Mood, sleepiness, and weight gain after three years on CPAP therapy for sleep apnoea

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ABSTRACT

Background: The prevalence of obstructive sleep apnoea syndrome (OSAS) keeps on rising. Daytime sleepiness resulting from fragmented sleep is the prime symptom, and obesity the major risk factor for OSAS. Quality of life with OSAS is often affected by depressive symptoms and anxiety. Nasal continuous positive airway pressure (CPAP) therapy reduces daytime sleepiness, but the results on the effect on mood, physical activity, and weight are controversial especially on long-term therapy. Purpose of this study was to evaluate these factors and predictors of weight gain during long-term CPAP therapy.

Methods: Consecutive patients (n = 223), referred to sleep study with suspected OSAS, were enrolled. Patients underwent a cardiorespiratory polygraphy at baseline and a battery of questionnaires was completed, both at baseline, and after three years of follow-up. Total of 149 (67%); M 65, F 84) patients completed the follow-up. Of the 149 patients, 76 (51.0%); M 32, F 44) used CPAP.

Results: In this study, depressive symptoms, anxiety, and sleepiness were alleviated during CPAP therapy. However, therapy did not have an influence on cravings of different food categories, or exercise habits and exercise duration. From the various factors studied, solely higher adherence to CPAP therapy was associated with weight gain.

Conclusions: This research provides further evidence that long-term CPAP therapy in patients with OSAS not only decreases sleepiness and improves sleep quality but could also alleviate depressive symptoms and anxiety. In addition, our study reinforces that CPAP therapy alone is not sufficient for weight management in patients with OSAS. Regardless of comprehensive battery of questionnaires, we were unable to establish markers predicting weight gain during therapy. We advise on life-style counselling and weight management program to all patients on CPAP therapy.

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Introduction

Obesity is a major risk factor for obstructive sleep apnoea syndrome (OSAS). More than 70% of people with OSAS are overweight or obese [1], and the prevalence estimates of OSAS in the middle-aged population are as high as 17% [2]. In OSAS, pauses in breathing, due to collapse in airways during sleep, lead to fragmented sleep and nocturnal hypoxia, often resulting in depressive symptoms, anxiety [3], and excessive daytime sleepiness (EDS) [4]. In addition, obesity or depression per se, are risk factors for daytime sleepiness [5]. Nasal continuous positive airway pressure (CPAP) therapy is currently the treatment of choice for OSAS [6,7]. Previous studies provide controversial results on the effect of CPAP therapy on depressive symptoms [8], and the studies on the effect on anxiety are scarce [9]. However, it has been suggested, that CPAP therapy alleviates anxiety particularly in women [10].

CPAP therapy is known to reduce daytime sleepiness [11], which could, in turn, improve diet, increase physical activity, and result in weight loss. The effect of CPAP therapy on energy balance is not fully known, but several mechanisms are likely. Currently, the best explanation is that when CPAP therapy is initiated, the sympathetic overdrive and the increased energy consumption caused by OSAS is diminished [12], and therefore, unfortunately, CPAP therapy seems not to promote weight loss in most patients [13]. Further, CPAP therapy does not seem to have an influence on diet or physical activity [14], although in women.

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a modest increase in recreational activity during CPAP treatment has been reported [15]. Therefore, it has been suggested that active weight reduction programs should be combined to CPAP therapy [16].

Our goal was to evaluate the effect of CPAP therapy on mood and sleepiness and to determine the factors that influence on weight during long-term CPAP therapy. We hypothesised, that in patients with OSAS, long-term adherence to CPAP therapy results in less depressive symptoms, less anxiety and sleepiness, improved sleep quality, decreased cravings to unhealthy food, and increased exercise duration and habits, but does not reduce weight. Further, we hypothesized, that not using CPAP for OSAS associates with weight gain without changes in mood, subjective sleep quality, cravings, or physical activity.

**Subjects and methods**

**Baseline**

The study population consisted of consecutive patients (n = 223, 54.7% women) referred to the Department of Pulmonary Diseases at Turku University Hospital, from March 2004 to October 2006, with symptoms suggesting OSAS, to rule out or confirm the diagnosis. All patients underwent a complete overnight in-hospital cardiorespiratory polygraphy (Embla*, Medcare Flaga hf, Medical Devices, Reykjavik, Iceland), their body mass index (BMI) was calculated based on measured height and weight, and after a standardised hospital meal, they completed a series of questionnaires around 6 PM to evaluate their current mood, sleep, exercise habits and duration, and cravings.

**Cardiorespiratory polygraphy**

The complete overnight in-hospital cardiorespiratory polygraphy included measurements of inspiratory flow pressure profile via nasal prongs, abdominal and thoracic movements, sleep position, periodic leg movements, electrocardiography, transcutaneous carbon dioxide partial pressure (PtCO₂; TCM3, Radiometer A/S, Copenhagen, Denmark), and arterial oxyhaemoglobin saturation (SaO₂). A finger probe pulse oximeter (Oximeter Embla A10 XN, Embla, Denver, Colorado USA) was used to measure SaO₂. From the SaO₂ signals, episodes of arterial oxyhaemoglobin desaturation of 4% units or more per hour (oxygen desaturation index, ODI₄), were automatically determined with Somnologica software. Artefacts were manually removed, and episodes of apnoea and hypopnea were determined visually by an experienced scorer, and expressed per hour (apnoea-hypopnea index, AHI) in bed from lights off to lights on, using internationally accepted criteria [17]. Electroencephalogram was not included in the set-up, therefore respiratory effort-related arousals (RERA) were not scored.

OSAS was diagnosed if AHI was ≥5 per hour, since all the patients experienced classical symptoms suggesting OSAS. CPAP therapy was commenced if AHI was over 15 per hour. Moreover, if the patient suffered from severe symptoms disturbing daily life, such as excessive daytime sleepiness, insomnia, or mood disorders, CPAP therapy was introduced with AHI 5–15 per hour.

**Questionnaires**

EDS was evaluated with Epworth Sleepiness Scale (ESS, range 0–24, score >10 considered EDS) [18]. Insomnia symptoms and sleep quality were evaluated with the help of the Pittsburgh Sleep Quality Index (PSQI, range 0–21) [19], in which higher points indicate worse sleep quality. Self-reported usual sleep duration and sleep timing were recorded. Depression was screened with depression scale (DEPS, range 0–30, scores ≥9 suggesting depression) [20]. Anxiety was evaluated with the State-Trait Anxiety Inventory (STAI, range 20–80) [21], where the score was based on the feeling at the moment of filling the questionnaire, and higher scores indicating higher feeling of anxiety, and score over 38 indicating present anxiety. Visual analogue scales (VAS) were used to assess hunger, thirst, appetite, food quantities, and nausea [22], and craving for different food categories, which included sweet, salty, starch, fruit, vegetables, meat/fish/egg, and dairies [23]. Patients provided a score based on the feeling at the moment of completing the VAS scale (score 0–100 mm), the higher score indicating stronger craving. Exercise habits were evaluated with the question ‘How often do you exercise on an average?’ The answer alternatives were 1) not at all, 2) less frequently than once a week, 3) once a week, 4) twice a week, 5) three times a week, 6) four times a week, or 7) five times a week. Exercise duration was determined by the question: ‘How long is your exercise duration?’ Alternatives were. 1) 0–20 minutes, 2) 20–40 minutes, 3) 40–60 minutes and 4) over 60 minutes.

**Follow-up study**

Three years after the cardiorespiratory polygraphy was recorded, all the patients from the original cohort were invited for a follow-up visit, when questionnaires and measurements of BMI were repeated, but the cardiorespiratory polygraphy was not included. The original
cohort was divided into CPAP users and non-users, according to their regular use of CPAP therapy. Patients, who still used CPAP therapy regularly (≥4 h/day), were considered as ‘users’, and those who did not commence or had discontinued their CPAP use, were considered ‘non-users’. As a standard treatment protocol, patients with CPAP therapy had follow-up visits once every year since CPAP initiation, when their CPAP pressure was checked, and average hours of use were documented with within-built clock counters, and if a patient did not meet the requirements of 4 hours daily use, the therapy was discontinued. Usage hours in clock counters, associated with the three-year follow-up point, were used in statistical analyses when comparing the change in usage hours from the beginning. Hours in clocks were available from the previous year.

At the end of the study, 149 (66.8%; 65 men, 84 women) patients participated in the follow-up visit. Of the 149, 76 patients (51.0%; 32 men, 44 women) used CPAP. Among the 73 non-users (33 men, 40 women), there were 52 patients who refused CPAP treatment, seven patients who used it less than three months, five for 3–11 months, and nine for 12–24 months (Figure 1). In non-users, there were 20 patients (14 men, 6 women) who did not have OSAS, as their AHI was <5/h, despite the classical symptoms of OSAS. The baseline characteristics of the study population are presented in Table 1. At baseline, there were missing values for PSQI in 4 (1.8%) patients, ESS in 6 (2.7%), appetite-VAS and hunger-VAS both in 27 (12%), and DEPS in 7 (3.1%) patients.

The main outcomes in this study were changes in depressive symptoms, anxiety, sleepiness, and weight.

**Ethics**

The study protocol was approved by the Ethics Committee of the Hospital District of Southwest Finland. Informed consent was obtained from all patients. All procedures performed were in accordance with the ethical standards of the Ethics Committee for the Hospital District of South West Finland and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Data analysis**

Data are presented as median with range. All the analyses, except regression analyses, were analysed with SAS (Statistical software package for Windows version 9.2). Differences between the variables in CPAP users and non-users at baseline and at three-year follow-up point, and the differences of changes in variables during the follow-up period were evaluated with Mann-Whitney U-test for continuous variables and chi-squared test for categorical variables. Correlations between all the variables and the change in BMI were determined with Spearman’s rank correlation coefficients due to distribution of the data, also separately for the CPAP users and the non-users. To find predictors of weight change during the follow-up period among the CPAP users, all the variables that differed significantly between the CPAP users and the non-users at baseline were included in the regression analysis. Regression analysis was performed with ordinary least squares linear regression model with IBM SPSS version 25 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). P-values less than 0.05 was considered statistically significant.

**Results**

**Baseline**

At baseline, the CPAP users had higher BMI and AHI compared to the non-users. The CPAP users also had more depressive symptoms and felt more thirst than
Table 1. Variables at baseline and differences between CPAP users and non-users.

|                      | CPAP-users | Non-users | p-value |
|----------------------|------------|-----------|---------|
|                      | n = 76     | n = 73    |         |
| **Gender**           |            |           |         |
| Male (n, %)          | 32/42      | 33/45     |         |
| Female (n, %)        | 44/58      | 40/55     |         |
| **Age**              | Median     | Range     | Median  | Range     |         |
|                      | 54         | 28–76     | 53      | 29–84     | 0.500   |
| BMI (kg/m²)          | 34.7       | 23.3–56.5 | 28.2    | 21.5–55.2 | <0.001  |
| AHI (#/h)            | 21         | 2.8–91.6  | 8.7     | 0.3–69.9  | <0.001  |
| ODI (#/h)            | 13.7       | 1.5–120.4 | 3.8     | 0–60.2    | <0.001  |
| DEPS (0–30)          | 10         | 0–24      | 6       | 0–21      | 0.011   |
| ESS (0–20)           | 10         | 0–22      | 9       | 1–22      | 0.572   |
| PSQI (0–21)          | 7          | 3–17      | 6       | 0–19      | 0.060   |
| STAI (8–80)          | 35         | 21–63     | 32.5    | 35–56     | 0.054   |
| Fruit VAS (0–100)    | 77         | 0–100     | 81.5    | 1–100     | 0.783   |
| Protein VAS (0–100)  | 77         | 0–100     | 67.5    | 0–100     | 0.420   |
| Dairy products VAS   | 68         | 0–100     | 60      | 1–100     | 0.783   |
| Salty VAS (0–100)    | 26.5       | 0–100     | 23      | 0–100     | 0.286   |
| Sweet VAS (0–100)    | 40         | 0–100     | 53      | 0–100     | 0.286   |
| High-carbohydrate    | 57         | 0–100     | 23      | 0–100     | 0.906   |
| products VAS (0–100) |            |           |         |           |         |
| Vegetables VAS (0–100)| 62        | 0–100     | 68      | 0–100     | 0.683   |
| Thirst VAS (0–100)   | 25         | 0–100     | 15      | 0–97      | 0.032   |
| Satiety VAS (0–100)  | 73         | 0–100     | 77.5    | 10–100    | 0.082   |
| Hunger VAS (0–100)   | 6          | 0–100     | 4       | 0–72      | 0.304   |
| Nausea VAS (0–100)   | 5          | 0–73      | 5       | 0–65      | 0.812   |
| Appetite VAS (0–100) | 8          | 0–100     | 7       | 0–69      | 0.310   |
| Food quantity VAS (0–100) | 13.5   | 0–99    | 10      | 0–100     | 0.422   |
| Exercise habits (0–7)| 4          | 1–7       | 4       | 1–7       | 0.412   |
| Exercise duration (0–7)| 3        | 1–4      | 2       | 1–4       | 0.712   |

Values are presented as number and %, or median (range). BMI: body mass index, AHI: apnea-hypopnea index, ODI: Oxygen desaturation index with the desaturation of 4% or more, DEPS: depression scale, ESS: Epworth sleepiness scale, PSQI: Pittsburg Sleep Quality Index, STAI: State-Trait Anxiety Inventory, VAS: Visual Analogue Scale (millimeters).

The BMI between the groups at the follow-up did not differ (35.3 kg/m² vs. 29.4 kg/m², p = 0.140), nor did the change in BMI (0.5 vs. 0.3, p = 0.674). Moreover, change in self-reported sleep duration did not differ between the CPAP users and the non-users (0.24 hours/night vs 0.09 hours/night, p = 0.881). The median use of CPAP was 6.6 hours per day (range 1.4–11.3 hours) and median pressure 11 cmH₂O (range 6–17 cmH₂O). The change of variables after three years of follow-up are presented in Table 2.

During the three-year follow-up, depressive symptoms decreased, and sleepiness and sleep quality improved more in the CPAP user group than in the non-user group. Anxiety decreased among the CPAP users whereas it increased slightly in non-users. Feeling of thirst did not change among the CPAP users but increased among the non-users. Otherwise, the groups did not differ.

Among the CPAP users, gaining weight during the follow-up period was associated with feeling of satiety after a full meal at baseline. Weight gain was not correlated with severity of OSAS, depressive symptoms, anxiety, sleep quality, exercise habits or duration, or craving for distinct food categories at baseline. Among the non-users, no associations between weight gain and the investigated variables at baseline were found (data not shown).

Moreover, weight gain in the CPAP users was associated with higher use of CPAP and craving less sweets at the three-year follow-up. Among the non-users, weight gain was associated with craving dairy products at the follow-up. Weight gain was not associated with other variables (Table 3).

### Regression analysis

In regression analysis, to determine the factors that influenced on weight, and were different between the CPAP users and the non-users, all the variables that differed significantly between the CPAP users and the non-users (Table 1). Otherwise, the groups did not differ.

Table 2. Change of variables during the 3-year follow-up and differences between CPAP-users and non-users.

|                      | CPAP-users | Non-users | p-value |
|----------------------|------------|-----------|---------|
|                      | n = 76     | n = 73    |         |
| **BMI (kg/m²)**      | Median     | Range     | Median  | Range     |         |
|                      | 0.5        | 67.7–7.5  | 0.3     | –13.4–6.5 | 0.674   |
| Hours of use (#/day) | 0          | –5.8–3.3  | –       | –         | N/A     |
| Pressure (cmH₂O)     | 1          | –1–6      | –       | –         | N/A     |
| DEPS (0–30)          | –3         | –20–9     | 0       | –11–21    | 0.002   |
| ESS (0–20)           | –3.5       | –14–8     | –2      | –10–8     | 0.031   |
| PSQI (0–21)          | –1         | –8–7      | 0       | –11–10    | <0.001  |
| STAI (8–80)          | –3         | –19–15    | 1       | –12–25    | <0.001  |
| Fruit VAS (0–100)    | 1.5        | 47–88     | 0       | –95–57    | 0.255   |
| Protein VAS (0–100)  | –9         | 85–40     | –1      | –59–96    | 0.077   |
| Dairy products VAS   | 8          | 79–90     | 0       | –78–93    | 0.312   |
| Salty VAS (0–100)    | –3         | 92–63     | 0       | –85–88    | 0.063   |
| Sweet VAS (0–100)    | –1         | 72–98     | 0       | –96–82    | 0.910   |
| High-carbohydrate    | 1          | 66–99     | –3.5    | –128–101  | 0.137   |
| products VAS (0–100) |            |           |         |           |         |
| Vegetables VAS (0–100)| 9         | 21–94     | 1       | –43–89    | 0.090   |
| Thirst VAS (0–100)   | 0          | –98–91    | 7.5     | –65–100   | 0.026   |
| Satiety VAS (0–100)  | –38        | –100–97   | –41.5   | –100–33   | 0.280   |
| Hunger VAS (0–100)   | 3          | 72–99     | 8.5     | –41–100   | 0.112   |
| Nausea VAS (0–100)   | –1         | 71–89     | 0       | –45–64    | 0.112   |
| Appetite VAS (0–100) | 5.5        | 56–99     | 10      | –59–98    | 0.387   |
| Food quantity VAS (0–100) | 4    | –11–68   | 13      | –71–95    | 0.154   |
| Exercise habits (0–7)| 0          | –5–3      | 0       | –3–4      | 0.230   |
| Exercise duration (0–7)| 0        | –3–2      | 0       | –2–2      | 0.484   |

Values are median (range: change from the baseline scores). BMI: body mass index, DEPS: depression scale, ESS: Epworth sleepiness scale, PSQI: Pittsburg Sleep Quality Index, STAI: State-Trait Anxiety Inventory (score), VAS: Visual Analogue Scale (millimeters).
the non-users, were included, consisting of baseline BMI, baseline AHI, baseline ODI4, baseline depressive symptoms, and baseline thirst. From these, only baseline BMI and depressive symptoms at baseline were associated with weight gain among the whole study population (Table 4). Further, when the CPAP users and the non-users were analysed separately, the results did not change. However, when the CPAP users were divided according to gender, the effect of depressive symptoms disappeared in men. In non-user men, the results remained. Among the non-user women, depressive symptoms was not a significant factor influencing on weight gain, whereas baseline BMI was (Table 4). Other variables did not have an effect.

Table 3. Correlations between the change in BMI and variables at the 3-year follow-up.

|                         | CPAP users | Non-users |
|-------------------------|------------|-----------|
|                         | n = 76     | n = 73    |
|                         | M 42%, F 58% | M 45%, F 55% |
|                         | r          | p-value   |
|                         | r          | p-value   |
| Hours of use (#/day)    | 0.283      | 0.015     |
| CPAP pressure (cmH2O)   | −0.040     | 0.737     |
| DEPS (0–30)             | 0.247      | 0.069     |
| ESS (0–20)              | 0.037      | 0.788     |
| PSQI (0–21)             | 0.019      | 0.888     |
| STAI (8–80)             | −0.08      | 0.587     |
| Fruit VAS (0–100)       | −0.040     | 0.775     |
| Protein VAS (0–100)     | 0.043      | 0.754     |
| Dairy products VAS (0–100) | −0.240    | 0.078     |
| Salty VAS (0–100)       | −0.026     | 0.852     |
| Sweet VAS (0–100)       | −0.339     | 0.011     |
| High-carbohydrate products VAS (0–100) | −0.156 | 0.254    |
| Vegetables VAS (0–100)  | −0.079     | 0.569     |
| Thirst VAS (0–100)      | 0.214      | 0.116     |
| Satiety VAS (0–100)     | 0.043      | 0.758     |
| Hunger VAS (0–100)      | 0.035      | 0.797     |
| Nausea VAS (0–100)      | 0.189      | 0.168     |
| Appetite VAS (0–100)    | −0.016     | 0.908     |
| Food quantity VAS (0–100) | −0.065    | 0.649     |
| Exercise habits (0–7)   | −0.144     | 0.313     |
| Exercise duration (0–7) | 0.019      | 0.898     |

DEPS depression scale, ESS Epworth sleepiness scale, PSQI Pittsburgh Sleep Quality Index, STAI State-Trait Anxiety Inventory, VAS Visual Analogue Scale (millimeters).

Discussion

This three-year prospective follow-up study showed that treating OSAS patients with CPAP therapy alleviated depressive symptoms, anxiety, and sleepiness as expected [24]. On the other hand, anxiety slightly increased among the CPAP non-users. In addition, study provided further evidence that weight gain among patients with OSAS associates with higher long-term adherence to CPAP therapy. Moreover, unexpectedly, craving less sweets at the three-year follow-up was associated with weight gain in CPAP user group. Weight gain was not associated with anxiety, improved sleepiness or sleep quality, or exercise habits and duration, or other cravings.

Depressive symptoms and depressive disorder are known to have a strong association with obstructive sleep apnoea [8]. In one of the first studies in this field, 24% of 25 male OSAS patients had depressive or anxiety symptoms [25]. Further, it has been reported, that women with OSAS have more depressive symptoms than men [26], but most of the previous studies have consisted mainly of men [27]. Our study had 46% of women, therefore being gender-balanced. Depressive symptoms overlap with OSAS symptoms. Therefore, treatment response to CPAP may reveal depression underlying OSAS. We propose that part of the depressive symptoms at baseline were secondary to the untreated OSAS, whereas the residual depressive symptoms observed at follow-up could have another etiology. Previous studies provide limited and contradictory data on the effect of CPAP therapy on depressive symptoms, especially during long-term therapy [8]. In one study, CPAP therapy for a few months alleviated depressive symptoms [28], whereas in another study no effect was found [29]. It is unlikely that reduction of depressive symptoms after three years on CPAP observed in our study was due to a placebo-response [30].

Anxiety is a common symptom in OSAS, with a reported prevalence as high as 53.9% [31]. Data on how anxiety responds to CPAP is scarce. Our results, derived from a cohort with a strong female representation, are in line with an earlier study, according to which CPAP

Table 4. Regression analysis of subgroups and significant factors that effect on weight gain.

|                         | Baseline BMI | Baseline DEPS |
|-------------------------|--------------|---------------|
|                         | β            | CI 95%        | p-value | β            | CI 95%        | p-value |
| All                     | 0.84         | 0.71–0.98     | <.001   | 0.167        | 0.03–0.33     | 0.017   |
| CPAP users (n = 76)     | 0.83         | 0.69–0.99     | <.001   | 0.20         | 0.05–0.38     | 0.01    |
| Men (n = 32)            | 0.94         | 0.55–0.92     | <.001   | 0.11         | −0.16–0.38    | 0.40    |
| Women (n = 44)          | 0.94         | 0.77–1.1      | <.001   | 0.26         | 0.07–0.47     | 0.01    |
| Non-users (n = 73)      | 0.90         | 0.77–0.95     | <.001   | 0.16         | 0.04–0.28     | 0.09    |
| Men (n = 33)            | 0.88         | 0.65–0.95     | <.001   | 0.30         | 0.08–0.53     | 0.01    |
| Women (n = 40)          | 0.98         | 0.88–1.1      | <.001   | 0.05         | −0.1–0.1      | 0.93    |

BMI Body mass index, DEPS Depression scale.
therapy alleviates anxiety particularly in women [10]. In our study, the level of anxiety, similar at baseline, started to deviate during the three-year follow-up, depending on whether OSAS was treated or not. Since sleep studies were not repeated, we were not able to assess, whether the increased anxiety in the untreated group would have been associated with aggravation of their sleep-disordered breathing during the follow-up period. One could also argue, that despite similar level of reported anxiety at baseline, the ones choosing not to be treated could be those with a tendency to respond with anxiety to various stresses, such as wearing a mask at night. This tendency to anxiety could have explained the non-adherence to CPAP, as well as the increased anxiety observed over time. The tools we used to assess the effect of CPAP therapy on depressive symptoms (DEPS), or anxiety (STAIS), are standard questionnaires, used to screen the corresponding diseases. Although statistically significant, one can question, whether the magnitude of these changes have biological significance. The observed changes should be interpreted as trends in the degree of depressive or anxiety symptoms, without any relevance to depression or anxiety as diseases.

Sleepiness and sleep quality improved among CPAP users in our study, which is in line with previous studies. Improved sleep quality in our study could explain the reduction of sleepiness. In 2003, Patel et al. stated in their meta-analysis, that CPAP therapy alleviates sleepiness in patients with OSA in a diverse range of populations. However, only three of the studies included in the analysis, had less than 75% of men. It has been previously shown, that women report excess daytime sleepiness more frequently than men [31] and that 12 weeks of CPAP therapy reduces the self-reported sleepiness in women [10]. Our study confirms this finding in long-term CPAP therapy.

CPAP users felt more thirst at baseline. However, only two of the CPAP users had a diagnosed diabetes at baseline, and their fasting blood glucose did not differ from those of the non-users (data not shown). Elevated levels of the cardiac natriuretic peptides (ANP, BNP) in patients with OSAS, particularly those with hypertension, could play a role in feeling thirst when untreated. However, other mechanisms are likely, since CPAP therapy effectively reduces ANP and BNP levels [32] but feeling thirst did not regress with long-term adherence to CPAP.

Feeling of thirst in the morning, can also result from snoring and mouth breathing, but is not usually the case later during the day, and may not explain our results. Therefore, other mechanisms inducing thirst must be involved.

Association of weight gain and satiety among CPAP users might simply imply, that they ate more than those not gaining weight. An alternative explanation could be that CPAP users gain weight, because the therapy reduces the resting metabolic rate [16]. Unexpectedly, weight gain was not associated with craving more sweet or high-carbohydrate products. This might be explained by the unfortunate fact, that the questionnaires were introduced to the patients right after a full meal, when cravings are usually absent. Severity of OSAS, anxiety, sleepiness or sleep quality, or exercise habits, or cravings were not associated with weight gain in our study. In regression analysis, the only factors influencing on weight were depressive symptoms and BMI at the beginning, and the results remained when the CPAP users and non-users were evaluated separately. It would be important to identify those OSAS patients who are going to gain weight, already when CPAP therapy is initiated. However, even using an extensive set of questionnaires, as well as cardiorespiratory polygraphy reports, we were unable to establish markers predicting weight gain during therapy. Of note, the CPAP users had higher BMI in the beginning, but the change in BMI did not differ between the CPAP users and the non-users. Moreover, the change in BMI was indeed minor in both groups during the follow-up period, and most likely without clinical significance.

The strength of our study is a gender-balanced, modest size, prospective clinical cohort, with relatively long follow-up period. Previous studies have consisted mainly of men, except the one recruiting only women [10]. Moreover, we utilized a comprehensive battery of questionnaires to evaluate possible association with weight gain. However, some limitations to our study must be considered. Our questionnaires were introduced in the evening, right after a full meal. This influences on mood and cravings and could alter the results compared to the questionnaires completed in the morning. We did not use food diaries which might provide a deeper insight into the issues related to weight gain than questionnaires administered at a single point at baseline and follow-up. In addition, sub-analyses should be interpreted with caution, due to a small number of patients in gender subgroups.

**Conclusion**

Our study provides further evidence, that long-term CPAP therapy in patients with OSAS might not only alleviate depressive symptoms and anxiety, but also decrease sleepiness. In addition, our study emphasises previous expectations, that weight continues to increase during long-term adherence to CPAP therapy, irrespectively of changes in cravings or exercise habits. Further studies are needed to establish biomarkers identifying the
subset of patients at risk of further weight gain during CPAP therapy and in need of preventive measures.

**Disclosure statement**

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