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# Change in weight and central obesity by positive airway pressure treatment in obstructive sleep apnea patients: longitudinal data from the ESADA cohort

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## Summary

The effect of positive airway pressure treatment on weight and markers of central obesity in patients with obstructive sleep apnea remains unclear. We studied the change in body weight and anthropometric measures following positive airway pressure treatment in a large clinical cohort. Patients with obstructive sleep apnea with positive airway pressure treatment from the European Sleep Apnea Database registry ($n$ = 1,415, 77% male, age 54 ± 11 [mean ± $SD$] years, body mass index 31.7 ± 6.4 kg/m$^2$, apnea–hypopnea index 37 ± 24 $n$ per hr, Epworth Sleepiness Scale 10.2 ± 5.0) were selected. Changes in body mass index and neck/waist/hip circumferences at baseline and at follow-up visit were analysed. Overall, body mass index (0.0 [95% confidence interval, −0.1 to 0.2] kg/m$^2$) and neck circumference (0.0 (95% confidence interval, −0.1 to 0.1] cm) were unchanged after positive airway pressure treatment compared with baseline (follow-up duration 1.1 ± 1.0 years and compliance 5.2 ± 2.1 hr per day). However, in non-obese (body mass index <30 kg/m$^2$) patients, positive airway pressure treatment was associated with an increased body mass index and waist circumference (0.4 [0.3–0.5] kg/m$^2$ and 0.8 [0.4–1.2] cm, respectively, all $p$ < 0.05), and weight gain was significantly associated with higher positive airway pressure compliance and longer positive airway pressure

  

treatment duration. In the obese subgroup, body mass index was reduced after positive airway pressure treatment (−0.3 [−0.5 to −0.1] kg/m$^2$, $p < 0.05$) mainly in patients with a strong reduction in Epworth Sleepiness Scale. In conclusion, positive airway pressure therapy was not found to systematically change body mass index in the European Sleep Apnea Database cohort, but the response was heterogeneous. Our findings suggest that weight gain may be restricted to an obstructive sleep apnea phenotype without established obesity. Lifestyle intervention needs to be considered in both lean and obese patients with obstructive sleep apnea receiving positive airway pressure treatment.

KEYWORDS
body weight, central obesity, excessive daytime sleepiness, obstructive sleep apnea, positive airway pressure

## 1 | INTRODUCTION

Obstructive sleep apnea (OSA) is a prevalent condition that affects up to 17% of adult women and 34% of adult men (Garvey, Pengo, Drakatos, & Kent, 2015; Peppard et al., 2013). Extensive research has identified obesity as a major risk factor for OSA. In particular, central adiposity is thought to increase pharyngeal collapsibility by mechanical effects on pharyngeal soft tissue and altered lung volume. Other data suggest a negative influence of adipokines on upper airway neuromuscular control (Isono, 2012). Consistent with these findings, it is the observation that weight gain increases whereas weight loss reduces severity of sleep-disordered breathing (Newman et al., 2005; Peppard, Young, Palta, Dempsey, & Skatrud, 2000). However, these associations are confounded by the progressive character of OSA as evidenced by epidemiological and experimental studies (Eikermann et al., 2007; Peppard et al., 2013).

Studies have linked untreated OSA to an increased metabolic rate, and this link was attributed to increased sympathetic activity as well as elevated work of breathing during apnoeic events (Shechter, 2017; Stenlöf, Grunstein, Hedner, & Sjostrom, 1996). Other studies suggested that OSA treatment with positive airway pressure (PAP) appears to increase body mass index (BMI), possibly due to a reduction of metabolic rate (Shechter, 2016; Tachikawa et al., 2016). However, lifestyle factors such as food intake habits and physical activity are considered to have an even stronger influence on energy balance, and PAP treatment does not appear to have an appreciable effect on these factors (Joosten, Hamilton, & Naughton, 2017). In a recent meta-analysis of 3,181 patients with OSA from randomized trials, body weight and BMI were found to increase after PAP treatment (Drager et al., 2015). There are data to suggest that weight gain is particularly evident in patients with higher adherence to PAP therapy (Quan et al., 2013). Whether these findings can be extended to the rather heterogeneous clinical population of patients with OSA needs to be further studied. Moreover, the association between reduced daytime sleepiness and weight change after PAP therapy has not been systematically explored in large clinical cohorts. The current study therefore aimed to evaluate the effect of PAP treatment on body weight and markers of central obesity in newly-diagnosed patients with OSA in the European Sleep Apnea Database (ESADA) cohort (Hedner et al., 2011). We hypothesized that weight gain is linked to PAP therapy and associated with the degree of compliance with therapy. We also hypothesized that the change of daytime sleepiness after PAP in OSA provides an influence on body weight.

## 2 | MATERIALS AND METHODS

### 2.1 | The ESADA cohort

The ESADA registry is a multi-centre, prospective patient cohort reflecting a network of 30 sleep centres in 20 countries in Europe and Israel (Hedner et al., 2011). The overall objective of ESADA is to generate a clinically representative cohort and to prospectively evaluate subjects with suspected sleep-disordered breathing. The registry also provides data to identify cross-sectional and longitudinal associations between OSA and various co-morbid conditions, including cardiovascular and metabolic disease as well as mortality. A central web-based platform is applied to collect patient information from the participating sleep centres. In brief, patients with suspected OSA and aged between 18 and 80 years are eligible for inclusion in the registry. Anthropometric characteristics, information on daytime symptoms and health-related lifestyle, such as smoking and alcohol consumption, blood tests, medical history, medication and sleep data are collected. Daytime sleepiness is quantified by the Epworth Sleepiness Scale (ESS; Johns, 1991). The severity of sleep-disordered breathing is assessed by polysomnography or

polygraphy according to the prevailing clinical routine at each participating sleep centre (Escourrou et al., 2015). The ESADA protocol was approved by the research ethics committee at each participating centre, and informed consent is obtained from all included patients.

### 2.2 | Anthropometric assessment

Weight and height are determined in every patient; BMI is defined as the body mass in kilograms divided by the square of the body height in metres, and is expressed in kg/m$^2$. Waist circumference is taken horizontally to within 1 cm. Hip circumference (cm) is measured at the level of greater trochanters, and the waist-to-hip ratio is calculated. Neck circumference (cm) is measured in the midway of the neck, between mid-cervical spine and mid-anterior neck.

### 2.3 | Treatment and follow-up procedure

The ESADA registry captures information on OSA treatment, including planned treatment procedures (e.g. PAP, oral device, surgery, active weight reduction, drug and/or other treatment), and allows for specific clinical follow-up routines practiced at each study site. At the treatment follow-up visit (if applicable), information on anthropometric assessments, clinical and biochemical data, and the ESS score were collected. Details on the type of PAP device (e.g. auto-titrated, continuous or bilevel), treatment start/stop time, mean administered pressure (mbar) and compliance (hours of use per day collected from machine time counter) were documented in PAP-treated patients.

### 2.4 | Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics 22.0 (IBM, Armonk, NY, USA). Results were reported as mean (standard deviation [*SD*]) or mean (95% confidence interval [CI]). Between-groups comparison was performed using the Chi-square test or independent-samples *t*-test. Analysis of covariance (ANCOVA) was used to compare the change of anthropometric measurements from baseline to the PAP treatment follow-up. Analysis of variance (ANOVA) was used to analyse weight change in relation to classes of ESS change. Subgroup analyses were performed using BMI cut-off of 30 kg/m$^2$ (median value). Generalized linear model (GLM) analyses were used to identify independent predictors of BMI change and the changes in other anthropometric variables. Age, gender, current smoking, baseline BMI and apnea–hypopnea index (AHI), subjective sleep time, cardiovascular/metabolic comorbidities, chronic obstructive pulmonary disease (COPD), psychiatric disease and intake of psychotropic medication (ATC N06) as well as change in ESS score by PAP, PAP compliance and PAP follow-up time were included in the multivariable analyses. All tests were two-tailed, and statistical significance is considered at $p < 0.05$.

## 3 | RESULTS

### 3.1 | Patient population

Data from a total of 19,556 patients with OSA from the ESADA registry were reviewed, and a subgroup of 4,313 subjects with PAP therapy and follow-up data was identified (Figure 1). Subjects with incomplete anthropometric and co-morbidity data at baseline and follow-up, short PAP therapy follow-up time (≤30 days), or combined PAP and active weight reduction treatment were excluded. The final study population consisted of 1,415 patients with OSA with PAP therapy alone. Characteristics of the whole study population or following allocation according to BMI (non-obese <30 kg/m$^2$ and obese ≥30 kg/m$^2$) are shown in Table 1.

### 3.2 | Change of anthropometric measures and daytime sleepiness at follow-up

Body weight, BMI, waist and neck circumferences did not change significantly after PAP treatment compared with baseline in the entire study population, but there was a modest reduction of hip circumference (−0.34 [95% CI, −0.65, −0.02] cm, $p < 0.05$; Table 2). However, when obese ($n = 731$) and non-obese ($n = 684$) patients were evaluated separately, BMI, body weight, waist and hip circumferences decreased at follow-up in obese patients with OSA (−0.3 [−0.5, −0.1] kg/m$^2$, −1.2 [−1.9, −0.5] kg, −1.0 [−1.5, −0.4] cm, −0.9 [−1.4, −0.3] cm, respectively, all $p < 0.05$). In contrast, these parameters increased in the non-obese group (0.4 [0.3, 0.5] kg/m$^2$, 1.1 [0.7, 1.4] kg, 0.8 [0.4, 1.2] cm, 0.2 [−0.1, 0.5] cm, $p < 0.01$, $p < 0.01$, $p < 0.01$, $p = 0.18$, respectively; Table 2). As expected, there was a significant reduction of the ESS score after PAP treatment in all patients (−4.4 [−4.7, −4.2], $p < 0.05$), and the extent of reduction did not differ between the obese and non-obese patients (Table 2). The degree of sleep apnea at baseline did not influence the change in anthropometric measures.

### 3.3 | Predictors of BMI increase with PAP treatment in non-obese patients ($n = 684$)

A post hoc analysis using multivariate GLMs was performed to identify predictors of weight gain in non-obese patients with OSA after PAP treatment (Table 3). In addition to baseline BMI, higher PAP compliance, longer PAP treatment duration and shorter subjective sleep time were associated with a BMI increase in non-obese patients after controlling for confounders ($\beta = -0.07 \pm 0.03$, $0.12 \pm 0.03$, $0.20 \pm 0.06$ and $-0.11 \pm 0.04$, $p = 0.008$, $p < 0.001$, $p = 0.001$ and $p = 0.012$, respectively). Patients with OSA with comorbid COPD also increased BMI after PAP treatment ($\beta = 0.56 \pm 0.28$, $p = 0.042$). The change of waist circumference was found to be positively correlated with PAP compliance and treatment duration at follow-up ($\beta = 0.21 \pm 0.11$ and $0.44 \pm 0.21$, $p = 0.042$ and 0.042, respectively).

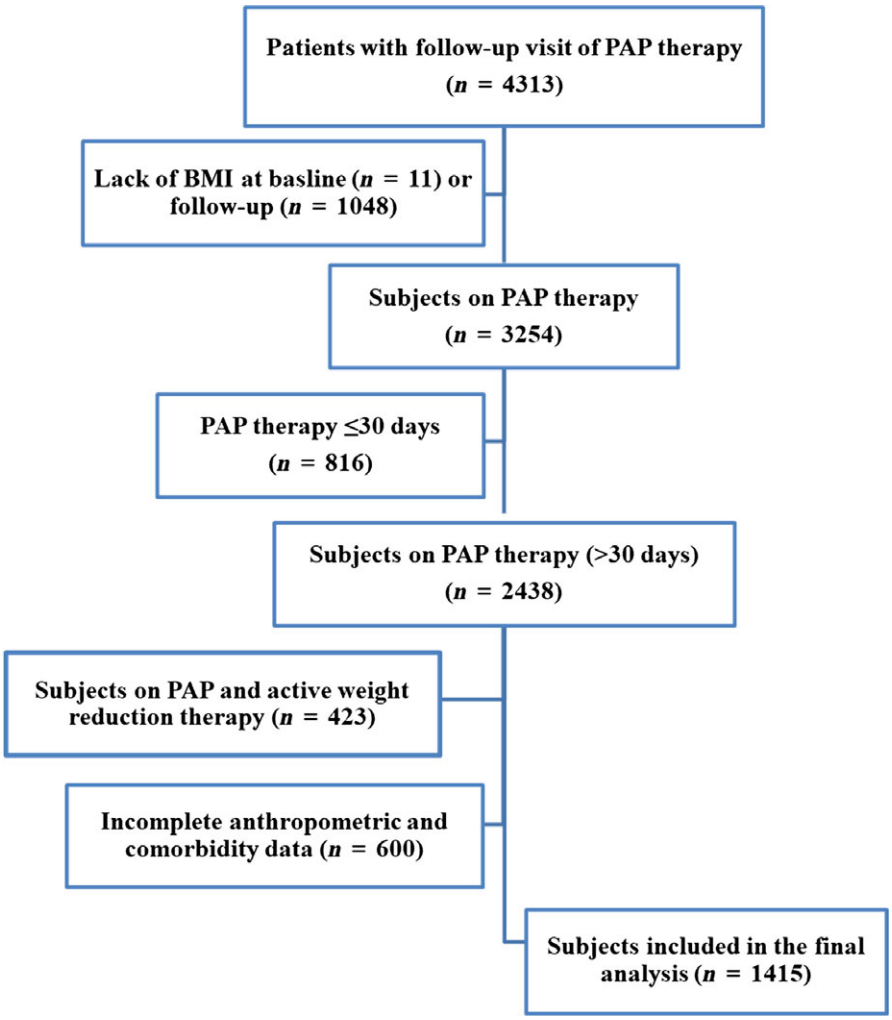


**FIGURE 1** Study flow chart. BMI, body mass index; PAP, positive airway pressure

In patients using PAP 4 hr per day or more, weight gain was significantly higher compared with non-compliant PAP users (0.49 ± 1.5 kg/m$^2$ and 0.13 ± 1.5 kg/m$^2$, $p = 0.014$; Figure 2). The change of ESS score following PAP did not systematically influence the amount of weight change (Figure 3).

### 3.4 | Predictors of BMI reduction following PAP treatment in obese patients ($n = 731$)

Predictors of weight change in obese patients with OSA after PAP treatment were addressed in a multivariate GLM analysis. The decrease of BMI in obese patients was associated with BMI at baseline ($\beta = -0.18 \pm 0.02$, $p < 0.001$), as well as with the change in ESS ($\beta = 0.06 \pm 0.02$, $p = 0.020$; Table 4). A strong reduction of daytime sleepiness (ESS score reduction 8 units or more) following PAP treatment was associated with a significantly more pronounced decrease in BMI compared with no or only mild modifications of the ESS score (ANOVA, $p = 0.006$; Figure 3). Obese patients with hyperlipidaemia appeared to increase the BMI compared with patients with a normal lipid status ($\beta = 0.63 \pm 0.14$, $p = 0.012$).

## 4 | DISCUSSION

The current large observational study suggests that PAP therapy is not associated with systematic weight change in a general clinical sleep laboratory cohort. However, weight gain was seen in a predominantly non-obese subgroup, while there was a modest weight reduction in obese patients under PAP therapy. We found that higher PAP compliance and longer treatment duration were associated with weight gain, while reduction of daytime sleepiness (ESS score) after PAP was linked to weight loss. Our study suggests that non-obese subjects with OSA are at particular risk for a modest weight gain following PAP.

### 4.1 | Weight change after PAP therapy

Successful PAP treatment of OSA leads to increased daytime alertness, which may allow a more active lifestyle, including intensified exercise, reduction of caloric intake and subsequent weight loss. However, studies addressing the effect of PAP therapy on body weight and composition have produced conflicting results. Stenlöf et al. (1996) reported an increased energy expenditure during sleep that could be

**TABLE 1** Characteristics of the study population

| Variables | All patients ($n$ = 1,415) | BMI < 30 kg/m$^2$ ($n$ = 684) | BMI ≥ 30 kg/m$^2$ ($n$ = 731) | Between group difference $p$-value |
|---|---|---|---|---|
| Age (years) | 54 (11) | 54 (12) | 54 (11) | n.s. |
| Male gender (%) | 77 | 78 | 75 | n.s. |
| Current smoker (%) | 23 | 23 | 22 | n.s. |
| BMI (kg/m$^2$) | 31.7 (6.4) | 26.8 (2.3) | 36.3 (5.6) | <0.001 |
| Body weight (kg) | 95.8 (21.2) | 81.4 (11.0) | 109.2 (19.5) | <0.001 |
| Neck circumference (cm) | 42 (4) | 40 (3) | 44 (4) | <0.001 |
| Waist circumference (cm) | 110 (15) | 99 (9) | 120 (13) | <0.001 |
| Hip circumference (cm) | 112 (12) | 103 (6) | 119 (12) | <0.001 |
| Waist-to-hip ratio | 0.99 (0.08) | 0.96 (0.07) | 1.01 (0.08) | <0.001 |
| Hypertension (%) | 46 | 35 | 57 | <0.001 |
| Coronary artery disease (%) | 9 | 9 | 9 | n.s. |
| Hyperlipidaemia (%) | 32 | 31 | 34 | n.s. |
| Diabetes (%) | 15 | 10 | 19 | <0.001 |
| COPD (%) | 6 | 5 | 6 | n.s. |
| Psychiatric disease (%) | 12 | 13 | 10 | n.s. |
| Psychotropic drug use (ATC N06, %) | 13 | 12 | 14 | n.s. |
| ESS | 10.2 (5.0) | 9.9 (5.0) | 10.5 (4.9) | 0.027 |
| AHI ($n$ per hr) | 37 (24) | 31 (20) | 43 (25) | <0.001 |
| ODI 4% ($n$ per hr) | 29 (24) | 21 (19) | 36 (25) | <0.001 |
| Subjective sleep time (hr) | 7.0 (1.4) | 7.0 (1.3) | 6.9 (1.5) | n.s. |
| PAP follow-up duration (years) | 1.1 (1.0) | 1.1 (1.0) | 1.0 (1.0) | n.s. |
| PAP usage (hr per day) | 5.2 (2.1) | 5.2 (2.0) | 5.2 (2.2) | n.s. |

Note: Values are mean (*SD*) or percentage of patients. AHI, apnea–hypopnea index; ATC, anatomical therapeutic chemical; BMI, body mass index; COPD, chronic obstructive pulmonary disease; ESS, Epworth sleepiness scale; ODI, oxygen desaturation index; PAP, positive airway pressure.

**TABLE 2** Change of anthropometric measurements and ESS at PAP follow-up

| | All patients ($n$ = 1,415) | BMI < 30 kg/m$^2$ ($n$ = 684) | BMI ≥ 30 kg/m$^2$ ($n$ = 731) | Between-group difference (ANCOVA) |
|---|---|---|---|---|
| Change of BMI (kg/m$^2$) | 0 (−0.1, 0.2) | 0.4 (0.3, 0.5)* | −0.3 (−0.5, −0.1)* | <0.001 |
| Change of body weight (kg) | −0.1 (−0.5, 0.3) | 1.1 (0.7, 1.4)* | −1.2 (−1.9, −0.5)* | 0.020 |
| Change of neck circumference (cm) | 0 (−0.1, 0.1) | 0.2 (0.1, 0.4)* | −0.2 (−0.3, 0)* | 0.45 |
| Change of waist circumference (cm) | −0.1 (−0.5, 0.2) | 0.8 (0.4, 1.2)* | −1.0 (−1.5, −0.4)* | <0.001 |
| Change of hip circumference (cm) | −0.34 (−0.65, −0.02)* | 0.2 (−0.1, 0.5) | −0.9 (−1.4, −0.3)* | <0.001 |
| Change of waist-to-hip ratio | 0 (0, 0.01) | 0.01 (0, 0.01)* | 0 (−0.01, 0) | 0.002 |
| Change of ESS | −4.4 (−4.7, −4.2)* | −4.3 (−4.7, −3.9)* | −4.6 (−4.9, −4.2)* | 0.59 |

Note: BMI, body mass index; ESS, Epworth sleepiness scale. Shown as mean (95% CI); *$p$ < 0.05.

reduced by PAP treatment in patients with OSA. Other studies (Bamberga et al., 2015) demonstrated that night energy expenditure was increased in obese patients with OSA and normalized in those compliant with therapy, but neither weight nor daily physical activity was changed. The overall effect of PAP therapy on body weight in patients with OSA is no change or modest weight gain. A small study (Garcia, Sharafkhaneh, Hirshkowitz, Elkhatib, & Sharafkhaneh, 2011) reported that 40% of obese patients gained weight during 6 months of PAP, and the change in body weight was associated with increased insulin resistance. A randomized trial of PAP suggested that weight gain, which was associated with PAP compliance, is a common phenomenon in patients with OSA receiving PAP therapy (Quan et al., 2013). On the other hand, both controlled and cohort studies assessing the effect of PAP on BMI and body fat composition have reported no change after therapy (Kritikou et al., 2013; Myllyla, Kurki, Anttalainen, Saaresranta, & Laitinen, 2016; Sivam et al., 2012). Another study (Redenius, Murphy, O'Neill, Al-Hamwi, & Zallek, 2008) investigating long-term effects of PAP treatment found an increase in BMI in non-obese, but not obese, PAP users. Data from our large multicentre ESADA cohort appeared to support this notion, and further demonstrated an association between therapy compliance/duration of therapy and weight change.

**TABLE 3** GLM analysis of predictors for the anthropometric measurement change in patients with BMI < 30 kg/m$^2$ ($n$ = 684)

| | Δ BMI (kg/m$^2$) | Δ Body weight (kg) | Δ Waist circumference (cm) | Δ Hip circumference (cm) | Δ Neck circumference (cm) |
|---|---|---|---|---|---|
| Male gender | β = 0.13 ± 0.14<br>$p$ = 0.36 | β = 0.13 ± 0.44<br>$p$ = 0.76 | β = −0.22 ± 0.52<br>$p$ = 0.67 | β = 0.35 ± 0.40<br>$p$ = 0.39 | β = 0.002 ± 0.16<br>$p$ = 0.99 |
| Age (years) | β = −0.008 ± 0.006<br>$p$ = 0.15 | β = −0.02 ± 0.02<br>$p$ = 0.18 | β = 0.01 ± 0.02<br>$p$ = 0.69 | β = −0.01 ± 0.02<br>$p$ = 0.46 | β = 0.003 ± 0.006<br>$p$ = 0.67 |
| Baseline BMI (kg/m$^2$) | β = −0.07 ± 0.03<br>$p$ = 0.008 | β = −0.22 ± 0.08<br>$p$ = 0.008 | β = −0.29 ± 0.10<br>$p$ = 0.002 | β = −0.10 ± 0.07<br>$p$ = 0.20 | β = −0.03 ± 0.03<br>$p$ = 0.36 |
| Smoking | β = 0.12 ± 0.14<br>$p$ = 0.37 | β = 0.45 ± 0.43<br>$p$ = 0.30 | β = 0.54 ± 0.50<br>$p$ = 0.29 | β = 0.09 ± 0.39<br>$p$ = 0.82 | β = 0.13 ± 0.16<br>$p$ = 0.41 |
| Subjective sleep time (hr) | β = −0.11 ± 0.04<br>$p$ = 0.012 | β = −0.30 ± 0.14<br>$p$ = 0.027 | β = −0.15 ± 0.16<br>$p$ = 0.33 | β = −0.03 ± 0.12<br>$p$ = 0.84 | β = −0.09 ± 0.05<br>$p$ = 0.087 |
| Diabetes mellitus | β = 0.19 ± 0.19<br>$p$ = 0.32 | β = 0.05 ± 0.60<br>$p$ = 0.94 | β = 1.21 ± 0.70<br>$p$ = 0.084 | β = 0.09 ± 0.55<br>$p$ = 0.88 | β = −0.007 ± 0.22<br>$p$ = 0.97 |
| Hyperlipidaemia | β = 0.03 ± 0.13<br>$p$ = 0.81 | β = 0.02 ± 0.39<br>$p$ = 0.97 | β = 0.003 ± 0.45<br>$p$ = 0.99 | β = −0.03 ± 0.35<br>$p$ = 0.93 | β = −0.03 ± 0.14<br>$p$ = 0.84 |
| Hypertension | β = 0.02 ± 0.13<br>$p$ = 0.88 | β = 0.15 ± 0.40<br>$p$ = 0.70 | β = −0.28 ± 0.46<br>$p$ = 0.55 | β = −0.14 ± 0.36<br>$p$ = 0.71 | β = 0.01 ± 0.15<br>$p$ = 0.94 |
| Coronary artery disease | β = 0.24 ± 0.21<br>$p$ = 0.27 | β = 0.37 ± 0.66<br>$p$ = 0.57 | β = −0.04 ± 0.76<br>$p$ = 0.96 | β = 0.05 ± 0.60<br>$p$ = 0.93 | β = 0.03 ± 0.24<br>$p$ = 0.91 |
| COPD | β = 0.56 ± 0.28<br>$p$ = 0.042 | β = 1.64 ± 0.86<br>$p$ = 0.057 | β = 1.89 ± 1.00<br>$p$ = 0.058 | β = −0.12 ± 0.78<br>$p$ = 0.88 | β = 0.43 ± 0.31<br>$p$ = 0.17 |
| Psychiatric disease | β = 0.24 ± 0.20<br>$p$ = 0.22 | β = 0.87 ± 0.62<br>$p$ = 0.16 | β = 1.65 ± 0.72<br>$p$ = 0.021 | β = −0.98 ± 0.56<br>$p$ = 0.08 | β = 0.32 ± 0.22<br>$p$ = 0.16 |
| Psychotropic medication (ATC N06) | β = 0.007 ± 0.21<br>$p$ = 0.97 | β = 0.15 ± 0.64<br>$p$ = 0.81 | β = 0.13 ± 0.74<br>$p$ = 0.86 | β = 1.00 ± 0.58<br>$p$ = 0.083 | β = 0.03 ± 0.23<br>$p$ = 0.91 |
| Baseline AHI ($n$ per hr) | β = −0.01 ± 0.003<br>$p$ = 0.016 | β = −0.02 ± 0.01<br>$p$ = 0.042 | β = −0.02 ± 0.01<br>$p$ = 0.10 | β = −0.02 ± 0.01<br>$p$ = 0.046 | β = −0.01 ± 0.003<br>$p$ = 0.045 |
| Change in ESS score with PAP | β = 0.002 ± 0.01<br>$p$ = 0.90 | β = 0.01 ± 0.04<br>$p$ = 0.75 | β = −0.03 ± 0.04<br>$p$ = 0.46 | β = −0.04 ± 0.03<br>$p$ = 0.25 | β = 0.008 ± 0.01<br>$p$ = 0.58 |
| PAP follow-up duration (years) | β = 0.20 ± 0.06<br>$p$ = 0.001 | β = 0.43 ± 0.19<br>$p$ = 0.019 | β = 0.44 ± 0.21<br>$p$ = 0.042 | β = 0.61 ± 0.17<br>$p$ < 0.001 | β = −0.06 ± 0.07<br>$p$ = 0.39 |
| PAP compliance (hr per day) | β = 0.12 ± 0.03<br>$p$ < 0.001 | β = 0.32 ± 0.09<br>$p$ < 0.001 | β = 0.21 ± 0.11<br>$p$ = 0.042 | β = 0.04 ± 0.08<br>$p$ = 0.60 | β = 0.07 ± 0.03<br>$p$ = 0.032 |

Note: Data shown as β ± $SE$. AHI, apnea–hypopnea index; ATC, anatomical therapeutic chemical; BMI, body mass index; COPD, chronic obstructive pulmonary disease; ESS, Epworth sleepiness scale; PAP, positive airway pressure.

Data from the population-based Penn State Adult Cohort (Fernadez-Mandoza et al., 2015) suggested that weight gain during a follow-up time of 7.5 years was associated with incidence and persistence of excessive daytime sleepiness, while weight loss was associated with its remission. In the current patient cohort study, we also identified a prominent link between the change of sleepiness and body weight after PAP in obese patients with OSA. It is possible that reduced body weight resulted in a reduction of sleepiness. Another possibility is that PAP-induced reduction of sleepiness led to a lifestyle modification in the obese group that was evidenced by a reduction of BMI. However, substantial weight reduction was only seen in patients with considerable decrease of sleepiness. The exact mechanisms behind weight changes in OSA still remain to be elucidated. According to data from the Sleep Heart Health study, approximately one-fifth of the relationship between weight change and excessive daytime sleepiness was mediated by severity of OSA (Ng, Orellana, Shaw, Wong, & Peeters, 2017). It is likely that PAP therapy in our study has modified body weight via this pathway.

## 4.2 | Factors associated with PAP-related weight change

Weight change during follow-up in the current study could have been influenced by a number of factors. Higher PAP compliance was associated with weight gain during follow-up in non-obese patients. In a longitudinal Finnish cohort study (Myllyla et al., 2016), high PAP adherence did not prevent continued weight gain. In the randomized APPLE study (Quan et al., 2013), there was a significant weight gain in the PAP group compared with a slight weight loss in the sham group. Moreover, the degree of weight gain was associated with adherence in the active PAP group. Our study findings add to these previous findings by identifying potential predictors behind weight

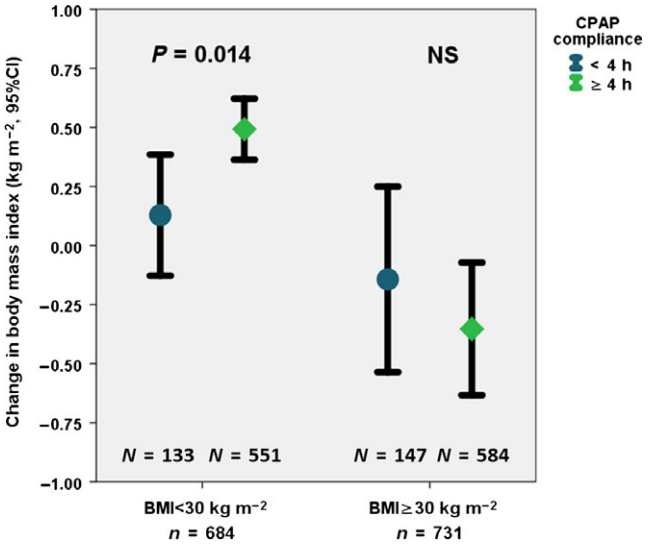


**FIGURE 2** Body weight change in relation to CPAP compliance in non-obese/obese OSA patients. BMI, body mass index; kg, kilogram; CI, confidence interval; CPAP, continuous positive airway pressure; NS, non-significant

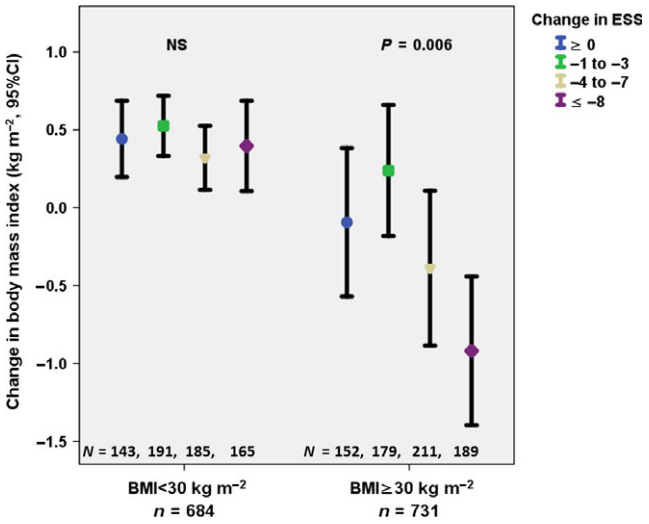


**FIGURE 3** Body weight change in relation to ESS reduction in non-obese/obese OSA patients. BMI, body mass index; ESS, Epworth sleepiness scale; CI, confidence interval; NS, non-significant

change during PAP treatment, including baseline BMI, subjective sleep time, hyperlipidaemia and COPD. Importantly, our findings further suggested that PAP therapy was associated with weight gain in non-obese patients with OSA. PAP therapy has been suggested to correct for an aberrant hormonal profile characterized by abnormally high leptin and ghrelin levels in patients with OSA (Shechter, 2017), and this may have modified food intake. However, further analysis in the APPLE study showed that CPAP did not substantially change diet or physical activity habits (Batool-Anwar et al., 2014). Our results also support the notion that PAP treatment alone will not lead to weight reduction, and that clinicians need to consider additional strategies aiming to facilitate weight loss in patients with OSA. A randomized study in patients with mild OSA (Tuomilehto et al., 2009) demonstrated that the effect of a very-low-calorie diet combined with supervised lifestyle counselling may be effective to achieve significant weight loss.

### 4.3 | Strengths and limitations

Our study has important strengths and limitations. First, the ESADA cohort contains representative patients with OSA recruited throughout different areas of Europe. Second, to the best of our knowledge, this is one of the larger studies that includes longitudinal data on body composition and body weight change following PAP treatment in OSA. The mean follow-up time is in excess of 1 year. A considerable number of confounding factors have been controlled in the analysis. However, while the ESADA confers advantages in terms of size, there are limitations in terms of completeness of follow-up data and the variability of treatment duration. Another limitation is that a selection bias cannot be excluded as only a subgroup of patients is followed up in the ESADA. These are likely to be those with higher PAP compliance. However, our statistical analysis still included a substantial number of individuals with a low PAP compliance of <4 hr per night ($n$ = 280). In addition, the phenomenon of regression to the mean may have attributed to the analysis results. Further, the important confounding effects of socio-economic background and the degree of physical activity on weight change were not controlled in our study. Finally, the lack of a control group and the observational character of the study need to be taken into account when postulating any causal associations between PAP treatment and weight change.

### 4.4 | Clinical implication and future research

Our study suggests that patients with OSA have a heterogeneous weight response to PAP treatment. Beside the necessary weight counselling that should be offered to all obese patients with OSA, our data suggest that non-obese individuals started on PAP therapy may need a long-term support in order to avoid weight gain. It is important to note that the overall weight reduction of 1.2 kg in obese patients with OSA in the current study is of clinical relevance. According to a recent meta-analysis of 34 randomized weight loss intervention trials, weight reduction of approximately 3.4 kg was associated with an 18% risk reduction of all-cause mortality (Ma et al., 2017). This number corresponded to six deaths fewer per 1,000 participants. Further research in the area might be directed towards mechanisms that potentially modify body weight following therapy of OSA with PAP. Our data may be helpful to calculate the statistical power for future interventional and mechanistic studies.

## 5 | CONCLUSIONS

In this large cohort of European patients with OSA, PAP treatment was not associated with a significant body weight change. In a subgroup analysis, non-obese patients increased their body weight over time, while obese patients with OSA showed a modest weight

**TABLE 4** GLM analysis of predictors for the anthropometric measurement change in patients with BMI ≥ 30 kg/m$^2$ ($n$ = 731)

| | Δ BMI (kg/m$^2$) | Δ Body weight (kg) | Δ Waist circumference (cm) | Δ Hip circumference (cm) | Δ Neck circumference (cm) |
|---|---|---|---|---|---|
| Male gender | β = −0.09 ± 0.28<br>$p$ = 0.77 | β = −0.08 ± 0.85<br>$p$ = 0.93 | β = −0.45 ± 0.69<br>$p$ = 0.51 | β = 0.36 ± 0.64<br>$p$ = 0.58 | β = −0.21 ± 0.21<br>$p$ = 0.30 |
| Age (years) | β = −0.02 ± 0.01<br>$p$ = 0.15 | β = −0.03 ± 0.04<br>$p$ = 0.38 | β = −0.01 ± 0.03<br>$p$ = 0.78 | β = −0.01 ± 0.03<br>$p$ = 0.73 | β = −0.02 ± 0.01<br>$p$ = 0.052 |
| Baseline BMI (kg/m$^2$) | β = −0.18 ± 0.02<br>$p$ < 0.001 | β = −0.59 ± 0.07<br>$p$ < 0.001 | β = −0.34 ± 0.06<br>$p$ < 0.001 | β = −0.36 ± 0.05<br>$p$ < 0.001 | β = −0.09 ± 0.02<br>$p$ < 0.001 |
| Smoking history | β = −0.31 ± 0.29<br>$p$ = 0.28 | β = −1.13 ± 0.86<br>$p$ = 0.19 | β = −1.19 ± 0.70<br>$p$ = 0.091 | β = −0.39 ± 0.65<br>$p$ = 0.55 | β = −0.11 ± 0.21<br>$p$ = 0.59 |
| Subjective sleep time (hr) | β = −0.09 ± 0.08<br>$p$ = 0.23 | β = −0.35 ± 0.24<br>$p$ = 0.14 | β = −0.38 ± 0.19<br>$p$ = 0.048 | β = −0.29 ± 0.18<br>$p$ = 0.10 | β = −0.08 ± 0.06<br>$p$ = 0.15 |
| Diabetes mellitus | β = 0.32 ± 0.31<br>$p$ = 0.29 | β = 0.57 ± 0.92<br>$p$ = 0.54 | β = −0.88 ± 0.75<br>$p$ = 0.24 | β = −0.30 ± 0.69<br>$p$ = 0.67 | β = −0.54 ± 0.22<br>$p$ = 0.015 |
| Hyperlipidaemia | β = 0.63 ± 0.14<br>$p$ = 0.012 | β = 1.61 ± 0.75<br>$p$ = 0.031 | β = 0.54 ± 0.61<br>$p$ = 0.38 | β = 0.58 ± 0.56<br>$p$ = 0.31 | β = 0.64 ± 0.18<br>$p$ < 0.001 |
| Hypertension | β = 0.20 ± 0.26<br>$p$ = 0.44 | β = 0.31 ± 0.77<br>$p$ = 0.69 | β = 0.90 ± 0.63<br>$p$ = 0.15 | β = −0.26 ± 0.58<br>$p$ = 0.65 | β = 0.32 ± 0.19<br>$p$ = 0.090 |
| Coronary artery disease | β = −0.53 ± 0.41<br>$p$ = 0.20 | β = −2.02 ± 1.23<br>$p$ = 0.10 | β = −1.98 ± 1.00<br>$p$ = 0.049 | β = −0.99 ± 0.93<br>$p$ = 0.29 | β = −0.35 ± 0.30<br>$p$ = 0.24 |
| COPD | β = 0.08 ± 0.47<br>$p$ = 0.87 | β = 0.39 ± 1.42<br>$p$ = 0.78 | β = 0.97 ± 1.16<br>$p$ = 0.40 | β = 2.06 ± 1.07<br>$p$ = 0.055 | β = −0.13 ± 0.34<br>$p$ = 0.71 |
| Psychiatric disease | β = −0.26 ± 0.45<br>$p$ = 0.56 | β = −1.30 ± 1.33<br>$p$ = 0.33 | β = −2.11 ± 1.09<br>$p$ = 0.052 | β = −1.16 ± 1.00<br>$p$ = 0.25 | β = −0.30 ± 0.32<br>$p$ = 0.35 |
| Psychotropic medication (ATC N06) | β = 0.36 ± 0.40<br>$p$ = 0.37 | β = 1.69 ± 1.20<br>$p$ = 0.16 | β = 1.21 ± 0.98<br>$p$ = 0.22 | β = 2.22 ± 0.90<br>$p$ = 0.014 | β = −0.34 ± 0.29<br>$p$ = 0.24 |
| Baseline AHI ($n$ per hr) | β = 0.003 ± 0.005<br>$p$ = 0.58 | β = 0.01 ± 0.01<br>$p$ = 0.52 | β = −0.01 ± 0.01<br>$p$ = 0.58 | β = 0.01 ± 0.01<br>$p$ = 0.48 | β = 0.002 ± 0.004<br>$p$ = 0.53 |
| Change in ESS score with PAP | β = 0.06 ± 0.02<br>$p$ = 0.020 | β = 0.14 ± 0.07<br>$p$ = 0.044 | β = 0.07 ± 0.06<br>$p$ = 0.20 | β = −0.005 ± 0.05<br>$p$ = 0.93 | β = 0.02 ± 0.02<br>$p$ = 0.18 |
| PAP follow-up duration (years) | β = −0.03 ± 0.12<br>$p$ = 0.83 | β = −0.22 ± 0.36<br>$p$ = 0.54 | β = 0.12 ± 0.29<br>$p$ = 0.68 | β = −0.28 ± 0.27<br>$p$ = 0.30 | β = −0.16 ± 0.09<br>$p$ = 0.075 |
| PAP compliance (hr per day) | β = 0.05 ± 0.06<br>$p$ = 0.42 | β = 0.11 ± 0.17<br>$p$ = 0.51 | β = 0.03 ± 0.14<br>$p$ = 0.85 | β = −0.03 ± 0.13<br>$p$ = 0.84 | β = 0.02 ± 0.04<br>$p$ = 0.58 |

Note: Data shown as β ± $SE$. AHI, apnea–hypopnea index; ATC, anatomical therapeutic chemical; BMI, body mass index; COPD, chronic obstructive pulmonary disease; ESS, Epworth sleepiness scale; PAP, positive airway pressure.

reduction. In addition, baseline BMI, subjective sleep time, change in sleepiness and PAP compliance were independent predictors for weight change following PAP treatment. Our study adds strong evidence to the recommendation that active weight reduction strategies, including lifestyle interventions, are implicated in the long-term management of both lean and obese patients with OSA on PAP therapy.

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## ETHICS APPROVAL

The ESADA protocol was approved by the research ethics committee at each participating centre, and informed consent is obtained from all included patients.

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## CONSENT FOR PUBLICATION

Not applicable.

## AVAILABILITY OF DATA AND MATERIALS

The datasets analysed during the current study are available from the corresponding author upon reasonable request.

## CONFLICT OF INTEREST

OKB, DZ, MST, SR, PE, UA, JAK, SS, JV, MRB declare that they have no competing interests. JH reports grants from Swedish Heart and Lung Foundation, and grants from University of Göteborg during the conduct of the study; grants from ResMed, grants from Philips Respironics, personal fees from Itamar, personal fees from Astra Zeneca, outside the submitted work; in addition, JH has two patents related to OSA therapy, one pending and one issued. LG reports grants from ResMed foundation, grants from Philips Respironics Foundation, during the conduct of the study; personal fees and non-financial support from Itamar, personal fees and non-financial support from Resmed, personal fees from Philips, personal fees from Astra Zeneca, personal fees from Weinmann, personal fees from Breas, outside the submitted work; in addition, LG has a patent sleep apnea treatment licensed to Desitin.

## AUTHOR CONTRIBUTIONS

OKB, DZ, JH and LG contributed to design and performed the study, analysed the data and wrote the draft paper. The work has been seen and approved by all co-authors, who revised the manuscript critically and approved the final version to be published.

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