Obstructive Sleep Apnea Treatment and Fasting Lipids: A Comparative Effectiveness Study

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Abstract

Obstructive sleep apnea (OSA) is associated with cardiovascular disease. Dyslipidemia has been implicated as one mechanism, but no consistent associations with lipids exist for OSA or positive airway pressure (PAP) treatment. We assessed relationships between fasting lipid levels and obesity and OSA severity, and explored the impact of PAP treatment on two-year fasting lipid level changes.

Analyses included moderate-to-severe OSA patients from the Icelandic Sleep Apnea Cohort. Fasting morning lipids were analyzed in 613 untreated participants not on lipid-lowering medications at baseline. Patients were then initiated on PAP and followed for two years. Sub-classification using propensity score quintiles, which aimed to replicate covariate balance associated with randomized trials and, therefore, minimize selection bias and allow causal inference, was used to design the treatment group comparisons; 199 PAP adherent patients and 118 non-users were identified.

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At baseline, obesity was positively correlated with triglycerides and negatively correlated with total, LDL and HDL cholesterol. A small correlation was observed between the apnea-hypopnea index and HDL cholesterol. No effect of PAP adherence on two-year fasting lipid changes was observed.

Results do not support the concept of changes in fasting lipids as a primary mechanism for the increased risk of atherosclerotic cardiovascular disease in OSA.

Keywords

Sleep Apnea Syndromes; Fasting Lipids; Continuous Positive Airway Pressure; Obesity; Cardiovascular Disease; Propensity Scores

INTRODUCTION

Obstructive sleep apnea (OSA) is independently associated with atherosclerotic disease,[1] but mechanisms remains unclear. Dyslipidemia is central to atherosclerosis, with a strong association between lipid levels and risk of atherosclerotic cardiovascular disease.[2] Consequently, dyslipidemia has been implicated as a possible mechanism linking OSA with atherosclerosis. However, studies to date have not definitively established a relationship between the lipid profile and either OSA or positive airway pressure (PAP) treatment.[3–16]

OSA is characterized by repetitive collapse of the upper airway causing chronic intermittent hypoxia (CIH). Animal models demonstrate dyslipidemia proportional to CIH severity and development of atherosclerotic lesions.[9–11, 17–21] However, while studies in mice support a causal relationship between CIH and dyslipidemia, human studies evaluating the effects of OSA[3–11] and PAP treatment[8–16] on lipid levels are inconsistent. Moreover, studies examining PAP are of limited duration, following patients for at most 6 months.[8–16]

When examining inconsistencies in the effect of PAP, one important consideration is the impact of selection bias within observational studies. Propensity score (PS) methodologies are well-established techniques used in numerous fields, including cardiovascular research, [22] to minimize bias and perform comparative effectiveness research in observational studies. A recent NHLBI working group highlighted the importance of such methods within observational samples,[23] which are more inclusive of real-world patients than typical randomized trials. As previously discussed,[24, 25] sub-classification using PS is done without regard to outcome data, allowing the 'design' of non-randomized comparisons to examine treatment effects. In observational studies, propensity scores are analogous to randomization, eliminating systematic biases in non-randomized group comparisons due to imbalance from measured covariates, thus improving causal inference.[25] Therefore, PS methods allow treatment effect analyses to proceed as if patients were randomized.[24, 25]

Using the Icelandic Sleep Apnea Cohort (ISAC),[26, 27] sub-classification by PS quintiles was employed to compare fasting lipid level changes between PAP adherent patients and non-users, two years after OSA diagnosis and treatment initiation. We also explored

associations for obesity and OSA severity with the fasting lipid profile. We hypothesized there would be a relationship between OSA severity and fasting lipids at baseline, and that PAP would improve fasting lipids in adherent subjects compared to non-users in the PS designed comparison.

METHODS

Study Subjects

Patients were diagnosed with moderate-to-severe OSA (apnea-hypopnea index [AHI] 15) and referred for PAP treatment. Participants completed standardized questionnaires, physical examination, a type 3 sleep study, fasting morning blood samples and abdominal MRI at baseline. Two years after PAP treatment initiation, participants were invited for a follow-up visit where they answered the same questionnaires, underwent physical examination and anthropometric measures and had fasting morning blood samples drawn, as in baseline assessment. Analyses were restricted to patients not using lipid-lowering medications. Details of the analysis sample obtained from ISAC are presented in the supplement (Figure E1) and previously.[26, 27] Written consent was obtained from every participant. The study protocol was approved by the National Bioethics Committee, the Data Protection Authority of Iceland and the University of Pennsylvania Institutional Review Board.

Blood Samples

Fasting blood samples were taken the morning after sleep in untreated participants at baseline and follow-up (see supplement). Total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and triglyceride (TG) concentrations were measured. Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedwald equation ($LDL\text{-}C = TC - HDL\text{-}C - TG/5$). Indicators of "abnormal" levels were defined using the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATPIII) criteria[28]: TC 200 mg/dL, LDL-C 130 mg/dL, TG 150 mg/dL and HDL-C<40 mg/dL.

PAP Adherence

Patients were followed for 2 years after PAP treatment initiation. PAP adherence was based on objective usage data from memory cards over the last 28 days, if available, or else on subjective questionnaires (for validation, see supplement). Adherent patients used PAP 4 hours/night and 20 of the last 28 nights by memory card download, or 60% of the night and 5 nights/week by questionnaire. Non-users did not use PAP and had no other specific OSA therapy, including surgery or mandibular advancement device. The sample included 240 (51%) adherent and 156 (33%) non-users. Seventy-one (15%) partial-users (patients using PAP, but not meeting 'adherent' criteria) were excluded from treatment effect analyses.

Statistical Analysis

Baseline Associations—Continuous and categorical covariates are summarized using means ± standard deviations and percentages, respectively, and compared among groups with T-tests or analysis of variance and chi-square or Fisher's exact tests. Baseline lipid

levels were natural log transformed for normality; associations with obesity and OSA severity were assessed using Pearson correlations.

Propensity Score Methodologies—We used sub-classification by PS quintiles to select samples of adherent patients and non-users in which to assess the PAP treatment effect, based on an established heuristic described by Maislin & Rubin.[24] Briefly, the heuristic consists of three stages that can be repeated as necessary in order to satisfy a set of "propensity score diagnostics" (described by Maislin & Rubin[24]). First, a main effects PS model including all desired covariates is fit to obtain PS quintiles. Second, within quintile bias effect sizes and other PS diagnostic information are analyzed to identify the most important cross-product and squared terms for inclusion in the PS model. Third, a PS model including all main effects and relevant cross-product and squared terms is estimated, and subjects in each treatment group with insufficient "covariate overlap" (as defined by the propensity scores) are excluded from the sample.

Of 240 adherent and 156 non-users in the observational sample, we identified 199 (83%) adherent and 118 (76%) non-users balanced within PS subclass for baseline age, gender, BMI, current smoking, presence of hypertension, cardiovascular disease and diabetes, exercise participation, excessive alcohol use, Epworth Sleepiness Scale (ESS), OSA severity (AHI, oxygen desaturation index [ODI], SaO_2 nadir, percentage sleep time $SaO_2<90$) and fasting lipid levels (TC, LDL-C, HDL-C, TG). Balance with respect to the included covariates was shown to be as good as that expected from randomization, strengthening causal inferences. See supplement for additional details and references about PS methodology.

Treatment Effect Analyses—Two-year fasting lipid changes were calculated within subject, using untransformed values. Treatment differences were assessed using analysis of covariance (ANCOVA), controlling for PS subclass and baseline lipid levels. Whether obesity moderated the association between PAP and lipid changes was tested using a PAP by BMI group interaction effect. Given limited power for interaction tests, treatment group comparisons were examined within BMI strata (<30, 30–35, ≥35 kg/m^2) regardless of interaction results. There was ~90% power to detect treatment differences explaining 2.5% of variability (R^2) in lipid changes (see online supplement for additional details).

RESULTS

Baseline Study Population

A comparison of the 193 (24%) users of lipid-lowering medication and 613 (76%) non-users is presented in Table E1. Users were older (p<0.0001), had higher AHI (p=0.039) and percentage time $SaO_2<90\%$ (p=0.023), and greater prevalence of hypertension (p<0.0001), diabetes (p<0.0001) and cardiovascular disease (p<0.0001) compared to lipid-lowering medication non-users. Medication users had similar BMI, HDL-C and TG levels as non-users, but lower TC (p<0.0001) and LDL-C (p<0.0001).

Table 1 shows baseline characteristics for lipid-lowering medication non-users, stratified by BMI. Obese patients were younger, participated less in exercise, and had more prevalent

hypertension and diabetes and more severe OSA. Compared to subjects with BMI<30, patients with BMI 35 had lower TC, LDL-C and HDL-C, but higher TG levels (all p<0.02).

Magnetic resonance imaging (MRI) was available in 501 (82%) subjects; reasons for missing MRI included: claustrophobia (n=66), poor quality (n=33), very high obesity (n=6) and nonspecific (n=7). Table E2 compares patients with and without MRI.

Baseline Associations with fasting lipids

Associations with baseline fasting lipids for obesity measures and OSA severity in lipid-lowering medication non-users are shown in Tables 2 and E3. BMI, weight, neck circumference and waist circumference were negatively correlated with TC, LDL-C, and HDL-C and positively correlated with TG. Waist-to-hip ratio correlated with HDL-C and TG only. All MRI fat measures were positively correlated with TG; visceral fat was negatively correlated with HDL-C. AHI was positively correlated with HDL-C. No other correlations between OSA severity and lipid levels were observed.

Propensity Score Designed Observational Study

Sub-classification using PS quintiles identified 199 (83%) adherent patients and 118 (76%) non-users meeting model assumptions assuring that, within subclass, distributions of included baseline covariates were the same for both groups. Table E4 compares patients included and excluded from the PS designed comparison.

Demographics and covariate balance—Figure 1 ("Love plot"[29]) and Table 3 show that our PS designed study resulted in baseline covariate balance between adherent patients and non-users (see Methods). In the original observational cohort, 8 of 18 covariates were significantly different between adherent and non-users (Figure 1). After adjusting for PS subclass in the designed study, no baseline covariate differences remained (see Table 3 for p-values).

Table 3 also summarizes two-year follow-up characteristics of the selected patients. We observed significant differences between groups in BMI, ESS and smoking status. Both PAP groups had lower ESS scores at follow-up, but adherent patients had greater decreases than non-users (p=0.002). Adherent patients also had increased BMI at follow-up compared to non-users (p<0.0001). Non-users were more likely to become smokers (p=0.004); 86% of patients who became smokers had a previous smoking history.

Differences in fasting lipid changes between PAP adherent and non-users—
Summary measures of fasting lipid levels are presented in Table 3. As baseline lipid levels were included in the PS heuristic, there were no baseline differences between adherent patients and non-users.

Table 4 and Figure 2 show two-year fasting lipid changes between adherent and non-users, adjusted for PS subclass and baseline lipid level. We observed no significant differences in lipid changes between PAP groups, overall or within BMI strata. There was no evidence for interaction between PAP and BMI group.

We examined differences in changes in the proportion of patients with abnormal lipid levels (Table E5); there were no differences between PAP adherent and non-users in the overall sample. Within BMI<30 subjects, the decrease in proportion of patients with abnormal HDL-C was greater in adherent compared to non-users (Table E5, p=0.024). The reason for this result is unclear, given no differences between PAP groups for mean HDL change (Table 4, p=0.750) or the proportion of patients near the abnormal HDL-C cut-point (p>0.46) in patients with BMI<30. We found no differences in the change in proportion abnormal between adherent and non-users for other BMI strata or lipid measures.

PAP Effect within Meaningful Subgroups

Patients with Abnormal Baseline Lipid Levels—We examined the patients exhibiting abnormal lipid levels at baseline, where we would expect the greatest PAP treatment effect. No group differences in fasting lipid changes were observed (Table E6). We found a PAP by BMI interaction for LDL-C change (p=0.041), likely driven by qualitative differences in the observed non-significant effects.

Patients with the Most Severe Hypoxia—To compare results with recent data from animal models,[9–11, 17–21] we limited our sample to patients in the top quartile of percent time $SaO_2<90\%$. No differences in fasting lipid changes between PAP adherent and non-users were observed (Table E7).

DISCUSSION

In a large cohort of moderate-to-severe OSA patients, this study used sub-classification by propensity score quintiles to minimize bias in the estimated differences between PAP adherent patients and non-users. This observational study design involved using an algorithm that selected patients without regard to outcome data, so that within sub-class, measured demographic and baseline variables achieved balance that was at least as good as that expected through randomization. Results do not support the hypothesis that PAP significantly impacts two-year changes in fasting lipid levels. Thus, increased risk of cardiovascular events and atherosclerosis in OSA patients is unlikely to be related to mechanisms involving the fasting lipid profile.

Despite evidence associating OSA with atherosclerotic cardiovascular disease,[1] and the relationship between dyslipidemia and atherosclerosis,[2] no definitive evidence points towards dyslipidemia as the mechanism linking OSA and atherosclerosis in humans.[3–16] We found no convincing association between OSA severity and fasting lipids, only a weak positive correlation between AHI and HDL-C, implying protection against atherosclerosis. Instead, we observed correlations between obesity and fasting lipids. Multiple obesity measures were positively correlated with triglycerides and negatively correlated with HDL-C, consistent with associations between obesity and "atherogenic dyslipidemia", characterized by elevated triglycerides and decreased HDL-C and associated with cardiovascular risk.[30] We found significant, but weak, negative correlations between obesity and TC and LDL-C. Obesity is associated with reduced lipoprotein lipase (LPL) activity and increased production of very low density lipoprotein (VLDL).[30] Given the

role of LPL in the conversion of VLDL into LDL-C, this reduced activity may explain these negative correlations with LDL, as well as the increased triglycerides.[31]

To our knowledge, our study is the longest to date exploring the relationship between PAP and fasting lipids. This manuscript focuses on the utility of propensity score methodologies in the principled design of observational studies, which substantially strengthens causal inference. These methods were used to select adherent patients and non-users with balance for measured covariates similar to that expected through randomization. Although balance is achieved for included variables, a limitation of the propensity score methodologies is the inability to address unobserved variables, which are theoretically controlled for in the context of a randomized controlled trial. While we recognize the potential for presently unknown or unmeasured confounders to influence results, we included as many relevant variables as possible. Given that unobserved confounders are controlled for to the degree that they are associated with included variables, including a large number of covariates reduces the likelihood of missing important confounders that are independent of measured variables.

We found no differences in two-year fasting lipid changes between PAP adherent patients and non-users. There is no definitive clinical evidence supporting lipid changes with PAP.[8–16] One randomized trial showing decreases in cholesterol was retracted.[32] Phillips et al[15] explored the effect of 2 months of PAP on postprandial lipidemia over 24 hours, observing decreased postprandial triglycerides and total cholesterol associated with PAP use, and a small corresponding *decrease* in HDL. We did not study postprandial lipids; it is possible that PAP use could have affected these. However, we note that Phillips et al[15] also observed no significant effect of PAP usage on fasting lipid levels, supporting our conclusions. Kohler et al[13] found that 2 weeks of PAP withdrawal was associated with a significant *decrease* in triglycerides compared to continued therapeutic PAP, as well as increased blood pressure and catecholamine levels.[13] Thus, over the short-term, there was no dyslipidemia produced by OSA.

Rodent models more convincingly demonstrate dyslipidemia proportional to duration and severity of CIH.[9–11, 17–21] Li et al[19] found increased fasting serum lipids in lean C57BL/6J mice exposed to 4 weeks of severe CIH (FiO_2=5%); no change was observed with moderate CIH (FiO_2=10%).[19] In an attempt to replicate this in humans, we restricted our sample to the top quartile of hypoxia severity, with little change in results (Table E7). Recent publications[20, 21] suggest CIH induces dyslipidemia and atherosclerosis by inhibiting clearance of triglyceride-rich lipoproteins (TRLP). In mice, CIH increases Angiopoietin-like 4 (Angptl4) expression in adipose tissue via up-regulation of hypoxia-inducible factor 1-alpha (HIF-1α).[20, 21] Increased Angptl4 inhibits activity of adipose LPL, inhibiting TRLP clearance and resulting in increased cholesterol and triglycerides.[20, 21] While nocturnal hypoxemia severity (but not BMI or AHI) correlated with Angptl4 mRNA levels in subcutaneous adipose tissue of obese bariatric surgery patients,[21] more research is needed to determine the relationship between Angptl4 and atherosclerosis in apneics. Conceivably, differences exist in molecular pathways between humans and mice. A mechanism other than dyslipidemia is suggested by Drager et al,[14] who observed no difference in lipid changes in severe OSA patients randomized to PAP versus no treatment,

but decreases in carotid intima-media thickness and carotid-femoral pulse-wave velocity, early atherosclerosis markers.[14]

Twenty-four percent of our patients used lipid-lowering medications. Given their known efficacy, analyses were performed in patients not using these medications. Conceivably, the effect of OSA on fasting lipids might be most apparent in patients on lipid-lowering medications, but the effect is masked by medication use. However, we observed no differences in lipid changes between PAP adherent patients and non-users with abnormal lipids *not* using lipid-lowering medications (Table E6). Ultimately, in human populations with widespread screening for lipid abnormalities and use of lipid-lowering medications, whether OSA contributes to lipid levels may be unanswerable. Based on current results and previous publications, we conclude that, given widespread use of lipid-lowering medications, changes in fasting lipid levels are not the mechanism by which OSA contributes to cardiovascular risk.

Despite no relationship between PAP and fasting lipid changes, we observed effects on BMI and subjective sleepiness changes, as in previous publications.[33, 34] Adherent patients had an average increase in BMI of 1 kg/m^2 over follow-up, compared to no change in non-users, confirming a recent report from the APPLES study.[33] While the mechanism causing increased BMI in PAP adherent patients in unclear, previous studies have suggested increased energy expenditure associated with OSA, and that PAP treatment reduces this expenditure.[33, 35, 36] Decreased energy expenditure among adherent patients, in the absence of increased exercise or dietary changes, could result in weight gain. Both PAP groups reported less subjective sleepiness at follow-up, but PAP adherent subjects had a significantly larger mean ESS decrease than non-users (4.0 vs. 2.5 points). Previous research with sham-CPAP showed reductions in subjective sleepiness attributed to a placebo effect.[34] While the reduction in sleepiness in our non-users is unexplained, it cannot be produced by a placebo effect.

Our study has strengths, but some limitations. The Icelandic population is a population of European descent and clinical practice in Iceland is identical to that in other countries. Results are expected to be generalizable to moderate-to-severe OSA patients of similar ethnicity. However, additional studies involving populations that include other ethnicities would be useful for increasing generalizability. The sample reflects the Icelandic population diagnosed with OSA, but consequently contains a relative lack of females. Our sample contained patients with moderate-to-severe OSA, and no control population, potentially limiting the ability to observe correlations between OSA severity and fasting lipids. However, PAP non-users provided a "control" sample for analyses of OSA treatment response. While patients were treated with PAP over two-years, the design of the cohort was such that adherence information was obtained over the period closest to follow-up. The reason for this was two-fold: 1) adherence information most proximal to the follow-up reassessments was believed to be the most relevant and 2) levels of compliance near the two-year follow-up are likely representative of overall adherence, as several publications have shown a significant relationship between early and long-term PAP compliance.[37–40] Detailed phenotyping allowed for assessment of various confounders, however, we cannot exclude the potential for unmeasured or unknown covariates to influence results.

We have shown how sub-classification by propensity scores strengthens the causal inferences permitted by the data. The approach allows simultaneous control for a greater number of covariates than multivariable regression. Compared to regression adjustment, propensity methods are applied at the design stage without access to outcome data, thereby reducing bias. Our approach was more inclusive of all real-world patients, a benefit compared to typical randomized trials, while addressing the challenge of selection bias by essentially reconstructing a stratified randomized design. Propensity score methodologies should be considered whenever non-randomized group comparisons are required, as advocated by the National Heart, Lung and Blood Institute.[23]

In conclusion, our study does not support a role for OSA in determining the fasting lipid profile. While dyslipidemia is a well-recognized atherosclerosis risk factor, our results suggest that changes in fasting lipids are not the mechanism for the increased atherosclerotic cardiovascular morbidity and mortality seen in OSA.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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"Take Home" Message:

Fasting lipid changes likely do not cause increased cardiovascular risk in OSA, as they are unaffected by PAP treatment

Figure 1.
This "Love Plot"[29] illustrates the balance in covariates between PAP adherent patients and non-users in the original cohort and after controlling for propensity score subclass within the designed cohort. The plot shows the T-statistic or signed square root of the chi-square comparing covariates between groups. While a number of covariates were significantly different prior to sub-classification, after controlling for PS subclass in the designed cohort, all statistics are close to zero. HDL: high-density lipoprotein; LDL: low-density lipoprotein; SaO_2: oxygen saturation; ODI: oxygen-desaturation index; AHI: apnea-hypopnea index; ESS: Epworth Sleepiness Scale; BMI: body mass index; CVD: cardiovascular disease; PS: propensity score.
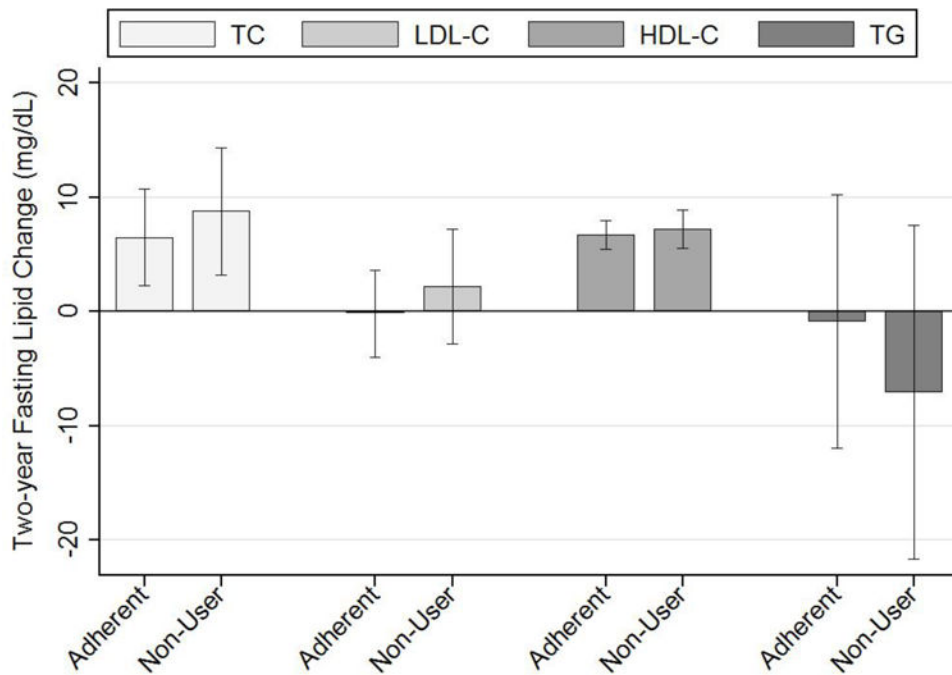
Figure 2.
The mean and 95% confidence interval for two-year lipid changes (mg/dL) are shown for adherent and non-users, adjusted for PS subclass and baseline lipid level. We saw significant increases in total and HDL cholesterol over two years, but no change in LDL or triglycerides. There were no differences in two-year lipid changes between adherent and non-users. PAP: positive airway pressure; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; TG: triglycerides.

Table 1:

Baseline characteristics of the study population, stratified by BMI group

Characteristic	BMI<30 (N=186)	BMI 30–35 (N=210)	BMI 35 (N=217)	p[†]
Age (years)	**54.4±9.6**	**53.8±10.8**	**50.5±10.8**	**<0.001**
Male	82.3%	81.0%	78.3%	0.597
BMI (kg/m^2)	**27.4±2.0**	**32.4±1.4**	**39.9±4.1**	**<0.0001**
Current Smoker	24.3%	20.5%	22.7%	0.654
Excessive Alcohol	3.3%	3.8%	3.7%	0.963
Hypertension	**25.4%**	**34.0%**	**50.9%**	**<0.0001**
Cardiovascular Disease	3.2%	4.8%	4.6%	0.769
Diabetes Mellitus	**2.2%**	**2.4%**	**6.5%**	**0.045**
Participate in Exercise	**73.6%**	**57.6%**	**51.9%**	**<0.0001**
Epworth Sleepiness Scale	11.7±4.8	11.4±5.1	12.3±5.3	0.183
AHI (events/hour)	**37.4±15.2**	**44.7±20.4**	**49.0±23.2**	**<0.0001**
ODI (events/hour)	**26.4±13.4**	**35.1±18.9**	**41.9±23.5**	**<0.0001**
SaO$_2$ Nadir	**79.0±6.6**	**76.9±7.5**	**73.2±8.9**	**<0.0001**
Percent Time SaO$_2$<90	**6.1±9.1**	**12.4±16.1**	**19.7±22.3**	**<0.0001**
Total Cholesterol (mg/dL)	**212.6±37.3**	**207.2±42.4**	**200.9±41.5**	**0.016**
Total Cholesterol 200[‡]	**65.6%**	**57.6%**	**52.5%**	**0.029**
LDL Cholesterol (mg/dL)	**156.1±35.2**	**152.1±38.2**	**145.4±36.9**	**0.012**
LDL Cholesterol 130[‡]	**76.3%**	**71.9%**	**65.0%**	**0.040**
HDL Cholesterol (mg/dL)	**43.6±14.3**	**39.6±9.2**	**38.2±9.4**	**<0.0001**
HDL Cholesterol <40[‡]	**48.4%**	**57.1%**	**67.3%**	**0.001**
Triglycerides (mg/dL)	**147.1±63.2**	**177.9±81.6**	**198.9±103.2**	**<0.0001**
Triglycerides 150[‡]	**43.0%**	**59.5%**	**68.7%**	**<0.0001**

Significant differences shown in **bold**.

[†] p-values from ANOVA and chi-square or Fisher's exact test

[‡] Based on the NCEP ATPIII published criteria[28]

BMI: body mass index; AHI: apnea-hypopnea index; ODI: oxygen desaturation index; LDL: low-density lipoprotein; HDL: high-density lipoprotein.

Table 2:

Pearson correlations[*] between obesity and OSA severity measures and natural log transformed lipid measures

Measure	Total Cholesterol		LDL Cholesterol		HDL Cholesterol		Triglycerides	
	rho	p	*rho*	p	*rho*	p	*rho*	p
BMI (kg/m^2)	**−0.13**	**0.001**	**−0.14**	**0.001**	**−0.16**	**<0.001**	**0.28**	**<0.0001**
Weight (kg)	**−0.16**	**<0.0001**	**−0.17**	**<0.0001**	**−0.16**	**<0.001**	**0.25**	**<0.0001**
Neck Circumference (cm)	**−0.13**	**0.002**	**−0.13**	**0.001**	**−0.20**	**<0.0001**	**0.34**	**<0.0001**
Waist Circumference (cm)	**−0.11**	**0.006**	**−0.13**	**0.001**	**−0.12**	**0.003**	**0.32**	**<0.0001**
Waist-to-hip Ratio	−0.04	0.290	−0.05	0.177	**−0.10**	**0.013**	**0.29**	**<0.0001**
Total Abdominal fat (cm^3)	−0.02	0.657	−0.05	0.239	−0.07	0.118	**0.29**	**<0.0001**
SAT (cm^3)	−0.03	0.502	−0.07	0.140	−0.04	0.402	**0.22**	**<0.0001**
VAT (cm^3)	0.00	0.937	−0.01	0.746	**−0.11**	**0.016**	**0.33**	**<0.0001**
AHI (events/hour)	0.04	0.300	0.01	0.725	**0.09**	**0.022**	0.03	0.428
ODI (events/hour)	−0.01	0.901	−0.02	0.559	0.02	0.606	0.06	0.157
SaO$_2$ Nadir	0.02	0.568	0.02	0.621	0.04	0.384	−0.01	0.804
Percent Time SaO$_2$<90[†]	−0.02	0.571	−0.04	0.360	0.01	0.792	0.02	0.619

Significant correlations shown in **bold**

[*] Correlations between obesity and lipids adjusted for age and gender, correlations for OSA severity adjusted for age, gender, and BMI

[†] natural log transformed for normality

OSA: obstructive sleep apnea; BMI: body mass index; SAT: subcutaneous abdominal fat; VAT: visceral abdominal fat; AHI: apnea-hypopnea index; ODI: oxygen desaturation index; LDL: low-density lipoprotein; HDL: high-density lipoprotein.

Table 3:

Baseline and follow-up characteristics[*] of the PAP adherent and non-users within the PS designed sample

Characteristic	Baseline			Follow-Up		
	Adherent (N=199)	Non-User (N=118)	p[†]	Adherent (N=199)	Non-User (N=118)	p[‡]
Age (years)	51.8±10.4	52.8±10.0	0.996	–	–	–
Male	81.9%	80.5%	0.967	–	–	–
BMI (kg/m^2)	33.9±5.9	33.1±5.9	0.975	**34.9±6.1**	**32.9±5.4**	**<0.0001**
Current Smoker	20.6%	20.3%	0.897	**18.7%**	**28.0%**	**0.004**
Excessive Alcohol	2.5%	2.5%	0.954	1.5%	2.5%	0.342
Hypertension	33.2%	28.8%	0.892	33.8%	30.5%	0.953
Cardiovascular Disease	2.5%	1.7%	0.949	2.5%	1.7%	0.688
Diabetes Mellitus	1.5%	0.9%	0.987	3.1%	3.5%	0.460
Participate in Exercise	58.8%	58.4%	0.988	67.9%	66.7%	0.726
Epworth Sleepiness Scale	12.0±5.0	11.5±4.8	0.966	**7.8±4.6**	**9.3±4.9**	**0.002**
AHI (events/hour)	44.8±19.6	40.8±19.8	0.931	–	–	–
ODI (events/hour)	36.1±19.3	32.1±19.0	0.990	–	–	–
SaO$_2$ Nadir	76.2±7.5	77.5±7.3	0.993	–	–	–
Percent Time SaO$_2$<90	2.1±1.0	1.8±1.0	0.942	–	–	–
Total Cholesterol (mg/dL)	204.7±41.6	204.9±35.4	0.917	211.4±41.6	213.3±36.0	0.528
Total Cholesterol 200[§]	56.3%	55.1%	0.727	64.3%	63.6%	0.771
LDL Cholesterol (mg/dL)	149.4±37.3	149.7±33.8	0.933	149.5±30.9	151.3±33.3	0.475
LDL Cholesterol 130[§]	70.9%	72.9%	0.905	75.9%	72.9%	0.475
HDL Cholesterol (mg/dL)	40.0±12.4	39.8±10.3	0.922	46.6±12.8	47.3±12.8	0.619
HDL Cholesterol <40[§]	60.8%	57.6%	0.978	30.6%	34.8%	0.144
Triglycerides (mg/dL)	174.8±86.1	176.0±102.9	0.998	174.6±88.9	167.9±96.1	0.517
Triglycerides 150[§]	59.8%	55.1%	0.737	54.8%	49.2%	0.544

Significant differences shown in **bold**

[*] Summary statistics presented as mean and standard deviations or percentages of the overall sample, not accounting for PS subclass

[†] p-value adjusted for PS subclass from ANCOVA model or conditional logistic regression

[‡] p-value from ANCOVA or conditional logistic examining the difference in follow-up values, adjusted for PS subclass and baseline value

[§] based on the NCEP ATPIII published criteria[28].

PAP: positive airway pressure; BMI: body mass index; AHI: apnea-hypopnea index; ODI: oxygen desaturation index; LDL: low-density lipoprotein; HDL: high-density lipoprotein

Table 4:

Differences in two-year lipid changes between PAP adherent and non-users

Lipid	BMI Group[*],[†]	LS Mean±SE Change		p[‡]
		Adherent	*Non-Users*	
Total Cholesterol	*Overall*	*6.5±2.2[§]*	*8.8±2.8[§]*	*0.528*
	<30	2.4±4.0	9.7±4.4[§]	0.248
	30–35	15.1±3.4[§]	10.9±4.9[§]	0.493
	35	1.8±3.6	6.7±5.3	0.468
LDL Cholesterol	*Overall*	*−0.2±1.9*	*2.2±2.5*	*0.475*
	<30	−5.7±3.8	1.6±4.1	0.210
	30–35	6.4±3.0[§]	2.6±4.3	0.481
	35	−1.4±3.3	2.0±4.8	0.579
HDL Cholesterol	*Overall*	*6.7±0.7[§]*	*7.3±0.9[§]*	*0.619*
	<30	6.7±1.2[§]	7.3±1.3[§]	0.750
	30–35	7.6±1.0[§]	8.2±1.5[§]	0.735
	35	5.6±1.1[§]	7.0±1.6[§]	0.501
Triglycerides	*Overall*	*−0.9±5.6*	*−7.1±7.4*	*0.517*
	<30	17.5±11.4	6.9±12.5	0.548
	30–35	8.9±10.5	8.3±14.9	0.976
	35	−26.4±7.3[§]	−29.1±10.8[§]	0.844

Significant differences shown in **bold**

[*] The propensity score sample included 199 adherent (56 with BMI<30; 65 with BMI 30–35; 78 with BMI 35) and 118 non-users (47 with BMI<30; 33 with BMI 30–35; 38 with BMI 35)

[†] p-values for PAP by BMI group interaction: p=0.557 for TC, p=0.500 for LDL, p=0.615 for HDL, p=0.563 for TG

[‡] p-value from ANCOVA comparing adherent and non-users within PS designed study, adjusted for PS subclass and baseline lipid level

[§] Within group estimate of lipid change significantly (p<0.05) different from zero

BMI: body mass index; LDL: low-density lipoprotein; HDL: high-density lipoprotein; LS: least squares; SE: standard error