrations translate into a 10% reduction of predicted risk for incident coronary heart disease according to the Framingham risk score for incident CHD.

OSA causes repetitive episodes of upper airway obstruction and results in intermittent hypoxia, increased sympathetic activity, inflammation, oxidative stress, endothelial and metabolic dysfunction. These pathophysiologic mechanisms may cause the increased risk of CV disease in patients with OSA [18]. Although there is extensive literature regarding the role of hypoxia induced factor (HIF) on the regulation of carbohydrate metabolism, the effects of hypoxia and HIF on lipid metabolism have recently become the focus of closer examination. Thus, the role of hypoxia in triggering complex intracellular molecular pathways and resulting in enhanced lipogenesis by HIF-dependent induction of genes involved in fatty acid uptake, synthesis and storage has been proven [19]. In a recent study with 15 OSA subjects without comorbid diseases, Drager et al. [20], have reported that severe OSA and nocturnal hypoxemia decreases lipolysis of triglyceride-rich lipoproteins and delays removal of remnants. Notably, our previous studies from the ESADA cohort suggested an independent association between intermittent nocturnal hypoxia and lipid concentrations as well as a diagnosis of hyperlipidemia [6,7]. Furthermore, there are studies indicating that PAP treatment reduces systemic oxidative stress, which is a consequence of CIH in OSA [21,22].

The direction and size of PAP treatment effects on cardiometabolic health in OSA patients has been studied extensively over the past decades. However, many of these studies have limited sample size and treatment duration was generally short. In a meta-regression analysis examining the change in lipid profile in 1,958 OSA subjects from 29 studies following PAP treatment, total cholesterol was the only parameter demonstrating a statistically significant reduction [8]. Treatment duration ranged from two days to six months and only

one study reached one year. The calculated mean reduction of cholesterol was -5.7 mg/dl in the unadjusted meta-regression analysis which compares well with the reduction of -4.9 mg/dl in cholesterol in our study. However, adjustments for duration of PAP treatment were not performed in the meta-regression. Nevertheless, a recent longitudinal pilot study following 31 OSA subjects for five years has reported positive effect of PAP on total cholesterol and LDL-cholesterol levels which supports our findings on positive effects of long-term PAP treatment on total cholesterol levels [23]. In contrast to these analyses, a review of randomized controlled trials found no consistent reduction of lipid levels when sham-CPAP was applied as a control condition [9]. In the study of Drager et al. [20], although there was no significant change in the lipid levels following three months of PAP treatment, CPAP treatment was still associated with improvement in the lipolysis process estimated by the 3H-triglyceride clearance and PAP was considered as effective in order to restore the lipolysis rates. It is also possible that other factors like weight reduction or life style intervention with increased physical activity may have influenced the lipid status during PAP treatment.

The current analysis applied several steps to better understand the effects of PAP treatment on lipid status and to account, at least in part, for the observational, non-randomized study design. The unadjusted analysis showed highly significant changes in all lipid parameters, and adjustment for important confounders like change in weight or age reinforced the significant overall reduction of total cholesterol by PAP. We also addressed treatment duration, which appeared to be dose dependently related to the reduction of cholesterol levels.

Of note, we identified the largest effects on cholesterol in patients without comorbidities like ischemic heart disease, diabetes mellitus, and hyperlipidemia as well as in patients without prior lipid lowering medication. It is speculated that patients with ischemic heart disease and diabetes were more likely to be aware of the health burden of hyperlipidemia and this might lead to better adherence to international guidelines for prevention. Furthermore, a considerable number of subjects with comorbidities like diabetes mellitus and ischemic heart disease were already treated with lipid lowering medication. In a meta-analysis with 21,303 randomized subjects, the overall effect size of lipid lowering medication on cholesterol levels was around -1.5 (-1.2 - -1.7) mmol/L (corresponding to approximately -27 (21-31) mg/dl). [24] Use of high intensity statin therapy is also expected to reduce LDL

cholesterol levels by approximately 1.5 (1-2) mmol/L depending on the pre-treatment lipid levels. [25] Indeed, our data demonstrate that PAP treatment has a far weaker effect on total cholesterol (-5 (3-7) mg/dl) compared with lipid lowering medication.

LDL cholesterol is a primary target for lipid lowering treatment and total cholesterol is suggested as an alternative target. The Joint British Societies' guidelines on prevention of CV disease in clinical practice proposes that a reduction of 25% in total cholesterol in patients with high risk for CV disease may be a target for a clinically meaningful change by treatment [17]. In our study, 5.5% subjects demonstrated a reduction of 25% in cholesterol. According to Rossouw [26], a cholesterol reduction by 10% may decrease clinical event rate by approximately 20%. In our study 27% subjects had a reduction of 10% in cholesterol which underlines the clinical impact of modest changes in cholesterol concentration. The statistically significant decrease in the Framingham risk score also emphasized this clinical impact.

In our previous studies from our ESADA cohort, significant differences in lipid levels across European regions were demonstrated and the influence of geographical regions were emphasized. The influence of European regions on lipid profiles following PAP treatment was also observed in the present study as OSA subjects in North European regions demonstrated a higher reduction in total cholesterol following PAP treatment compared with subjects from South European regions. These findings suggest the importance of regional differences in regards to factors like diet, physical activity, health care systems as well as patients' attitude and compliance.

A number of methodological strengths and limitations of the study need to be considered. This is a prospective cohort study based on a large sample size and a multicenter study design. Our findings add evidence to the literature characterized by conflicting data. Important potential confounders like measures of obesity, weight change over time, long and short term of treatment duration, intake of lipid lowering drugs and anthropometric factors were accounted for. On the other hand, a clinical referral bias cannot be excluded in our study since the majority of ESADA centers represent academic tertiary health institutions and this may have resulted in an enrichment of patients with multiple important comorbidities including diabetes and ischemic heart disease. Since the ESADA reflects clinical practice, the influence of patients' comorbidities on the physicians' decisions to perform

repeated lipid analyses in this high risk groups cannot be ruled out. However, the association of diabetes with an increase in total cholesterol levels following PAP treatment suggest that a potential selection bias was rather in favor for an underestimation of the overall effect of PAP treatment on the changes in lipid levels. Another limitation is that PAP follow-up data and a second lipid sample was obtained only in a subgroup of the ESADA population. However, anthropometric data and sleep apnea severity did not differ in a clinically meaningful manner between the analysis population and the remaining ESADA on PAP treatment. Data on cholesterol was available in more than 1,500 subjects whereas the statistical power for the analysis of LDL and HDL cholesterol and fasting triglycerides was substantially lower. This may at least explain the lack of significant findings for these three parameters of lipid metabolism. As an important strength, the ESADA database captures the use of concomitant lipid lowering medication both at baseline and at follow up. Only very few patients changed medication status and the observed changes in lipid lowering medication were not associated with a relevant change in lipid levels. However, we were not able to adjust for the exact dosage or any change in dosage for concomitant medication as this information is of high uncertainty. Another limitation was the decentralized analysis of lipids, which may have generated differences between centers. Similarly, sleep study methodologies differ between ESADA centers but a sensitivity analysis confirmed that there was no systematic influence of the type of different sleep study recording equipment used on the PAP treatment effect. Although we controlled for several factors that may confound the change in cholesterol following PAP treatment, we did not monitor potential confounders such as dietary modifications and changes in physical activity over the treatment period.

In conclusion, this observational study reports a reduction in total cholesterol as well as in coronary heart disease risk score after PAP treatment. Identification and treatment of OSA patients with dyslipidemia may be relevant considering the close association between hypercholesterolemia and increased CV mortality. In fact, a multimodal treatment approach with traditional risk factor management including implementation of a healthier lifestyle is warranted as a step towards individualized OSA patient care.

Acknowledgement

The authors acknowledge the guidance imparted by the ATS MECOR Program for this study, especially from Ahmet Demir MD and Phil Hopewell MD.

Financial support for the study: The ESADA network has received support from the European Union COST action B26 and the European Respiratory Society (ERS) funded Clinical Research Collaboration (CRC). Unrestricted seeding grants from the ResMed Foundation and the Philips Respironics Foundation for establishment of the database in 2007 and 2011 are gratefully acknowledged. The ESADA network has a scientific collaboration with Bayer AG.

Nonfinancial support was provided by the European Sleep Research Society (ESRS) and the European Respiratory Society (ERS) in terms of logistics for communication, meetings and data presentations for the ESADA collaborators.

Dr. Verbraecken reports grants and personal fees from ResMed, Bioprojet, Jazz Pharmaceutics; personal fees from Philips, Sanofi, Agfa-Gevaert, grants from AirLiquide; personal fees from Springer, Westfalen Medical, SomnoMed, Vivisol, Total Care, Medidis, Fisher & Paykel, Wave Medical, OSG, Mediq Tefa, NightBalance, Heinen & Löwenstein, AstraZen, Accuramed, Bekaert Deslee Academy and UCB Pharma, outside the submitted work. Dr. Hedner reports grants from ResMed, Philips Respironics, and the European Respiratory Society all related to maintenance of database on behalf of the ESADA group during the conduct of the study. Dr. Grote reports grants from Bayer, Resmed, Respironics/Philips, and from the European Respiratory Society during the conduct of the study; non-financial support and other from Itamar Medical, Resmed, Philips, and Astra Zeneca, outside the submitted work. In addition, Dr. Grote has a patent on sleep apnea therapy licensed. The remaining co-authors have no conflict of interest to declare.

References

[1] Franklin KA, Lindberg E. Obstructive sleep apnea is a common disorder in the population-A review on the epidemiology of sleep apnea. J Thorac Dis 2015;7:1311–22. https://doi.org/10.3978/j.issn.2072-1439.2015.06.11.

[2] Patil SP, Schneider H, Schwartz AR, Smith PL. Adult Obstructive Sleep Apnea. Chest 2007;132:325–37.

[3] McNicholas W, Bonsignore M. Sleep apnoea as an independent risk factor for cardiovascular disease: current evidence, basic mechanisms and research priorities. Eur Respir J 2006;29:156–78.

[4] Lévy P, Kohler M, McNicholas WT, Barbé F, McEvoy RD, Somers VK, et al. Obstructive sleep apnoea syndrome. Nat Rev Dis Prim 2015;1:15015.

[5] Ryan S, McNicholas WT. Intermittent hypoxia and activation of inflammatory molecular pathways in OSAS. Arch Physiol Biochem 2008;114:261–6.

[6] Gündüz C, Basoglu OK, Hedner J, Zou D, Bonsignore MR, Hein H, et al. Obstructive sleep apnoea independently predicts lipid levels: Data from the European Sleep Apnea

Database. Respirology 2018;23:1180–9.

[7] Gunduz C, Basoglu OK, Hedner J, Bonsignore MR, Hein H, Staats R, et al. Hyperlipidemia prevalence and cholesterol control in obstructive sleep apnea: Data from the European Sleep Apnea Database (ESADA). J Intern Med 2019;286:676–88.

[8] Nadeem R, Singh M, Nida M, Kwon S, Sajid H, Witkowski J, et al. Effect of CPAP treatment for obstructive sleep apnea hypopnea syndrome on lipid profile: a meta-regression analysis. J Clin Sleep Med 2014;10:1295–302.

[9] Jullian-Desayes I, Joyeux-Faure M, Tamisier R, Launois S, Borel AL, Levy P, et al. Impact of obstructive sleep apnea treatment by continuous positive airway pressure on cardiometabolic biomarkers: A systematic review from sham CPAP randomized controlled trials. Sleep Med Rev 2015;21:23–38. https://doi.org/10.1016/j.smrv.2014.07.004.

[10] Hedner J, Grote L, Bonsignore M, McNicholas W, Lavie P, Parati G, et al. The European Sleep Apnoea Database (ESADA): Report from 22 European sleep laboratories. Eur Respir J 2011;38:635–42. https://doi.org/10.1183/09031936.00046710.

[11] Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991;14:540–5.

[12] Iber C, Ancoli-Israel S, Chesson A, Quan S. The AASM Manual for the scoring of sleep and associated events: Rules, terminology, and technical specification. 2007.

[13] Escourrou P, Grote L, Penzel T, Mcnicholas WT, Verbraecken J, Tkacova R, et al. The diagnostic method has a strong influence on classification of obstructive sleep apnea. J Sleep Res 2015;24:730–8. https://doi.org/10.1111/jsr.12318.

[14] Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. JAMA 2001;285:40.

[15] Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation 1998;97:1837–47.

[16] Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972;18:499–502.

[17] JBS 2: Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice. Heart 2005;91:v1 LP-v52.

[18] Ryan S. Mechanisms of cardiovascular disease in obstructive sleep apnoea. J Thorac Dis 2018;10:S4201–11.

[19] Mylonis I, Simos G, Paraskeva E. Hypoxia-inducible factors and the regulation of lipid metabolism. Cells 2019;8:214.

[20] Drager LF, Tavoni TM, Silva VM, Santos RD, Pedrosa RP, Bortolotto LA, et al. Obstructive sleep apnea and effects of CPAP on triglyceride-rich lipoprotein

metabolism. J Lipid Res 2018;59:1027–33.

[21] Christou K, Kostikas K, Pastaka C, Tanou K, Antoniadou I, Gourgoulianis KI. Nasal continuous positive airway pressure treatment reduces systemic oxidative stress in patients with severe obstructive sleep apnea syndrome. Sleep Med 2009;10:87–94.

[22] Barceló A, Barbé F, de la Peña M, Vila M, Pérez G, Piérola J, et al. Antioxidant status in patients with sleep apnoea and impact of continuous positive airway pressure treatment. Eur Respir J 2006;27:756–60.

[23] Simon B, Gabor B, Barta I, Paska C, Boszormenyi Nagy G, Vizi E, et al. Effect of 5-year continuous positive airway pressure treatment on the lipid profile of patients with obstructive sleep apnea: A pilot study. J Sleep Res 2019:e12874. https://doi.org/10.1111/jsr.12874.

[24] Ross SD, Allen IE, Connelly JE, Korenblat BM, Smith ME, Bishop D, et al. Clinical outcomes in statin treatment trials: A meta-analysis. Arch Intern Med 1999;159:1793–802. https://doi.org/10.1001/archinte.159.15.1793.

[25] Collins R, Reith C, Emberson J, Armitage J, Baigent C, Blackwell L, et al. Interpretation of the evidence for the efficacy and safety of statin therapy. Lancet 2016;388:2532–61.

[26] Rossouw JE. The effects of lowering serum cholesterol on coronary heart disease risk. Med Clin North Am 1994;78:181–95.

Collaborators in the ESADA project (Current and past, in alphabetical order)

Alexandroupolis, Greece

- Steiropoulos P, Sleep Unit, Department of Pneumonology, Democritus University of Thrace, Alexandroupolis, Greece

Antwerp, Belgium

- Verbraecken J, Multidisciplinary Sleep Disorders Centre, Antwerp University Hospital and University of Antwerp, Antwerp, Belgium
- Petiet E, Multidisciplinary Sleep Disorders Centre, Antwerp University Hospital and University of Antwerp, Antwerp, Belgium

Athens, Greece

- Trakada G, Division of Pulmonology, Department of Clinical Therapeutics, National and Kapodistrian University of Athens, School of Medicine, Alexandra Hospital, Athens, Greece

Barcelona, Spain

- Montserrat JM, Hospital Clinic i Provincial de Barcelona, Barcelona, IDIBAPS Barcelona and CIBERes, Madrid, Spain

Berlin, Germany

- Fietze I, Schlafmedizinisches Zentrum, Charité – Universitätsmedizin Berlin, Germany
- Penzel T, Schlafmedizinisches Zentrum, Charité – Universitätsmedizin Berlin, Germany

Brno and Klecany, Czech Republic
- Ondrej L, Department of Cardiology, University Hospital Brno and International Clinical Research Center, St. Ann´s University Hospital, Brno, Czech Republic

Brussels, Belgium
- Rodenstein D, Cliniques Universitaires Saint-Luc (Brussels, Belgium)

Caeceres, Spain
- Masa JF, Hospital San Pedro de Alcàntara, Cáceres, Spain

Crete, Greece
- Bouloukaki I. Sleep Disorders Unit, Department of Respiratory Medicine, Medical School, University of Crete, Crete, Greece
- Schiza S, Sleep Disorders Unit, Department of Respiratory Medicine, Medical School, University of Crete, Greece

Dublin, Ireland
- Kent B, Guy's and St Thomas' NHS Foundation Trust, Guy's Hospital, London, UK
- McNicholas WT, Department of Respiratory Medicine, St. Vincent´s University Hospital, Dublin, Ireland
- Ryan S, Pulmonary and Sleep Disorders Unit, St. Vincent's University Hospital, Dublin, Ireland

Edinburgh, United Kingdom
- Riha RL, Department of Sleep Medicine, Royal Infirmary Edinburgh, Scotland

Førde, Norway
- Kvamme JA, Sleep Laboratory, ENT Department, Førde Central Hospital, Førde, Norway

Geesthacht, Germany
- Hein H, Sleep Disorders Centers, Johanniter-Krankenhaus, Geestacht, Germany

Giessen, Germany
- Schulz R, Sleep Disorders Centre, University of Giessen, Lung Centre, Giessen, Germany

Gothenburg, Sweden
- Grote L, Sleep Disorders Center, Pulmonary Department, Sahlgrenska University Hospital, and Center of Sleep and Wake Disorders, Sahlgrenska Academy, Gothenburg University, Göteborg, Sweden
- Hedner J, Sleep Disorders Center, Pulmonary Department, Sahlgrenska University Hospital, and Center of Sleep and Wake Disorders, Sahlgrenska Academy, Gothenburg University, Göteborg, Sweden
- Zou D, Center of Sleep and Wake Disorders, Sahlgrenska Academy, Gothenburg University, Göteborg, Sweden

Grenoble, France
- Pépin JL, Université Grenoble Alpes, INSERM HP2 (U1042) and Grenoble University Hospital, Grenoble, France
- Levy P, Université Grenoble Alpes, INSERM HP2 (U1042) and Grenoble University Hospital, Grenoble, France

- Bailly S, Université Grenoble Alpes, INSERM HP2 (U1042) and Grenoble University Hospital, Grenoble, France

Haifa, Israel
- Lavie L and Peretz Lavie, Centre for Sleep Medicine, Technion Institute of Technology, Haifa, Israel
- Lavie P, Centre for Sleep Medicine, Technion Institute of Technology, Haifa, Israel

Izmir, Turkey
- Basoglu OK, Department of Chest Diseases, Ege University, Izmir, Turkey
- Tasbakan MS, Department of Chest Diseases, Ege University, Izmir, Turkey

Klapeida, Lithuania
- Varoneckas G, Institute Psychophysiology and Rehabilitation, Palanga, Lithuania

Kosice, Slovakia
- Joppa P, Department of Respiratory Medicine and Tuberculosis, Faculty of Medicine, P.J.Safarik University and L. Pasteur University Hospital, Kosice, Slovakia
- Tkacova R, Department of Respiratory Medicine and Tuberculosis, Faculty of Medicine, P.J.Safarik University and L. Pasteur University Hospital, Kosice, Slovakia

Lisbon, Portugal
- Staats R, Department of Respiratory Medicine, Clínica Universitária de Pneumologia, Hospital de Santa Maria, CHLN. Lisbon, Portugal

Lleida, Spain
- Barbé F, Servei Pneumologia Hospital Arnau de Vilanova and Hospital Santa Maria, Lleida, and CIBERes, Madrid, Spain

Milano, Italy
- Lombardi C, Istituto Auxologico Italiano, IRCCS, Department of Cardiovascular, Neural and Metabolic Sciences, St. Luke Hospital, Milan & Department of Medicine and Surgery; University of Milano-Bicocca, Milan, Italy.
- Parati G, Istituto Auxologico Italiano, IRCCS, Department of Cardiovascular, Neural and Metabolic Sciences, St. Luke Hospital, Milan & Department of Medicine and Surgery; University of Milano-Bicocca, Milan, Italy.

Porto, Portugal
- Drummond M, Pulmonology Department Hospital São João, Medicine Faculty of Porto University, Porto, Portugal
- van Zeller M, Pulmonology Department Hospital São João, Medicine Faculty of Porto University, Porto, Portugal

Palermo, Italy
- Bonsignore MR, Biomedical Department of Internal and Specialistic Medicine (DiBiMIS), Section of Pneumology, University of Palermo; and CNR, Istituto per la Ricerca e l'Innovazione Biomedica, Palermo, Italy
- Marrone O, CNR, Istituto per la Ricerca e l'Innovazione Biomedica, Palermo, Italy

Paris, France
- Petitjean M, Sleep Disorders Center, Antoine Beclere Hospital, Clamart, France

- Roisman G, Sleep Disorders Center, Hopital Antoine-Beclere, Clamart, France

Prague, Czech Republic

- Pretl M, Centre for Sleep and Waking Disorders, Department of Neurology, First Faculty of Medicine, Charles University, Prague, and Inspamed, Neurology and Sleep Laboratory, Prague, Czech Republic

Riga, Latvia

- Vitols A, Institute of Cardiology, University of Latvia, Riga, Latvia

Split, Croatia

- Dogas Z, Sleep Medicine Center, Department of Neuroscience, University of Split School of Medicine, Split, Croatia
- Galic T, Sleep Medicine Center, Department of Neuroscience, University of Split School of Medicine, Split, Croatia

Thessaloniki, Greece

- Pataka A, Respiratory Failure Unit, G. Papanikolaou Hospital, Thessalonika, Greece

Turku, Finland

- Anttalainen U, Division of Medicine, Department of Pulmonary Diseases, Turku University Hospital and Sleep Research Centre, Department of Pulmonary Diseases and Clinical Allergology, University of Turku, Finland
- Saaresranta T, Division of Medicine, Department of Pulmonary Diseases, Turku University Hospital and Sleep Research Centre, Department of Pulmonary Diseases and Clinical Allergology, University of Turku, Finland

Warsaw, Poland

Institute of Tuberculosis and Lung Diseases

- Plywaczewski R, 2nd Department of Respiratory Medicine, Institute of Tuberculosis and Lung Diseases, Warsaw, Poland
- Sliwinski P, 2nd Department of Respiratory Medicine, Institute of Tuberculosis and Lung Diseases, Warsaw, Poland

Medical University of Warzaw

- Bielicki P, Department of Internal Medicine, Pneumonology and Allergology, Medical University of Warsaw, Warsaw, Poland

- Total cholesterol decreases after long-term PAP treatment in OSA
- PAP treatment reduces coronary heart disease risk score in subjects with OSA
- PAP treatment may reduce overall cardiovascular risk in subjects with OSA
- Currently, this is the largest study on the current topic from a multicenter multinational cohort

CRediT author statement

Canan Gunduz: Conceptualization, methodology, formal analysis, writing - Original Draft. **Ozen K Basoglu**: Conceptualization, writing - Review & Editing. **John Arthur Kvamme**: Investigation, writing - Review & Editing. **Johan Verbraecken**: Investigation, writing - Review & Editing. **Ulla Anttalainen**: Investigation, writing - Review & Editing. **Oreste Marrone**: Investigation, writing - Review & Editing. **Paschalis Steiropoulos**: Investigation, writing - Review & Editing. **Gabriel Roisman**: Investigation, writing - Review & Editing. **Pavol Joppa**: Investigation, writing - Review & Editing. **Holger Hein**: Investigation, writing - Review & Editing. **Georgia Trakada**: Investigation, writing - Review & Editing . **Jan Hedner**: Investigation, methodology, writing - Review & Editing, supervision, funding acquisition. **Ludger Grote**: Conceptualization, methodology, investigation, writing - Review & Editing, project administration, funding acquisition.