SUPPLEMENTAL MATERIAL

Adhesion Molecule Increases in Sleep Apnea: **Protective-Beneficial** Effect of Positive Airway Pressure and Moderation by Obesity

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SUPPLEMENTAL METHODS

Study subjects

The Icelandic Sleep Apnea Cohort (ISAC) was assembled from patients diagnosed with moderate to severe OSA [apnea hypopnea index (AHI) ≥ 15] with a clinical sleep study at one of 5 sites in Iceland, who were subsequently referred for PAP treatment to the Landspitali University Hospital in Reykjavik from September 2005 to December 2009. Over 90% of approached subjects agreed to participate in the study. This clinical cohort is therefore representative of the obesity levels and comorbidities found in the Icelandic sleep apnea population offered PAP treatment for their disease. All participants were initially stratified by BMI category into three groups (BMI < 30 kg/m^2; BMI ≥ 30 and < 35 kg/m^2; and BMI ≥ 35 kg/m^2) in order to provide a comparison of the inflammatory response to OSA severity and PAP usage across participants with varying degrees of obesity. Patients were contacted again 2 years after the initiation of PAP for follow-up. Additional information on the ISAC sample is presented in previous publications(1-4). This study was approved with the consent of the National Bioethics Committee, the Data Protection Authority of Iceland and the Institutional Review Board of the University of Pennsylvania. Written consent was obtained from all research subjects.

Participants included in the study reported here were chosen based on data quality and completeness as of June 2011 and illustrated in Figure E1. PAP users included All included patients were those participants with good quality sleep studies at baseline (defined as non-missing measures of apnea-hypopnea index ([AHI]) and oxygen desaturation index ([ODI])), good quality abdominal magnetic resonance imaging (MRI) at baseline, PAP users were
required to have and with available smartcard download for assessment of objective PAP usage adherence information at the 2 year follow-up. Based on these criteria, a total of 228 subjects with at least some PAP usage were available for analysis. Of these, 7 (3%) participants were missing blood samples at baseline or follow-up, resulting in our final sample of 221 PAP users (177 full, 44 partial) for analysis. For non-PAP users, good quality sleep studies and abdominal MRIs at baseline were again required. PAP non-usersTo assure these subjects accurately represented the untreated OSA population, were also required that they returned their PAP device within 1 year of starting therapy and did not have throat surgery between baseline and 2-year follow-up; a subset (n=16) patients had a prescribed mandibular advancement device. Given these criteria, a total of 89 non-PAP users were available for analysis, 1 (1%) of which was missing blood at baseline, resulting in our final sample of 88 non-users for analysis.

Procedures Baseline Evaluation

At baseline, subjects received a physical examination, completed standardized questionnaires, overnight polysomnography, abdominal MRI, and blood was drawn in the morning after sleep from the antecubital vein of fasting untreated subjects. The physical examination included measurements of height, weight, BMI, neck and waist circumferences. The standardized questionnaires included demographics, general medical history including hypertension and cardiovascular disease, sleep history, including the Epworth Sleepiness Scale and the Basic Nordic Sleep Questionnaire, and current medications coded according to the Anatomic
Therapeutic Chemical (ATC) drug classification system (WHO Collaborating Centre for Drug Statistics Methodology) and lifestyle habits, including smoking history and exercise habits.

Patients completed the same questionnaires, physical examination and fasting morning blood sample as baseline assessment following approximately 2 years of PAP treatment [mean (SD) follow-up = 2.0 (0.2) years; range = 1.7–2.9 years].

**Questionnaires:** Standardized questionnaires were administered by trained interviewers. The questionnaires included information that included 1) Demographics; 2) Medical history, including diagnosis of hypertension, coronary artery disease, heart failure, stroke and diabetes mellitus; 3) Sleep history, including the Epworth Sleepiness Scale and the Basic Nordic Sleep Questionnaire; 4) Current medications coded according to the Anatomic Therapeutic Chemical (ATC) drug classification system (WHO Collaborating Centre for Drug Statistics Methodology); and 5) Lifestyle habits, including smoking history and exercise habits. Patients were identified as current smokers if they reported smoking in the past month and exercise was assessed by asking the yes/no question: “Do you currently participate in sports or regular physical exercise (e.g. walking, swimming, bicycling etc)?”

**Physical Examination:** Physical examination was performed the same day, together with anthropometric measurements including neck and waist circumference. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Blood pressure was measured twice by manual sphygmomanometer after a 10-minute resting period, separated by a 2-minute interval, and averaged for analysis.
**Sleep Study and OSA Severity Measures**

*Polysomnography (PSG):*

Subjects had a sleep study while untreated with an Emblettta type 3 portable monitor or Embla 12 channel system that records the same channels (Embla; Flaga Inc., Reykjavik, Iceland). Sleep study recordings were scored in a uniform manner at the Sleep Study Reading Unit of the University of Pennsylvania. An apnea-hypopnea index (AHI) and oxygen desaturation index (ODI) were measured. The apnea-hypopnea index (AHI) was defined as the average number of apneas. An apnea was defined as (a ≥80% drop in airflow for ≥10 seconds), and a hypopneas as (either a ≥ 30% drop in airflow for ≥10 seconds with ≥ 4% oxyhemoglobin desaturation or ≥50% drop in airflow for ≥10 seconds with sudden increase in airflow towards the end of the event) per hour of recording. The oxygen desaturation index (ODI) was defined as the average number of oxyhemoglobin desaturations ≥4% for ≥ 10 seconds per hour of recording. The SaO₂ nadir was defined as the lowest oxygen saturation reached during the study. Hypoxia time was defined as the percentage of time during the sleep recording with SaO₂ <90%.

*Magnetic Resonance Imaging (MRI) of Abdomen:*

All patients underwent MRI of the entire abdomen. Axial, coronal and sagittal images were acquired using a 1.5 Tesla scanner with a body coil (Siemens Avanto, Germany). The adipose areas from each slice were summed in order to assess the visceral, subcutaneous and total (visceral + subcutaneous) abdominal fat volumes and visceral fat volume. Assessment of
reliability by comparing results obtained on 2 occasions by 2 different observers showed negligible variance due to analysis procedures, as described (for further details, see in previous publications(2, 4)).

**Blood Sampling**

Blood was drawn in the morning after sleep from the antecubital vein of fasting untreated participants at baseline and again two-years after treatment initiation. Specimens were collected in SST vacutainers (Greiner, Kremsmunster, Austria) and allowed to clot at room temperature for 20 minutes prior to centrifugation for 10 minutes at 3,000 rpm. The serum samples were subsequently stored at -20°C after separation. Enzyme-linked immunosorbent assay was used in order to determine the serum levels of ICAM-1 and VCAM-1 (R&D Systems, Minneapolis, MN). The assay was performed according to directions of the manufacturer. We ensured quality control in the samples by inserting internal controls (running high and low concentration quality controls) with known values to monitor the variability of the assays.

**Follow Up Evaluation and PAP Adherence**

Patients completed the same questionnaires, physical examination and fasting morning blood sample as baseline assessment following approximately 2 years of PAP treatment [mean (SD) follow-up = 2.0 (0.2) years; range = 1.7-2.9 years].
**PAP Usage Definitions:** All PAP treatment was administered by the Department of Respiratory Medicine and Sleep at Landspitali Hospital. Patients were initially treated with autoPAP or continuous PAP (CPAP) units (ResMed Corp., San Diego, CA, USA). Treatment was only changed to bilevel PAP (biPAP) or adaptive seroventilation (ASV) if treatment efficacy was proven to be inadequate, defined as AHI≥15 using PAP and/or persistent patient complaints (1% of subjects were treated with BiPAP and 1% with ASV). Objective compliance data was available from smartcard download, which included the average nightly use of PAP usage and total nights PAP was used for the past 28 nights. Based on objective data, we defined three PAP usage groups: full users, partial users, and non-users. Full users were defined as average use ≥4 hours per night and ≥20 out of 28 nights of use. Partial users were defined as average use <4 hours per night or <20 out of 28 nights. As described above, PAP non-users did not use PAP, had returned their device within 1 year of initiation, and did not have upper airway surgery for OSA.

The mean (SD) hours/night of PAP usage was 6.8 (1.2) and 4.1 (2.1) for full and partial users, respectively. Of those who used PAP and had objective usage data, 96% were on ResMed S8 machines, 2% on S7, 1% on biPAP, 1% ASV. Of the 98% of patients not on biPAP or ASV, 37% had a CPAP and 61% had autoPAP. Non users were defined as those who did not continue to have a PAP machine and had no other therapy for their OSA.

**Statistical Analysis**

Statistical analyses were performed using Stata Version 12, StataCorp (College Station, Texas) or SAS Software, version 9.3 (SAS Institute, Cary, NC).
Demographics:

Continuous and categorical characteristics are summarized as means and standard deviations or frequencies and percentages, respectively. Comparisons among BMI categories (BMI<30 kg/m²; BMI≥30 kg/m² and <35 kg/m²; and BMI≥35 kg/m²) and PAP usage groups (full user, partial user, non-user) were performed using ANOVA and Chi-square or Fisher’s exact tests. Our primary outcome measures were the changes in ICAM-1 and VCAM-1, calculated as within subject follow-up levels minus baseline levels.

Linear Correlation Analyses:

We initially examined whether there was a significant linear correlations between ICAM-1 and VCAM-1 levels and between baseline levels and change scores using Pearson correlation coefficients \((r)\). A strong correlation between baseline and change level was observed, and therefore we adjusted for baseline levels in all of our statistical analyses of change scores. To determine which measures of obesity best captured the variability in ICAM-1 and VCAM-1 levels, we assessed the Pearson correlations between clinical (BMI, waist, neck and hip circumference, and waist-to-hip ratio) and MRI (total, subcutaneous, and visceral abdominal fat volume) measures of obesity and baseline ICAM-1 and VCAM-1 levels. Statistical tests and comparing the strength of the correlations between obesity measures and baseline levels were obtained using a nonparametric bootstrap re-sampling procedure (1,000 replications). Similarly, we examined whether there was any correlation between baseline OSA severity
measures (Apnea-Hypopnea Index, Oxygen Desaturation Index, \( \text{SaO}_2 \) nadir, and percent time \( \text{SaO}_2 < 90 \)) and baseline ICAM-1 and VCAM-1 levels.

Association with PAP usage:

In our primary analyses, we assessed whether there was a significant association between changes in cellular adhesion molecule two-year changes in CAM levels and PAP usage groups (full, partial, non) using an analysis of covariance (ANCOVA), comparing mean change among PAP usage groups. If significant differences were observed among PAP usage groups, we then examined the pairwise differences between full, partial, and non-users. Results are presented as predicted least square mean change (\( \Delta \)) ± standard error (SE). As a complementary analysis, given the ordinal nature of our PAP usage, we also assessed whether there was evidence for a linear trend (or dose effect of PAP use) across the usage groups. This analysis was performed by including PAP usage group in our models as a continuous variable (1=full, 2=partial, 3=non), rather than a categorical variable. Finally, within the full and partial users only, we examined the relationship between continuously measured PAP use during the 28 nights prior to follow-up visit, which was measured as both the average number of hours used per day as well as the total number of nights used, using a linear regression (results presented as \( \beta \)-estimate ± SE).

We next assessed whether the relationship between PAP and change in adhesion molecules was moderated by obesity severity as reflected in BMI-defined strata (<30, 30-35 and \( \geq 35 \text{ kg/m}^2 \)). This was assessed by firstly examining whether there was evidence for significant interaction between PAP usage and BMI strata, as well as and subsequently by examining
the associations within BMI strata. Interaction was assessed by including main effect terms (PAP use and BMI group) as well as an interaction term (PAP use x BMI group) in our models. If we observed evidence for significant interaction between PAP and BMI group, we were able to conclude that the observed suggests that the relationship between PAP usage and CAM changes in biomarker levels was likely is different across within BMI strata. Analyses within BMI strata were performed using identical methods to those described above for the overall population. Complementary analyses replacing BMI strata with visceral abdominal fat tertiles were performed.

**Exploratory Analysis:**

As an exploratory analysis, within the full and partial users only, we examined the relationship between continuous PAP usage, measured as both the average hours/day and the total number of nights used over the last 28 days. Among non-users only, we examined whether there was evidence of an association between baseline OSA severity measures (measured as apnea hypopnea index, oxygen desaturation index, SaO2 nadir, and percent time SaO2<90) and change in cellular adhesion molecule levels—among the non-users only. Both analyses were conducted using linear regression. Similar methods to those described above were used for assessing the relationship between baseline OSA severity and change in ICAM-1 or VCAM-1. Due to the continuous nature of our OSA severity measures, we used a linear regression analysis and results are presented as β-estimate ± SE.

**Assessment of Confounders:**
In addition to the baseline biomarker levels, we considered as potential confounders any variable for which we had information that showed either significant differences among our PAP usage or BMI groups or that was previously mentioned in the literature as effecting cellular adhesion molecules. This list of potential confounders included age, gender, BMI, Epworth Sleepiness Score (ESS), hypertension, obstructive lung disease, smoking status, statin use, exercise, and baseline OSA severity. To control for both baseline levels and potential change in covariates, continuous confounders (e.g. BMI) were modeled as baseline levels and change from baseline (when available) and dichotomous covariates (e.g. hypertension, statin use) were modeled using variables representing possible baseline and follow-up combinations (no, no; no, yes; yes, no; yes, yes). Inclusion of covariates to control for confounding was based on whether control for the covariate materially changed the estimated effect of PAP use on biomarker change. That is, this was done by adding potential confounders were included in a forward stepwise fashion, retaining the variable that resulted in the largest percent change in coefficients at each step and stopping when inclusion of another variable resulted in a change in coefficient of <15%. This strategy was chosen to provide adequate control for confounding while reducing the number of variables required, an important consideration for strata with smaller sample sizes.

Based on these analyses, our final adjusted model for ICAM-1 change included covariates for baseline ICAM-1, BMI, BMI change, and hypertension status at baseline and follow-up. The model was similar for VCAM-1, but also included statin use at baseline and follow-up. The results of this process are presented in Tables E1A and E1B. Due to the high level of correlation among OSA severity measures and PAP usage group, we assessed the impact of adjustment for the four OSA severity measures separately and report this in the results.
Propensity Score Matching Sub-Sample Analysis

-To better control for bias due to baseline covariate imbalance in our assessment of the effect of PAP treatment, we used sub-classification based on propensity score (PS) quintiles based implemented a propensity score (PS) matching analysis based on an established sequential heuristic and diagnostic conditions described by Maislin and Rubin(7) and other previous publications(8-12). Briefly, the heuristic consists of 3 steps that can be repeated as necessary to satisfy a set of “propensity score diagnostics” (described by Maislin & Rubin(7)).

First, a model including main effects for all desired covariates is fit to obtain PS quintiles. Second, within quintile differences 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. Through the PS heuristic, a subset of PAP full and non-users are identified, such that there was within subclass balance with respect to measured covariates. This resulting covariate balance is similar to that expected through randomization, and thus selection bias is minimized and causal inferences can be made from the observed results.

Covariates included in the heuristic were: baseline ICAM-1, baseline VCAM-1, age, BMI, Epworth Sleepiness Scale (ESS), AHI, ODI, SaO2 nadir, percentage of sleep time with SaO2<90, gender, exercise participation, diabetes, hypertension, cardiovascular disease, current smoking, obstructive lung disease, and statin use. The goal of this analysis was to create a subsample of PAP full and non-users divided into PS quintiles, with minimized selection bias and balanced...
covariate distributions. This approach creates a sample from the overall observational data that is similar to what would have resulted had participants been randomized to PAP group, allowing causal inferences to be made from statistical analyses. Briefly, the heuristic consists of 3 stages that may be repeated as many times as necessary until the covariates are balanced and the PS diagnostics met:

1. Estimating a main effects PS model, which includes all relevant covariates for matching
2. Assessment of within subclass bias effect sizes and other PS diagnostic information in order to identify required cross-product and squared terms for inclusion in PS model
3. Exclusions of subjects in each treatment group with insufficient “covariate overlap” as defined by the PS distributions.

For the PS matching heuristic, the following continuous covariates were used: baseline ICAM-1 (ng/mL); baseline VCAM-1 (ng/mL); age (years); body mass index (BMI, kg/m²); Epworth Sleepiness Scale (ESS); apnea hypopnea index (AHI, events/hour); oxygen desaturation index (ODI, events/hour); SaO₂ nadir; and natural log transformed percentage of sleep time with SaO₂<90 plus one. In addition, the following dichotomous covariates were included: gender [male vs. female]; participation in exercise [yes vs. no]; diabetes [yes vs. no]; hypertension [yes vs. no]; cardiovascular disease [yes vs. no]; current smoking [yes vs. no]; obstructive lung disease [yes vs. no]; and statin use [yes vs. no]. In order to retain all potential patients, a single imputation was used to impute missing values. The imputation included 7 patients missing data on exercise participation and ≤ 2 patients missing information on ESS, diabetes, CVD, smoking status, and/or obstructive lung disease.
After the PS matched sample was created, analyses comparing the change in ICAM-1 and VCAM-1 between full and non-users were conducted using a linear regression-ANCOVA model, as described above, with PAP usage group as a predictor. The models were adjusted for PS quintile, as well as baseline ICAM-1 or VCAM-1, in order to further control for any potential residual differences after matching. The results from these analyses were then compared to those from the overall observational study.

Significance Level:

Primary tests for PAP use differences in changes in ICAM-1 and VCAM-1 were each evaluated with type 1 error set to $\alpha = 0.05$. For each variable, if $p<0.05$ then a Tukey multiple comparisons correction was used for significance in our post hoc pairwise comparisons. Interaction tests were conducted using $\alpha = 0.10$ to account for the generally low power of such tests in order to reduce the likelihood of missing an important interaction.

Post Hoc Power Calculation:

Based on our observed results, we estimate that PAP usage explains approximately 3.5% of the variability in ICAM-1 changes and 2.5% of the variability in VCAM-1 change. Given our sample size of 309 for analysis and our alpha level of 0.05, we have 95% and 82% power to find these effect sizes for ICAM-1 and VCAM-1, respectively. We note that due to the reduction in sample size, we have more limited power to find similar effects within our BMI strata, which have approximately 100 participants in each. Using this sample size, our estimated power is 52%
for ICAM-1 change and 37% power for VCAM-1 change. We would have 80% power to find an association in our BMI strata if PAP usage explains 6.4% of the variance, which reflects a small to moderate effect size based on Cohen’s effect size definitions–(13). Therefore, while our negative results in BMI strata should be interpreted with caution, we have adequate power to find clinically meaningful effect sizes in our analyses.

SUPPLEMENTAL RESULTS

Correlations between Obesity and CAM Levels

The results of analyses exploring the correlations between clinical and MRI measures of obesity and both ICAM-1 and VCAM-1 are presented in Table E12. Results are presented as Pearson correlation coefficients and ICAM-1 and VCAM-1 were natural log transformed for normality. We observed significant associations between ICAM-1 and BMI (p=0.002), subcutaneous abdominal fat (p=0.002), total abdominal fat (p=0.004), and hip circumference (p=0.03). No association was seen between ICAM-1 and visceral fat volume and no associations were seen between obesity measures and VCAM-1 levels.

PAP usage and BMI Subgroup Specific Change in ICAM-1 and VCAM-1

The unadjusted mean ± standard deviation levels of ICAM-1 and VCAM-1 at baseline and follow-up are presented in Figure E2E1 and Table E3E2, stratified by PAP usage and BMI group. The p-values presented test whether the change from baseline to follow-up was significantly different from
In these unadjusted analyses, we observed significant decreases in ICAM-1 for full users, overall (p=0.01) and when restricted to the most obese patients only (p=0.04). For VCAM-1, we observed significant increases in the overall population for all 3 PAP usage groups (p<0.01 for each), as well as for full (p=0.01) and non-users (p=0.02) with BMI≥35, partial users with BMI 30-35 (p=0.04), and non-users with BMI<30 (p=0.03).

Subgroup-specific adjusted least square mean changes are presented in Table E4. Similar to Table E3, the p-values in this table are testing whether the subgroup specific mean change is significantly different from zero, adjusted for baseline CAM level, BMI, change in BMI, hypertension and baseline and follow-up statin use at baseline and follow-up (for VCAM-1 change only). We observed significant decreases in ICAM-1 for full users overall (p<0.001) and in both the BMI 30-35 (p=0.002) and BMI≥35 (p=0.04) strata, and for partial users with BMI<30 (p=0.03). We observed significant increases in ICAM-1 for non-users, both overall (p=0.02) and when restricted to the most obese (p<0.001). For VCAM-1, we observed significant increases for all 3 PAP usage groups in the overall population (p<0.05 for each comparison), for the most obese full users (p=0.009) and for non-users in each of the 3 BMI strata (p<0.006 in each strata).

Associations between continuous PAP use and Change in ICAM-1 and VCAM-1

Complementary analyses examining the relationship between both average hours of PAP use and total nights of PAP use over the last 28 nights and CAM change are presented in Table E35. Analyses were performed only in the subgroup of full and partial PAP users (n=221) and results are presented as β-estimates ± standard errors, adjusted for baseline CAM level, BMI, change in BMI,
hypertension and baseline and follow-up and statin use at baseline and follow-up (for VCAM-1 change only). We found significant associations within the BMI≥35 group between ICAM-1 change and both average hours (p=0.02) and total nights (p=0.04) used; for each outcome, more use resulted in larger decreases in ICAM-1.

**Impact of OSA Severity Adjustment on Association between PAP usage and CAM Change**

Results from analyses exploring the impact of adjustment for baseline OSA severity on our primary analyses are presented in Table E6. OSA severity was measured using 4 different metrics: 1) Apnea Hypopnea Index (AHI), 2) Oxygen Desaturation Index (number of desaturation events >4% per hour), 3) minimum SaO2 reached during the night (SaO2-nadir) and 4) percent of night time with SaO2<90. Each variable was added to the fully-adjusted model (presented in the manuscript Table 3) separately to assess any impact on the significance, magnitude or interpretation of results. Overall, adjustment for OSA severity had no significant impact on the observed ICAM-1 result. For VCAM-1, results remained significant when adjusted for SaO2-nadir and percent time SaO2<90, but became non-significant after adjustment for AHI (p=0.18) and ODI (p=0.06). However, the overall relationship between the PAP groups remains similar, as evidenced by suggestive linear trends (p<0.08) in all analyses.

**Association between baseline OSA Severity and CAM Change**

The associations between baseline measures of OSA severity and the magnitude of change in ICAM-1 and VCAM-1 among PAP non-users are presented in Table E7. Analyses are restricted
to non-PAP users (n=88) and results are presented as β estimates ± standard errors, adjusted for baseline CAM level, BMI, change in BMI, hypertension and baseline and follow-up and statin use at baseline and follow-up (for VCAM-1 change only). We observe significant associations between ODI (p=0.02), SaO2 nadir (p=0.02) and percent time SaO2<90 (p=0.03) and ICAM-1 change in the most obese patients. In each case, more severe OSA led to larger increases in ICAM-1. We also found significant associations with AHI in the BMI 30-35 strata (p=0.03) and for SaO2 nadir in the overall population (p=0.009).

Comparison of patients included and excluded from propensity score sub-sample

A comparison of the relevant covariates for participants included in and excluded from our propensity-scorePS quintile-matched-designed subsample is shown in Table E48, for full and non-PAP users separately. We observe that on average, excluded full users were heavier, had more severe OSA, were sleepier, had more hypertension, and more likely to use statins. Excluded non-PAP users had higher baseline ICAM-1 levels, lower BMI, less severe AHI, and were more likely to be smokers.

Comparison of change in ICAM-1 and VCAM-1 in the PS Matched and Observational Samples

A comparison of the CAM changes between full and non-users within a propensity-score designed sample and an observational study is shown in Table E9. We observe that the differences between PAP groups were similar in magnitude in the PS matched group compared to the overall observational study results.
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### Table E1A: Impact of Additional Covariates on PAP effect on change in ICAM-1 Levels

| Model | \(\beta_{\text{Full User}}\) | \(|\% \text{ Change}|_{\text{Full User}}\) | \(\beta_{\text{Partial User}}\) | \(|\% \text{ Change}|_{\text{Partial User}}\) |
|-------|----------------|----------------|----------------|----------------|
| **Step 1: Baseline ICAM-1 Adjusted** | | | | |
| + Baseline Age | -22.7 | 4% | -16.7 | 24% |
| + Gender | -22.5 | 3% | -16.0 | 16% |
| + BMI | -32.0 | 47% | -17.4 | 26% |
| + Epworth Sleepiness Scale | -17.9 | 18% | -14.8 | 7% |
| + Hypertension | -27.1 | 24% | -24.4 | 77% |
| + Obstructive Lung Disease | -23.0 | 5% | -16.5 | 20% |
| + Current Smoking | -20.3 | 6% | -16.8 | 22% |
| + Statin Use | -23.2 | 6% | -17.9 | 30% |
| + Exercise | -23.0 | 5% | -17.3 | 25% |
| **Step 2: Baseline ICAM-1 + Hypertension Adjusted** | | | | |
| + Baseline Age | -27.4 | 1% | -24.5 | 0% |
| + Gender | -26.9 | 1% | -23.7 | 3% |
| + BMI | -35.1 | 30% | -25.0 | 3% |
| + Epworth Sleepiness Scale | -22.0 | 19% | -22.6 | 7% |
| + Obstructive Lung Disease | -27.5 | 2% | -24.5 | 1% |
| + Current Smoking | -25.0 | 8% | -24.6 | 1% |
| + Statin Use | -28.0 | 3% | -25.9 | 7% |
| + Exercise | -27.5 | 1% | -25.0 | 2% |
| **Step 3: Baseline ICAM-1 + Hypertension + BMI Adjusted** | | | | |
| + Baseline Age | -35.3 | 0% | -25.1 | 0% |
| + Gender | -34.3 | 2% | -24 | 4% |
| + Epworth Sleepiness Scale | -31.0 | 12% | -24.3 | 3% |
| + Obstructive Lung Disease | -36.0 | 2% | -25.2 | 1% |
| + Current Smoking | -33.7 | 4% | -25.7 | 3% |
| + Statin Use | -36.0 | 3% | -26.9 | 7% |
| + Exercise | -35.4 | 1% | -25.5 | 2% |

The result of our model assessment of potential confounding variables is presented for models assessing the relationship between PAP usage and change in ICAM-1. Each potential confounder was added separately to the indicated model in a forward stepwise fashion, retaining the variable that resulted in the largest absolute percent change in the coefficient (\(\beta\)) for full or partial PAP use at each step (shown in bold) and stopping when inclusion of another variable resulted in an absolute change of <15%. Age and gender were modeled as baseline values only. Other continuous covariates (BMI, Epworth Sleepiness Scale) were included in the models as baseline and change from baseline and dichotomous covariates (hypertension, obstructive lung disease, current smoking, statin use and exercise) were included as the combination of baseline and follow-up status (no/no, no/yes, yes/no, yes/yes). *The final adjusted covariate model for change in ICAM-1, which includes ICAM-1 at baseline, hypertension at baseline and follow-up, baseline BMI, and change in BMI. Abbreviations: ICAM-1: Intracellular Adhesion Molecule 1; PAP: Positive Airway Pressure; BMI: Body Mass Index; \(\beta_{\text{Full User}}\): Regression coefficient for full PAP usage; \(\beta_{\text{Partial User}}\): Regression coefficient for partial PAP use; \(|\% \text{ Change}|\): Absolute value of percent change.
Table E1B: Impact of Additional Covariates on PAP effect on change in VCAM-1 Levels.

| Model                        | β Full User | % Change in β Full User | β Partial User | % Change in β Partial User |
|------------------------------|------------|-------------------------|----------------|----------------------------|
| **Step 1: Baseline VCAM-1 Adjusted** |            |                        |                |                            |
| + Baseline Age               | -58.2      |                        | -27.3          |                            |
| + Gender                     | -58.5      | 4%                      | -28.4          | 4%                         |
| + BMI                        | -107.2     | 84%                     | -45.2          | 66%                        |
| + Epworth Sleepiness Scale   | -108.8     | 4%                      | -22.9          | 16%                        |
| + Hypertension               | -90.7      | 56%                     | -75.8          | 177%                       |
| + Obstructive Lung Disease   | -56.9      | 3%                      | -40.9          | 13%                        |
| + Current Smoking            | -58.2      | 0%                      | -23.6          | 14%                        |
| + Statin Use                 | -64.3      | 10%                     | -43.2          | 58%                        |
| + Exercise                   | -59.3      | 2%                      | -29.2          | 7%                         |
| **Step 2: Baseline VCAM-1 + Hypertension Adjusted** | -90.7 |                        | -75.8          |                            |
| + Baseline Age               | -90.0      | 1%                      | -76.4          | 0%                         |
| + Gender                     | -91.0      | 0%                      | -76.7          | 1%                         |
| + BMI                        | -127.1     | 40%                     | -81.2          | 7%                         |
| + Epworth Sleepiness Scale   | -92.3      | 2%                      | -72.2          | 5%                         |
| + Obstructive Lung Disease   | -91.2      | 1%                      | -83.6          | 10%                        |
| + Current Smoking            | -89.6      | 1%                      | -69.7          | 8%                         |
| + Statin Use                 | -97.0      | 7%                      | -90.4          | 10%                        |
| + Exercise                   | -94.5      | 4%                      | -81.9          | 8%                         |
| **Step 3: Baseline VCAM-1 + Hypertension + BMI Adjusted** | -127.1 |                        | -81.2          |                            |
| + Baseline Age               | -127.9     | 1%                      | -82.6          | 2%                         |
| + Gender                     | -128.4     | 1%                      | -83.0          | 2%                         |
| + Epworth Sleepiness Scale   | -132.9     | 5%                      | -80.6          | 1%                         |
| + Obstructive Lung Disease   | -128.4     | 1%                      | -90.1          | 11%                        |
| + Current Smoking            | -122.6     | 4%                      | -74.5          | 8%                         |
| + Statin Use                 | -134.0     | 5%                      | -97.0          | 19%                        |
| + Exercise                   | -130.7     | 3%                      | -86.2          | 6%                         |
| **Step 4: Baseline VCAM-1 + Hypertension + BMI + Statin Use Adjusted** | -134.0 |                        | -97.0          |                            |
| + Baseline Age               | -135.1     | 1%                      | -98.6          | 2%                         |
| + Gender                     | -135.8     | 1%                      | -99.5          | 3%                         |
| + Epworth Sleepiness Scale   | -138.0     | 3%                      | -96.7          | 0%                         |
| + Obstructive Lung Disease   | -137.6     | 3%                      | -111.0         | 14%                        |
| + Current Smoking            | -129.8     | 3%                      | -89.5          | 8%                         |
| + Exercise                   | -137.4     | 3%                      | -102.0         | 5%                         |

The result of our model assessment of potential confounding variables is presented for models assessing the relationship between PAP usage and change in VCAM-1. Each potential confounder was added separately to the indicated model in a forward stepwise fashion, retaining the variable that resulted in the largest absolute percent change in the coefficient (β) for full or partial PAP use at each step (shown in bold) and stopping when inclusion of another variable resulted in an absolute change in both the PAP coefficients of <15%. Age and gender were modeled as baseline values only. Other continuous covariates (BMI, Epworth Sleepiness Scale) were included in the models as baseline and change from baseline and dichotomous covariates (hypertension, obstructive lung disease, current smoking, statin use and exercise) were included as the combination of baseline and follow-up status (no/no, no/yes, yes/no, yes/yes); *The final adjusted covariate model for change in VCAM-1, which includes VCAM-1 at baseline, hypertension at baseline and follow-up, statin use at baseline and follow-up, baseline BMI, and change in BMI. 

Abbreviations: VCAM-1: Vascular Cell Adhesion Molecule 1; PAP: Positive Airway Pressure; BMI: Body Mass
**Table E2E1: Correlations between obesity measures and baseline cellular adhesion molecule levels.**

| Obesity Measure                  | ICAM-1*   | VCAM-1*   |
|---------------------------------|-----------|-----------|
|                                 | rho       | p-value   | rho       | p-value   |
| Subcutaneous fat volume (cm³)   | 0.18      | 0.0015    | 0.02      | 0.6809    |
| Body mass index (kg/m²)         | 0.18      | 0.0018    | 0.02      | 0.7048    |
| Total abdominal fat volume (cm³)| 0.16      | 0.0042    | 0.02      | 0.6765    |
| Hip circumference (cm)          | 0.12      | 0.0297    | 0.06      | 0.2737    |
| Waist circumference (cm)        | 0.10‡     | 0.0893    | 0.01      | 0.8240    |
| Visceral fat volume (cm³)       | 0.07†     | 0.2310    | 0.01      | 0.8023    |
| Neck circumference (cm)         | 0.04‡     | 0.4706    | -0.02     | 0.6665    |
| Waist-to-hip ratio              | 0.02‡     | 0.7763    | -0.04     | 0.4598    |

Pearson correlation coefficients (rho) and p-values are shown for the associations between obesity measures and natural log transformed levels of ICAM-1 and VCAM-1 at baseline. *Baseline ICAM-1 and VCAM-1 levels were natural log transformed in order to achieve normality and allow for parametric analyses. †magnitude of Pearson correlation is borderline significantly smaller than correlation between BMI and ICAM-1 (p<0.06); ‡magnitude of Pearson correlation is significantly smaller than correlation between BMI and ICAM-1 (p<0.05); Significant correlations (p<0.05) shown in **bold. Abbreviations: ICAM-1: Intracellular Adhesion Molecule 1; VCAM-1: Vascular Cell Adhesion Molecule 1**
### Table E3E2: ICAM-1 and VCAM-1 Baseline and Follow-Up Levels within PAP Usage and BMI Subgroups.

| PAP Usage | BMI Group | N  | ICAM-1 (Mean ± SD) | VCAM-1 (Mean ± SD) | p*  |
|------------|-----------|----|--------------------|--------------------|-----|
|            |           |    | Baseline           | Follow-Up          |      |
| Full Users | All       | 177| 299 ± 80           | 287 ± 71           | 0.0105 |
|            | < 30      | 51 | 287 ± 78           | 284 ± 73           | 0.6932 |
|            | 30-35     | 67 | 297 ± 77           | 283 ± 60           | 0.0588 |
|            | ≥ 35      | 59 | 312 ± 84           | 295 ± 81           | 0.0385 |
|            | All       | 44 | 295 ± 92           | 293 ± 85           | 0.8004 |
|            | < 30      | 14 | 259 ± 44           | 240 ± 52           | 0.0689 |
|            | 30-35     | 16 | 299 ± 75           | 302 ± 80           | 0.8094 |
|            | ≥ 35      | 14 | 328 ± 131          | 335 ± 94           | 0.8008 |
|            | All       | 88 | 312 ± 110          | 316 ± 103          | 0.6963 |
|            | < 30      | 46 | 302 ± 104          | 304 ± 86           | 0.8133 |
|            | 30-35     | 27 | 331 ± 127          | 302 ± 80           | 0.1307 |
|            | ≥ 35      | 15 | 308 ± 99           | 376 ± 160          | 0.0807 |
| Partial Users | All | 44 | 295 ± 92           | 293 ± 85           | 0.8004 |
|            | < 30      | 14 | 259 ± 44           | 240 ± 52           | 0.0689 |
|            | 30-35     | 16 | 299 ± 75           | 302 ± 80           | 0.8094 |
|            | ≥ 35      | 14 | 328 ± 131          | 335 ± 94           | 0.8008 |
|            | All       | 88 | 312 ± 110          | 316 ± 103          | 0.6963 |
|            | < 30      | 46 | 302 ± 104          | 304 ± 86           | 0.8133 |
|            | 30-35     | 27 | 331 ± 127          | 302 ± 80           | 0.1307 |
|            | ≥ 35      | 15 | 308 ± 99           | 376 ± 160          | 0.0807 |
| Non-Users  | All       | 88 | 312 ± 110          | 316 ± 103          | 0.6963 |
|            | < 30      | 46 | 302 ± 104          | 304 ± 86           | 0.8133 |
|            | 30-35     | 27 | 331 ± 127          | 302 ± 80           | 0.1307 |
|            | ≥ 35      | 15 | 308 ± 99           | 376 ± 160          | 0.0807 |

Levels of ICAM-1 and VCAM-1 are shown at baseline and follow-up for CPAP usage groups overall and stratified by BMI. Values are summarized using means ± standard deviations (SD); *p-value from paired t-test assessing whether there was a significant change in molecule levels from baseline to follow-up; significant changes from baseline to follow-up (p<0.05) shown in **bold**. **Abbreviations**: ICAM-1: Intracellular Adhesion Molecule 1; VCAM-1: Vascular Cell Adhesion Molecule 1; BMI: body mass index; PAP: positive airway pressure; N: number of participants included in analyses; SD: standard deviation.
Table E4: Predicted Within PAP and BMI subgroup Mean Change in ICAM-1 and VCAM-1.

| PAP Group | BMI Group | N   | ICAM-1 Change | VCAM-1 Change |
|-----------|-----------|-----|---------------|---------------|
|           |           |     | LS Mean ± SE  | p*            |
|           |           |     |               | LS Mean ± SE  | p*            |
| **Full Users** |          |     |               |               |
| All       | All       | 177 | -17.7 ± 4.8   | 0.0003        |
|           | <30       | 51  | -6.5 ± 8.1    | 0.4211        |
|           | 30-35     | 67  | -20.4 ± 6.6   | 0.0025        |
|           | ≥35       | 59  | -20.7 ± 9.9   | 0.0393        |
| All       | <30       | 44  | -6.2 ± 9.6    | 0.5213        |
|           | 30-35     | 14  | -33.6 ± 15.4  | 0.0321        |
|           | ≥35       | 14  | 15.7 ± 20.5   | 0.4463        |
| **Partial Users** |          |     |               |               |
| All       | All       | 44  | 16.5 ± 7      | 0.0190        |
|           | <30       | 14  | -33.6 ± 15.4  | 0.0321        |
|           | 30-35     | 14  | 15.7 ± 20.5   | 0.4463        |
|           | ≥35       | 14  | 15.7 ± 20.5   | 0.4463        |
| **Non-Users** |          |     |               |               |
| All       | All       | 88  | 16.5 ± 7      | 0.0190        |
|           | <30       | 44  | 9.9 ± 8.7     | 0.2567        |
|           | 30-35     | 27  | -15 ± 10.5    | 0.1560        |
|           | ≥35       | 15  | 73.4 ± 19.3   | 0.0003        |

Subgroup specific predicted mean change and standard errors from ANCOVA models testing whether there was a significant association between PAP usage and change in cellular adhesion molecules are presented. *p-value testing whether the predicted least square mean change is significantly different from zero; models adjusted for baseline ICAM-1 or VCAM-1 levels, BMI, change in BMI, hypertension at baseline and follow-up, and statin use at baseline and follow-up (for VCAM-1 change only); Significant within group changes (p<0.05) shown in bold.

Abbreviations: ICAM-1: Intracellular Adhesion Molecule 1; VCAM-1: Vascular Cell Adhesion Molecule 1; BMI: Body Mass Index; PAP: Positive Airway Pressure; N: Number of participants included in analyses; LS Mean: Least Squares Mean; SE: Standard Error.
### Table E3: Associations between continuous PAP usage and both ICAM-1 and VCAM-1 change.

| **PAP Usage in last 28 Days** | **BMI Group** | **N** | **ICAM-1 Change** | **p²** | **VCAM-1 Change** | **p²** |
|-----------------|-------------|------|-------------------|-------|-------------------|-------|
|                 |             |      | **β ± SE** |       | **β ± SE** |       |
| **Average Hours Used** | All | 221 | -3.7 ± 2.1 | 0.0865 | 8.4 ± 13.4 | 0.5299 |
| <30 | 65 | -0.1 ± 4.2 | 0.9805 | -35.7 ± 24.4 | 0.1008 |
| 30-35 | 83 | -0.5 ± 4.0 | 0.9052 | 31.1 ± 29.3 | 0.2927 |
| ≥35 | 73 | -8.9 ± 3.7 | **0.0181** | 9.4 ± 22.7 | 0.6805 |
| **Total Nights Used** | All | 221 | -0.5 ± 0.7 | 0.4868 | 2.8 ± 4.2 | 0.5051 |
| <30 | 65 | 1.4 ± 1.3 | 0.2803 | 3.8 ± 6.6 | 0.5652 |
| 30-35 | 83 | -0.2 ± 1.1 | 0.8564 | 4.8 ± 8.6 | 0.5807 |
| ≥35 | 73 | **-2.5 ± 1.2** | **0.0355** | 2.8 ± 7.2 | 0.7030 |

The associations between continuous measures of PAP usage (average hours used and average nights used during the last 28 nights) and cellular adhesion molecule change are presented. *p-value from linear regression model with subject specific change scores as the outcome and PAP usage as a predictor, restricted to the subset of participants who were full or partial users (n=221). Models adjusted for baseline ICAM-1 or VCAM-1 levels, BMI, change in BMI, hypertension at baseline and follow-up, and statin use at baseline and follow-up (for VCAM-1 change only); Significant associations (p<0.05) shown in **bold**. **Abbreviations:** ICAM-1: Intracellular Adhesion Molecule 1; VCAM-1: Vascular Cell Adhesion Molecule 1; PAP: Positive Airway Pressure; BMI: Body Mass Index; N: Number of participants included in analyses; β: Coefficient from linear regression model; SE: Standard error.
Table E6: Impact of baseline OSA severity adjustments on associations between PAP and cellular adhesion molecule change.

| BMI Group | ICAM-1 Change | VCAM-1 Change |
|-----------|---------------|---------------|
|           | Full Users    | Partial Users | Non-Users | p<sup>a</sup> | p<sub>TREND</sub> | Full Users | Partial Users | Non-Users | p<sup>a</sup> | p<sub>TREND</sub> |
| Overall   | -15.8 ± 4.9   | -6.6 ± 9.6    | 43 ± 7.2  | 0.0074      | 0.0020         | 78.8 ± 24.3 | 92.6 ± 47.5 | 162.5 ± 35.9 | 0.1807 | 0.0765        |
| <30       | -17.8 ± 8.3   | -34.1 ± 15.2  | 4.9 ± 8.9 | 0.0872      | 0.7103         | 35.1 ± 41.0 | 32.5 ± 73.9 | 105 ± 43.9 | 0.5080 | 0.2866        |
| 30-35     | -17.6 ± 6.6   | 3.7 ± 13.4    | -23.4 ± 11.0 | 0.2730 | 0.8641         | 87.1 ± 41.7 | 125.9 ± 85.9 | 137.5 ± 70.7 | 0.8116 | 0.5272        |
| ≥35       | -21.3 ± 10.9  | 16.2 ± 20.6   | 75.4 ± 19.7 | 0.0004      | <0.0004        | 126.6 ± 46.3 | 117.2 ± 96.6 | 307.0 ± 95.9 | 0.2326 | 0.1442        |

| BMI Group | Baseline + Covariate + ODI Adjusted Analyses<sup>b</sup> | Baseline + Covariate + SaO2 Nadir Adjusted Analyses<sup>b</sup> | Baseline + Covariate + % Time SaO2<90 Adjusted Analyses<sup>b</sup> |
|-----------|-------------------------------------------------|-----------------------------------------------------------------|-------------------------------------------------|
|           | Full Users | Partial Users | Non-Users | p<sup>a</sup> | p<sub>TREND</sub> | Full Users | Partial Users | Non-Users | p<sup>a</sup> | p<sub>TREND</sub> | Full Users | Partial Users | Non-Users | p<sup>a</sup> | p<sub>TREND</sub> |
| Overall   | -17.7 ± 4.9 | -6.2 ± 9.7    | 16.6 ± 7.2 | 0.0009      | 0.0002         | 70.5 ± 24.4 | 94.8 ± 48.4 | 178.1 ± 35.9 | 0.0601 | 0.0213        |
| <30       | -5 ± 8.4    | 32.6 ± 15.5   | 7.9 ± 9.2  | 0.0988      | 0.4519         | 43.2 ± 40.2 | 51.7 ± 73.8 | 90.4 ± 43.7 | 0.7548 | 0.4675        |
| 30-35     | -18.3 ± 6.7 | 2.2 ± 13.6    | -10.1 ± 10.8 | 0.3749 | 0.8604         | 73.6 ± 42.4 | 113.6 ± 88.4 | 171.7 ± 70.4 | 0.5362 | 0.2651        |
| ≥35       | -22.2 ± 9.8 | 17.4 ± 20.3   | 78 ± 19.4  | 0.0001      | <0.0004        | 119.4 ± 46.3 | 123.7 ± 96.7 | 320 ± 95 | 0.1494 | 0.0826        |

<sup>a</sup>Results from ANCOVA models testing whether there was a significant association between PAP usage and change in cellular adhesion molecules are presented after adjustment for the denoted OSA severity measure, baseline ICAM-1 or VCAM-1 levels, BMI, change in BMI, hypertension at baseline and follow-up, and statin use at baseline and follow-up (for VCAM-1 change only). Results are presented as group specific least square mean change ± standard errors (SE);<sup>b</sup>p-value testing the global null hypothesis of no differences between PAP usage groups and cellular adhesion molecule change;<sup>c</sup>p-value testing whether there is a linear dose response in the effect of PAP usage; Significant differences or linear trends (p<0.05) shown in **bold**.

**Abbreviations:** ICAM-1: Intracellular Adhesion Molecule 1; VCAM-1: Vascular Cell Adhesion Molecule 1; PAP: Positive Airway Pressure; BMI: Body Mass Index; SE: standard error; AHI: Apnea hypopnea index; ODI: Oxygen desaturation index; SaO2: Oxygen saturation percentage
Table E73: Associations* between baseline OSA severity measures and cellular adhesion molecule changes among non-PAP users.

| OSA Severity Measure† | BMI Group | N | ICAM-1 Change β ± SE | p | VCAM-1 Change β ± SE | p |
|-----------------------|-----------|---|----------------------|---|----------------------|---|
| **AHI**               | All       | 88 | 0.0 ± 0.6            | 0.9867 | 0.1 ± 1.9            | 0.9707 |
|                       | <30       | 46 | -0.1 ± 0.9           | 0.8689 | 1.5 ± 3.3            | 0.6529 |
|                       | 30-35     | 27 | **-2.0 ± 0.9**       | **0.0314** | **-2.9 ± 3.0**       | **0.3405** |
|                       | ≥35       | 15 | 2.5 ± 1.6            | 0.1746 | -0.3 ± 6.1           | 0.9601 |
| **ODI**               | All       | 88 | 0.9 ± 0.7            | 0.2166 | -0.3 ± 2.2           | 0.8973 |
|                       | <30       | 46 | -0.1 ± 1.1           | 0.9225 | -0.3 ± 4.2           | 0.9443 |
|                       | 30-35     | 27 | -2.6 ± 1.2           | 0.0525 | -5.0 ± 4.1           | 0.2374 |
|                       | ≥35       | 15 | **3.8 ± 1.5**        | **0.0228** | 0.2 ± 6.9           | 0.9807 |
| **SaO₂ Nadir**        | All       | 88 | **-3.3 ± 1.2**       | **0.0085** | 1.2 ± 4.0           | 0.7615 |
|                       | <30       | 46 | -1.2 ± 1.8           | 0.5197 | 7.5 ± 7.2            | 0.3068 |
|                       | 30-35     | 27 | 2.6 ± 1.8            | 0.1748 | 9.1 ± 5.9            | 0.1403 |
|                       | ≥35       | 15 | **-10.1 ± 3.4**      | **0.0210** | 14.9 ± 15.4         | 0.3704 |
| **% Time SaO₂<90**    | All       | 88 | 6.7 ± 9.5            | 0.4828 | -45.6 ± 29.4         | 0.1245 |
|                       | <30       | 46 | 5.8 ± 11.6           | 0.6204 | -43.5 ± 45.5         | 0.3452 |
|                       | 30-35     | 27 | -22.5 ± 13.2         | 0.1054 | -84.6 ± 45.4         | 0.0807 |
|                       | ≥35       | 15 | **69.4 ± 26.1**      | **0.0327** | -170.1 ± 171.7      | 0.3601 |

*Associations were assessed using a linear regression model with subject specific change scores as the outcome and OSA severity as a predictor, restricted to non-PAP users only. Models adjusted for baseline ICAM-1 or VCAM-1 levels, BMI, change in BMI, hypertension at baseline and follow-up, and statin use at baseline and follow-up (for VCAM-1 change only); †Percent time O₂<90 natural log transformed for normality; Significant linear associations (p<0.05) shown in bold. Abbreviations: ICAM-1: Intracellular Adhesion Molecule 1; VCAM-1: Vascular Cell Adhesion Molecule 1; PAP: Positive Airway Pressure; OSA: Obstructive Sleep Apnea; BMI: Body Mass Index; N: Number of participants included in analyses; β: Coefficient from linear regression model; SE: Standard error;
Table E8E4: Covariate comparisons for patients included in and excluded from PS-propensity score matched sample

| Variable* | Full Users Included (N=90) | Excluded (N=87) | p† | Non-Users Included (N=62) | Excluded (N=26) | p† |
|-----------|---------------------------|----------------|----|---------------------------|----------------|----|
| ICAM-1    | 301.0 ± 88.5              | 297.6 ± 70.2   | 0.7761 | 289.0 ± 75.4              | 366.1 ± 155.6  | 0.0222 |
| VCAM-1    | 880.2 ± 351.7             | 841.4 ± 284.4  | 0.4194 | 930.2 ± 250.5             | 1,038.8 ± 361.5 | 0.1711 |
| Age       | 54.7 ± 10.5               | 55.7 ± 9.8     | 0.4777 | 55.3 ± 8.9                | 55.4 ± 9.0     | 0.9793 |
| BMI       | 31.7 ± 4.2                | 34.7 ± 5.2     | <0.0001 | 31.2 ± 4.8                | 28.7 ± 4.3     | 0.0210 |
| AHI       | 40.7 ± 15.1               | 61.5 ± 19.5    | <0.0001 | 36.3 ± 12.5               | 27.2 ± 19.3    | 0.0342 |
| ODI       | 30.2 ± 12.3               | 52.5 ± 21.6    | <0.0001 | 26.4 ± 11.2               | 22.3 ± 20.3    | 0.3381 |
| SaO2 Nadir| 78.4 ± 5.6                | 73.3 ± 8.8     | <0.0001 | 79.3 ± 6.4                | 78.7 ± 8.5     | 0.7273 |
| % Time SaO2<90| 1.7 ± 0.9     | 2.8 ± 1.0     | <0.0001 | 1.5 ± 0.9                 | 1.3 ± 1.1      | 0.2733 |
| ESS       | 11.8 ± 4.7                | 13.5 ± 4.8     | 0.0193 | 10.6 ± 4.4                | 10.1 ± 5.6     | 0.6207 |
| Male      | 75 (83.3%)                | 67 (77.0%)     | 0.2911 | 49 (79.0%)                | 18 (69.2%)     | 0.3250 |
| Exercise  | 62 (68.9%)                | 51 (58.6%)     | 0.1552 | 45 (75.6%)                | 19 (73.1%)     | 0.9620 |
| Diabetes  | 3 (3.3%)                  | 8 (9.2%)       | 0.1063 | 2 (3.2%)                  | 1 (3.9%)       | >0.999 |
| Hypertension| 31 (34.4%)           | 55 (63.2%)     | 0.0001 | 17 (27.4%)                | 7 (26.9%)      | 0.9620 |
| CVD       | 9 (10.0%)                 | 14 (16.1%)     | 0.2282 | 9 (14.5%)                 | 6 (23.1%)      | 0.3606 |
| Smoking   | 11 (12.2%)                | 20 (23.0%)     | 0.0596 | 8 (12.9%)                 | 10 (38.5%)     | 0.0067 |
| Obstructive Lung Dx| 18 (20.0%) | 10 (11.5%)       | 0.1211 | 15 (24.2%)                | 7 (26.9%)      | 0.7873 |
| Statin Use| 13 (14.4%)                | 26 (29.9%)     | 0.0132 | 8 (12.9%)                 | 7 (26.9%)      | 0.1283 |

Significant differences (p<0.05) are shown in bold; *Continuous characteristics are presented as means ± standard deviations (SD) and categorical covariates as frequencies and percentages; †p-value from T-test (continuous variables) or chi-square or exact test (categorical variables) testing whether there were differences between participant included and excluded; Abbreviations: PS: Propensity Score; ICAM-1: Intracellular Adhesion Molecule 1; VCAM-1: Vascular Adhesion Molecule 1; BMI: body mass index; AHI: apnea hypopnea index; ODI: oxygen desaturation index; SaO2: oxygen saturation; ESS: Epworth Sleepiness Scale; CVD: Cardiovascular Disease; Dx: Disease.
| Biomarker | PS Matched Sample |  | Observational Study |  |
|-----------|------------------|--|---------------------|--|
|           | Mean ± SE Change | p* | Mean ± SE Change | p* |
| ICAM-1    | -14.1±7.3        | 0.005 | -17.7±4.8 | <0.001 |
| VCAM-1    | 71.9±36.4        | 0.087 | 62.3±24.1 | 0.009 |

Significant differences shown in **bold**. *Model adjusted for PS quintile and baseline biomarker level; †Adjusted for baseline ICAM-1 or VCAM-1 levels, BMI, change in BMI, hypertension at baseline and follow-up, and statin use at baseline and follow-up (for VCAM-1 change only). Abbreviations: ICAM-1: Intracellular Adhesion Molecule 1; VCAM-1: Vascular Adhesion Molecule 1; PS: Propensity Score; SE: Standard Error
Figure E1: Diagram of the study population included in analyses. The figure diagrams the flow of patients that resulted in our analysis sample, beginning with participants in the ISAC prospective cohort with completed follow-up as of June 2011 and progressing through our applied exclusion criteria. The final sample used in the manuscript included 309 patients meeting all criteria and with available baseline and follow-up cellular adhesion molecule levels. Based on objective PAP compliance data, this sample included 177 full, 44 partial, and 88 non-PAP users.
Figure E2: Mean and 95% confidence interval for change in levels of ICAM-1 and VCAM-1. The mean changes in ICAM-1 (left) and VCAM-1 (right) are shown, along with the associated 95% confidence intervals. Results are presented separately for each of the 3 PAP usage groups [full user, partial user (part), non-user (non)] in the overall sample (n=309) and within strata defined by BMI groups (<30, 30-35, ≥35). Estimates with 95% confidence intervals not crossing 0 represent significant changes within specific subgroups: *p<0.05. We observed a significant difference among PAP groups (p=0.004) and evidence for a linear trend (p=0.001) for ICAM-1 change within the BMI≥35 group. Abbreviations: ICAM-1: intracellular adhesion molecule 1; VCAM-1: vascular adhesion molecule 1; BMI: body mass index; PAP: positive airway pressure
The predicted least square mean change in ICAM-1 and VCAM-1 levels for each PAP usage group within each BMI group are presented, along with the associated 95% confidence intervals. Results are adjusted for baseline ICAM-1 or VCAM-1 levels, BMI, change in BMI, hypertension at baseline and follow-up, and statin use at baseline and follow-up (for VCAM-1 change only). Estimates with 95% confidence intervals not crossing 0 represent significant changes: *p<0.05. **Abbreviations:** LS: least squares; ICAM-1: Intracellular Adhesion Molecule 1; VCAM-1: Vascular Adhesion Molecule 1; BMI: body mass index; PAP: positive airway pressure