Changes in Energy Metabolism after Continuous Positive Airway Pressure for Obstructive Sleep Apnea

Ryo Tachikawa[1], Kaori Ikeda[2], Takuma Minami[1], Takeshi Matsumoto[1], Satoshi Hamada[1], Kimihiko Murase[1], Kiminobu Tanizawa[3], Morito Inouchi[3], Toru Oga[3], Takashi Akamizu [4], Michiaki Mishima[1], Kazuo Chin[3]

[1]Department of Respiratory Medicine, [2] Department of Diabetes, Endocrinology and Nutrition, [3]Department of Respiratory Care and Sleep Control Medicine, Graduate School of Medicine, Kyoto University, Kyoto, Japan

[4]The First Department of Medicine, Wakayama Medical University, Wakayama, Japan

Correspondence: Kazuo Chin, MD, PhD; chink@kuhp.kyoto-u.ac.jp

54 Shogoinkawahara-cho, Sakyo-ku, Kyoto, 606-8507, Japan

TEL:+81-75-751-3852 FAX:+81-75-751-3854

Authors' Contributions

Conception and design: RT, KI, and KC; collection of data: RT, TM, TM, SH, KM, KT, TO, TA, and KC ; analysis and interpretation of data: RT, KI, TA, MM, and KC; drafting the manuscript: RT, and KI; critical revision for intellectual content: TM, TM, SH, KM, MI, TO, TA, MM, and KC; and approval of the final version of manuscript: RT, KI, TM, TM, SH, KM, KT, MI, TO, TA, MM, and KC

Acknowledgement of Grant Support

This work was supported by grants from the Japanese Ministry of Education, Culture,

Sports, Science and Technology, Respiratory Failure Research Group; and Health science Research Grants (Comprehensive Research on Life-Style Relate Diseases including Cardiovascular Diseases and Diabetes Mellitus) from the Ministry of Health, Labor and Welfare of Japan, and the Japan Vascular Disease Research Foundation. The Department of Respiratory Care and Sleep Control Medicine is funded by endowments from Philips-Respironics, Teijin Pharma, Fukuda Denshi and Fukuda Lifetec-Keiji to Kyoto University.

Running title: Energy metabolism after CPAP for OSA

Descriptor number: 15-9 (Sleep Disordered Breathing: Outcomes)

Number of Tables and Figures: 4 tables and 3 figures

Word Count: 3630

At a Glance Summary

Scientific Knowledge on the Subject

Recent studies indicated that treating obstructive sleep apnea (OSA) with continuous positive airway pressure (CPAP) might promote weight gain although the underlying mechanism remains unclear. An integrative assessment of energy metabolism is needed to elucidate how CPAP can affect the energy balance in patients with OSA.

What This Study Adds to the Field

Three months of CPAP therapy reduced the basal metabolic rate in the absence of changes in physical activity, thus favoring a positive energy balance in terms of energy expenditure. However, increased energy intake with disordered eating behavior had a greater impact on weight gain beyond the shift in energy expenditure, highlighting the importance of lifestyle modifications combined with CPAP therapy.

This article has an online data supplement, which is accessible from this issue's Table of Contents at www.atsjournals.org

ABSTRACT

Rationale: Disrupted energy homeostasis in obstructive sleep apnea (OSA) may lead to weight gain. Paradoxically, treating OSA with continuous positive airway pressure (CPAP) may also promote weight gain although the underlying mechanism remains unclear.

Objectives: To explore the underlying mechanism(s) by which OSA patients gain weight after CPAP.

Methods: A comprehensive assessment of energy metabolism was performed in 63 newly diagnosed OSA study participants (51 men, 60.8 ± 10.1 y, apnea-hypopnea index [AHI] >20 h^{-1}) at baseline, CPAP initiation, and at a 3-month follow-up. Measurements included polysomnography, body weight, body composition, basal metabolic rate (BMR), hormones (norepinephrine, cortisol, leptin, ghrelin, insulin-like growth factor-1), dietary intake, eating behavior, and physical activity.

Measurements and Main Results: BMR significantly decreased after CPAP (1584 kcal/day at baseline, 1561 kcal/day at CPAP initiation, and 1508 kcal/day at follow-up, $p < 0.001$) while physical activity and total caloric intake did not significantly change. In multivariate regression, baseline AHI, Δurine norepinephrine, and CPAP adherence were significant predictors of ΔBMR. The weight gainers had higher leptin levels, lower ghrelin levels, and higher eating behavior scores than the non-weight gainers, indicating a positive energy balance and disordered eating behavior among the weight gainers. Among the parameters related to energy metabolism, increased caloric intake was a particularly significant predictor of weight gain.

Conclusions: Although a reduction in BMR after CPAP predisposes to a positive energy balance, dietary intake and eating behavior had greater impacts on weight change. These

findings highlight the importance of lifestyle modifications combined with CPAP.

Abstract Word Count: 247

Key words: appetite regulating hormones, basal metabolic rate, body weight, eating behavior, energy balance

Introduction

Obesity has become a serious public health concern worldwide in recent decades, leading to multiple health consequences and adverse outcomes (1). Obesity is also a major risk factor for obstructive sleep apnea (OSA), and as high as 70% of OSA patients are obese (2). Conversely, prior studies revealed a disruptive impact of OSA on energy metabolism, and there is an emerging concept that OSA itself may in turn reinforce the obese state (2-5). In fact, studies have indicated that OSA may affect both energy expenditure (i.e., elevated basal/sleeping energy expenditure plausibly due to increased sympathetic activity and breathing efforts) (6-11) and energy intake (i.e., increased preference for high-fat or calorie-dense food) (12-15) via a complex mechanism that includes neurohormonal and behavioral changes, an imbalance of which may result in excess energy intake leading to weight gain.

Given the plausible reciprocal relationship between obesity and OSA, treating OSA with continuous positive airway pressure (CPAP) in theory could act against weight gain. On the other hand, recent studies revealed that CPAP therapy actually resulted in weight gain although the underlying mechanism remains unclear (16-19). Importantly, changes in energy intake, energy expenditure, and body weight under free-living conditions need to be assessed together to elucidate how CPAP can affect the energy balance in patients with OSA. However, available clinical studies have examined these factors independently; thus an integrative assessment has been lacking (5-7, 16, 17, 20-22).

In the present study, we therefore performed a comprehensive assessment of energy metabolism before and after CPAP in patients with OSA to explore the underlying mechanism(s) by which OSA patients may be susceptible to weight gain after CPAP. We

hypothesized that 1) CPAP may reduce the basal metabolic rate (BMR), 2) CPAP may affect dietary habits and caloric intake, and 3) changes in energy expenditure and energy intake after CPAP may collectively lead to an energy balance that determines weight change. Some of the results of this study have been previously reported in the form of an abstract (23).

Methods

Study Participants

Participants were consecutively recruited from clinically stable patients aged 20–80 y who underwent diagnostic polysomnography for the evaluation of suspected OSA at the Sleep Laboratory of Kyoto University Hospital. Recruitment started in March 2014 and ended in April 2015. Exclusion criteria included a premenopausal status, previous treatment for OSA, dominant central sleep apnea, physical incapacity, abnormal thyroid function, chronic corticosteroid use, long-term oxygen therapy, hemodialysis, and implantation of a pacemaker. This study was approved by the Kyoto University Graduate School and Faculty of Medicine Ethics Committee, and was registered with the University Hospital Medical Information Network (UMIN in Japan) Clinical Trials Registry (identification number UMIN000012639). All participants provided written informed consent.

Study Protocol

Energy metabolism was comprehensively assessed in participants with an apnea-hypopnea index (AHI) >20. Assessments were performed in an inpatient setting 3

times as follows: 1) at the first diagnostic polysomnography (baseline); 2) at CPAP initiation on average 6 weeks after the first sleep study when participants underwent titration of the auto-adjusting CPAP (CPAP initiation); and 3) at follow-up polysomnography after 3 mo of CPAP therapy (3-mo follow-up). Finally, 63 OSA patients with AHI >20 were included in the analysis (Figure 1). No specific advice regarding diet and exercise was newly given to the participants during the study period. Medications that influence body weight or BMR were not changed during the study period (Table S1). CPAP adherence was measured based on objective usage data from memory cards.

Collection of Data

Polysomnography

Overnight in-laboratory attended polysomnography was performed on each admission from 2200 until 0600 h using standard techniques (24) (for details, see the online supplement).

Basal metabolic rate

Measurements of BMR were performed in the morning (0630–0730 h) after overnight polysomnography and after a 12-h fast using indirect calorimetry (AE310S; Minato Medical Science, Osaka, Japan) by one investigator according to previously described methods (25). Those analyzing data were blinded to clinical information. (for details, see the online supplement)

Body weight and body composition

Post-voiding body weight and body composition were measured after a 5-h fast between 1700 and 1800 h on each admission day. Weight was measured with the patient in a hospital gown to the nearest 0.1 kg using a stand-on scale (model 764, Seca, Hamburg, Germany). Body composition was assessed with the patient in a supine position by bioelectrical impedance analysis using a body composition analyzer (InBody S20; Biospace, Seoul, Korea).

Blood and urine samples

Peripheral venous blood samples were collected from 0630 to 0700 h after completion of polysomnography. Samples were analyzed for plasma norepinephrine, plasma cortisol, plasma leptin, plasma ghrelin, and serum insulin-like growth factor-1 (IGF-1). Urine norepinephrine was measured from 12-h overnight urine. Urine norepinephrine excretion was adjusted for urinary creatinine excretion to account for urine dilution and possible lack of a complete collection, and was expressed as μg/g creatinine (for details, see the online supplement).

Dietary intake

Dietary habits during the preceding month were assessed with a brief validated self-administered diet history questionnaire (BDHQ). The BDHQ is a 4-page fixed-portion questionnaire that asks about the consumption of selected foods to estimate the dietary intake of 58 food and beverage items commonly consumed by Japanese people. Daily energy intake and intake of nutrients were estimated using an ad hoc computer algorithm for the BDHQ (26, 27) (for details, see the online supplement).

Eating behavior

Eating behavior was assessed using the Eating Behavior Questionnaire issued by the Japan Society for the Study of Obesity (28, 29). The questionnaire is a 55-item self-rated questionnaire with 7 categories. All items are rated on a 4-point scale from 1 indicating 'No, it is not so' to 4 indicating 'Yes, exactly so'. Responses to each question are added together for the 7 categories, in which higher scores indicate disordered eating behavior predisposing to weight gain (for details, see the online supplement).

Physical activity

Physical activity was measured before CPAP initiation and after the follow-up polysomnography on 7 consecutive days under free-living conditions (except while bathing) using a wrist-worn accelerometer (Actiwatch 2, Philips Respironics, Murrysville, PA, USA) (30, 31). (for details, see the online supplement).

Statistical analysis

Continuous variables were expressed as mean ± standard deviation unless stated otherwise, and categorical variables were expressed as numerals or percentages. Differences between two groups were tested by an unpaired Student's t-test, Mann–Whitney U test, or paired t-test for continuous variables and by a chi-squared test or Fisher's exact test for categorical variables, as appropriate. Differences among CPAP adherence categories were determined by analysis of variance (ANOVA), and post-hoc pair-wise comparisons were performed by the Tukey-Kramer test. Two-way ANOVA was used to analyze differences in eating behavior scores between body weight gainers and non-weight gainers. Multivariate analysis of variance was used to examine the

overall difference in repeated measurements, and post-hoc paired t-tests with Bonferroni correction were used to determine pairwise differences.

Stepwise linear regressions were performed to identify the predictors of change in BMR or body weight. Potential variables for ΔBMR included age, sex, body mass index (BMI), Δfat mass, Δfat-free mass, Δplasma cortisol, Δplasma norepinephrine, Δurine norepinephrine, Δleptin, and baseline AHI. CPAP adherence expressed as percent of days of CPAP use >4 h was also entered as a covariate in the model for the 3-mo follow-up. The potential variables for ΔBMI at the 3-mo follow-up included age, sex, baseline BMI, smoking status, ΔBMR, Δtotal caloric intake, Δphysical activity, Δplasma cortisol, ΔIGF-1, Δacylated ghrelin, baseline AHI, and CPAP adherence. Cutoff values for the bidirectional stepwise procedure were $P = 0.10$ for the forward processes and $P = 0.20$ for the backward processes. A two-sided P-value <0.05 was considered to be statistically significant for all tests. Sample size estimation was performed based on the primary outcome parameter (ΔBMR) (for details, see the online supplement). All statistical analyses were performed using JMP Pro 12 software (SAS Institute Inc., Cary, NC, USA).

Results

Participant's characteristics

Characteristics of the study participants are summarized in Table 1. Changes in body weight varied among participants: weight increased in 33 participants at the 3-mo follow-up compared to baseline while it decreased or did not change in 30 participants.

Changes in parameters related to energy metabolism

BMR, physical activity, and dietary intake

As shown in Table 2, BMR was significantly decreased over baseline after 3 mo but not after 1 night of CPAP (1584 kcal/day at baseline, 1561 kcal/day after 1 night of CPAP, and 1508 kcal/day at follow-up, $p < 0.001$). Participants with moderate and high CPAP adherence had a significant reduction in BMR at follow-up compared to those with low CPAP adherence (-107.6, -91.7, and 7.6 kcal/day, respectively, $p = 0.006$) (Figure S1). There were no significant changes in physical activity, total caloric intake, and nutrition intake during the study period.

Body weight and body composition

Body weight significantly increased after CPAP therapy (77.8 kg at baseline, 77.6 kg at CPAP initiation, and 78.2 kg at follow-up, $p = 0.010$) (Table 2). Among body composition parameters, fat-free mass increased after CPAP therapy but not significantly.

Hormones

IGF-1 was significantly increased after CPAP therapy (Table 2). No significant changes were observed in other hormones among the overall participant group.

Multivariate linear regression model for ΔBMR and ΔBMI

ΔFat-free mass, Δurine norepinephrine, and baseline AHI were significant predictors of ΔBMR after 1 night of CPAP whereas CPAP adherence was the only significant predictor of ΔBMR at the 3-mo follow-up (Table 3). With regard to weight change, younger age, female sex, lower baseline BMI, non-smoking, decrease in plasma cortisol,

and increase in total caloric intake were significant predictors of an increase in BMI after CPAP therapy (Table 4).

Comparison of weight gainers with non-weight gainers

Baseline characteristics

When stratified by weight change, baseline variables were comparable between weight gainers and non-weight gainers except that the proportion of non-smokers and the baseline AHI tended to be higher in the weight gainers (Table 1). The weight gainers experienced a significant increase in fat mass (1.1 kg, 95% confidence interval [CI]: 0.4 to 1.8, p = 0.002), fat-free mass (0.9 kg, 95% CI: 0.4 to 1.4, p = 0.002), and muscle mass (0.5 kg, 95% CI: 0.1 to 0.8, p = 0.006) after CPAP therapy while fat mass was decreased in the non-weight gainers (-1.2 kg, 95% CI: -2.1 to -0.3, p = 0.010) (Table S2).

Energy expenditure and energy intake

BMR was similarly decreased after CPAP therapy both among weight gainers (-78 kcal/day, 95% CI: -114 to -41, p < 0.001) and non-weight gainers (-74 kcal/day, 95% CI: -118 to -30, p = 0.002) (Figure 2, Table S2). There were no significant interval changes in physical activity and total caloric intake in either group, but weight gainers had a significantly higher total caloric intake at the 3-mo follow-up compared to non-weight gainers (2099 ± 521 and 1853 ± 353 kcal/day, respectively, p = 0.034) (Figure 2, Table S2). The non-weight gainers consciously changed their dietary habits more frequently than the weight gainers during the study period or within one year before study enrollment (10/30 vs. 3/33, p = 0.028).

Hormones

Plasma cortisol was decreased in the weight gainers compared to non-weight gainers (interval change: -1.3 ± 5.4 vs. 1.1 ± 3.8 μg/dl, p = 0.008) (Figure 2, Table S2). Serum IGF-1 was increased after CPAP therapy in both groups, but the interval change was significant only in non-weight gainers (Table S2). The plasma leptin level was significantly increased after CPAP among weight gainers and was significantly higher at follow-up compared with non-weight gainers (19.0 ± 10.7 and 13.2 ± 8.8 ng/ml, respectively, p = 0.005). Meanwhile, plasma acylated and des-acyl ghrelin levels were consistently lower in the weight gainers (Figure 2, Table S2).

Eating behavior

Eating behavior scores were significantly higher in weight gainers compared to non-weight gainers throughout the study period ($p < 0.001$ at baseline, CPAP initiation, and 3-mo follow-up) (Figure 3). Differences between groups were remarkable in the category of awareness about weight and constitution and food preferences. Scores for awareness about weight and constitution, eating as diversion, and food preferences significantly decreased during the study period in non-weight gainers while only the score for awareness about weight and constitution decreased in weight gainers.

Discussion

The current study is the first to our knowledge to comprehensively assess energy metabolism in patients with OSA before and after CPAP therapy. The major findings

were: 1) CPAP therapy significantly reduced BMR by 5% from baseline, thereby favoring a positive energy balance; 2) the decrease in BMR was associated with decreased urine norepinephrine and CPAP adherence; and 3) factors related to energy intake, including eating behavior, had a larger impact on weight change than those related to energy expenditure. These findings not only explained the mechanism by which OSA subjects may be susceptible to weight gain following CPAP therapy but further underscore the importance of incorporating lifestyle modifications into the treatment of OSA.

We found that 3 mo of CPAP therapy significantly reduced the BMR in patients with OSA, which is in contrast to findings of two small studies that did not show a significant effect of CPAP on BMR. However, one of these studies, which used a metabolic cart, might have underrated the BMR since they used only the lowest values among the measurements to calculate the BMR (6), while the other study that used a metabolic chamber might have been too underpowered to detect a significant difference (7). Indeed, our result is in line with reports of a higher basal (or resting) metabolic rate in patients with OSA than in controls (7-10), and we further demonstrated a causal link between OSA and an elevated BMR by examining the effect of CPAP. We also found that the decrease in urine norepinephrine was a modest but significant predictor of a decrease in BMR after one night of CPAP, supporting the concept that increased sympathetic activity may partially mediate OSA and an elevated BMR (9).

The BMR usually accounts for 60–70% of the daily total energy expenditure, and the reduction in BMR of 75 kcal/day achieved by CPAP therapy is substantial, as it corresponds to approximately a 1 kg fat gain in 3 mo. In addition, sleep energy expenditure was shown to decrease after treatment of OSA, which may also shift the

energy balance in favor of weight gain (7, 11, 22). Meanwhile, CPAP does not appear to significantly affect activity-related energy expenditure because our study and other available data indicate that the physical activity level does not increase after CPAP (20, 21). Taken together, successful treatment of OSA with CPAP would result in a decrease in total energy expenditure compared with the pre-treatment level, thus potentially favoring a positive energy balance and subsequent weight gain.

Of note, BMR was similarly reduced in both weight gainers and non-weight gainers in the absence of changes in physical activity, suggesting that both groups were equally predisposed to a positive energy balance in terms of energy expenditure. On the other hand, while the total caloric intake did not significantly change in the total participants overall as previously reported (21), the weight gainers had a higher caloric intake than the non-weight gainers at follow-up, and the increased energy intake was shown to be the determinant of weight gain. This indicates that diet may be the key factor accounting for inter-individual differences in weight change beyond the shift in energy expenditure. Intriguingly, noticeable differences existed in the baseline eating behavior profile between weight gainers and non-weight gainers. Moreover, scores for “eating as diversion” and “food preferences” decreased only in the non-weight gainers, part of which was presumably achieved by voluntary attempts to change dietary habits in this group of participants. These findings implicate disordered eating behavior (e.g., misperception of the reasons for gaining weight, disinhibited responsiveness to food cues, and selection of obesogenic foods) as a plausible mechanism that underlies the increased propensity for excessive caloric intake in weight gainers. Collectively, our results are analogous with previous observations consistently showing that increased caloric intake, rather than the shift in energy expenditure, is the primary cause of weight

gain in sleep deprivation, which is in part dependent on disordered eating behaviors (32-35).

We examined a wide array of humoral factors that might explain the weight change after CPAP. Unexpectedly, the concentrations of potent orexigenic hormones, including plasma acylated (active) ghrelin and cortisol, were lower in the weight gainers at the 3-mo follow-up. The plasma leptin level, known as a satiety hormone, was increased in the weight gainers. Although seemingly counterintuitive, these associations can be rationalized by assuming that the hormones actually represented the consequence of an energy imbalance rather than a cause of weight change. In fact, ghrelin secretion is down-regulated in a positive energy balance and up-regulated in a negative energy balance due to a negative feedback mechanism (36-38). Binge-eating disorder was also shown to reduce the plasma ghrelin level (39). Therefore, the consistently lower ghrelin levels in the weight gainers probably reflect the tendency toward an excessive energy intake throughout the study period. Likewise, circulating leptin levels were shown to increase with excessive adiposity and were reduced during caloric restriction (40, 41). Furthermore, voluntary diet changes in the non-weight gainers might have affected the plasma cortisol level because cognitive dietary restraint increases cortisol secretion as a physiological stress response (42, 43). Taken together, these observations support the idea that the hormonal changes were a secondary physiological response. On the other hand, an increased level of IGF-1 after CPAP may have the potential to increase lean body weight rather than fat mass as reported by Munzer et.al. (44). Although our study did not find a significant difference in body composition among the participants overall, the finding that weight gainers experienced a significant gain not only in fat mass but also in fat-free mass implies that the additional weight resulting from CPAP may, at

least in part, represent a favorable change.

This study has several important clinical implications. First, our findings illustrate that CPAP therapy alone is not a treatment for obesity in terms of energy expenditure, thereby providing a compelling rationale for combining weight loss instructions with CPAP therapy in all overweight OSA patients. This is of particular clinical importance given that the impact of weight change on cardiometabolic risk factors outweighs the potential benefits of CPAP (45). At the same time, this study highlighted that the constellation of changes in factors involved in energy metabolism would collectively determine the direction of weight change after the initiation of CPAP. Therefore, weight change following CPAP can substantially vary among individuals according to the extent of lifestyle alterations accompanying CPAP therapy. It is also possible that sustained lifestyle alterations may lead to changes in body composition or body fat distribution independent of weight change (44, 46, 47). Second, increased energy intake and disordered eating behavior were found to be the major determinants of weight gain after CPAP. Hence, it is imperative to incorporate behavioral strategies, including dietary modification, into OSA treatment in high-risk patients possibly characterized by lower ghrelin levels and disordered eating behavior. Third, the finding that appetite-regulating hormone levels were strongly influenced by weight change warrants a multifactorial approach in research studies in real-life settings, where biological, behavioral, and environmental factors may act as critical confounders that overshadow the therapeutic effect of CPAP. This perspective may also potentially reconcile previous discordant observations on the effects of CPAP on these hormones involved in energy homeostasis (46, 48-54).

We acknowledge several limitations in the present study. First, lack of a control

group not receiving CPAP did not allow us to infer the true therapeutic effect of CPAP on reducing BMR. However, given the strictly controlled measurement conditions, the time-dependent decrease in BMR following CPAP therapy, and a positive association between CPAP adherence and decrease in BMR, it is more plausible that CPAP itself produced the positive effect rather than that other factors had a greater influence. Second, due to the need for multiple measurements in the relatively large number of participants, it was not feasible to use methods that could measure total energy expenditure (e.g., metabolic chamber). Alternatively, we estimated the shift in energy expenditure by separately assessing its components using standard methods to assess BMR and physical activity under free-living conditions. Third, although widely used in clinical studies, the accuracy of a self-report questionnaire to estimate energy intake is generally poor due to inherent reporting biases. Also, we used questionnaires specifically developed for the Japanese to assess dietary intake and eating behavior because they are widely used and well established in domestic studies and seemed to be the most suitable for our study population. Therefore, the impact of dietary intake and eating behavior in this setting needs to be confirmed in other populations. Fourth, a 3-mo period of CPAP therapy might not be sufficient to assess changes in some parameters and it is unclear whether the trend of weight gain or weight loss would continue in the future. Long-term longitudinal studies are needed to better understand the changes in energy metabolism and weight change following CPAP therapy.

In conclusion, our study demonstrated that CPAP therapy reduced BMR, thereby predisposing OSA patients to a positive energy balance and subsequent weight gain. However, dietary intake and eating behavior seemed to have a greater impact on weight change than the shift in energy expenditure; therefore it is imperative to incorporate

lifestyle modifications into the treatment of OSA.

Acknowledgements

We thank Kazuyuki Ueda, Yuko Yamanishi, Akemi Ishii, Yuri Masuda, Yumiko Narita, and Rie Imai for analyzing polysomnographic data. We thank Dr. Chisato Miyakoshi for his statistical advice. We thank Dr. Masakatsu Sone who provided helpful comments on the interpretation of the results. We also thank Prof. Nobuya Inagaki who offered continuing support and constant encouragement. In particular, we are deeply grateful to Dr. Toshiie Sakata who supervised the translation of the Eating Behavior Questionnaire into English.

References

1. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, Amann M, Anderson HR, Andrews KG, Aryee M, Atkinson C, Bacchus LJ, Bahalim AN, Balakrishnan K, Balmes J, Barker-Collo S, Baxter A, Bell ML, Blore JD, Blyth F, Bonner C, Borges G, Bourne R, Boussinesq M, Brauer M, Brooks P, Bruce NG, Brunekreef B, Bryan-Hancock C, Bucello C, Buchbinder R, Bull F, Burnett RT, Byers TE, Calabria B, Carapetis J, Carnahan E, Chafe Z, Charlson F, Chen H, Chen JS, Cheng AT, Child JC, Cohen A, Colson KE, Cowie BC, Darby S, Darling S, Davis A, Degenhardt L, Dentener F, Des Jarlais DC, Devries K, Dherani M, Ding EL, Dorsey ER, Driscoll T, Edmond K, Ali SE, Engell RE, Erwin PJ, Fahimi S, Falder G, Farzadfar F, Ferrari A, Finucane MM, Flaxman S, Fowkes FG, Freedman G, Freeman MK, Gakidou E, Ghosh S, Giovannucci E, Gmel G, Graham K, Grainger R, Grant B, Gunnell D, Gutierrez HR, Hall W, Hoek HW, Hogan A, Hosgood HD, 3rd, Hoy D, Hu H, Hubbell BJ, Hutchings SJ, Ibeanusi SE, Jacklyn GL, Jasrasaria R, Jonas JB, Kan H, Kanis JA, Kassebaum N, Kawakami N, Khang YH, Khatibzadeh S, Khoo JP, Kok C, Laden F, Lalloo R, Lan Q, Lathlean T, Leasher JL, Leigh J, Li Y, Lin JK, Lipshultz SE, London S, Lozano R, Lu Y, Mak J, Malekzadeh R, Mallinger L, Marcenes W, March L, Marks R, Martin R, McGale P, McGrath J, Mehta S, Mensah GA, Merriman TR, Micha R, Michaud C, Mishra V, Mohd Hanafiah K, Mokdad AA, Morawska L, Mozaffarian D, Murphy T, Naghavi M, Neal B, Nelson PK, Nolla JM, Norman R, Olives C, Omer SB, Orchard J, Osborne R, Ostro B, Page A, Pandey KD, Parry CD, Passmore E, Patra J, Pearce N, Pelizzari PM, Petzold M, Phillips MR, Pope D, Pope CA, 3rd, Powles J, Rao M, Razavi H, Rehfuess EA, Rehm JT, Ritz B, Rivara FP, Roberts T, Robinson C, Rodriguez-Portales JA, Romieu I, Room R, Rosenfeld LC, Roy A, Rushton L, Salomon

JA, Sampson U, Sanchez-Riera L, Sanman E, Sapkota A, Seedat S, Shi P, Shield K, Shivakoti R, Singh GM, Sleet DA, Smith E, Smith KR, Stapelberg NJ, Steenland K, Stockl H, Stovner LJ, Straif K, Straney L, Thurston GD, Tran JH, Van Dingenen R, van Donkelaar A, Veerman JL, Vijayakumar L, Weintraub R, Weissman MM, White RA, Whiteford H, Wiersma ST, Wilkinson JD, Williams HC, Williams W, Wilson N, Woolf AD, Yip P, Zielinski JM, Lopez AD, Murray CJ, Ezzati M, AlMazroa MA, Memish ZA. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;380:2224-2260.

2. Romero-Corral A, Caples SM, Lopez-Jimenez F, Somers VK. Interactions between obesity and obstructive sleep apnea: implications for treatment. *Chest* 2010;137:711-719.

3. Phillips BG, Hisel TM, Kato M, Pesek CA, Dyken ME, Narkiewicz K, Somers VK. Recent weight gain in patients with newly diagnosed obstructive sleep apnea. *J Hypertens* 1999;17:1297-1300.

4. Brown MA, Goodwin JL, Silva GE, Behari A, Newman AB, Punjabi NM, Resnick HE, Robbins JA, Quan SF. The impact of sleep-disordered breathing on body mass index (BMI): The sleep heart health study (SHHS). *Southwest J Pulm Crit Care* 2011;3:159-168.

5. Ong CW, O'Driscoll DM, Truby H, Naughton MT, Hamilton GS. The reciprocal interaction between obesity and obstructive sleep apnoea. *Sleep Med Rev* 2013;17:123-131.

6. Ryan CF, Love LL, Buckley PA. Energy expenditure in obstructive sleep apnea. *Sleep* 1995;18:180-187.

7. Stenlof K, Grunstein R, Hedner J, Sjostrom L. Energy expenditure in obstructive sleep apnea: effects of treatment with continuous positive airway pressure. *Am J Physiol* 1996;271:E1036-1043.

8. Ucok K, Aycicek A, Sezer M, Fidan F, Akgun L, Akkaya M, Unlu M. Resting metabolic rate and anthropometric measurements in male sleep apnea patients. *Intern Med* 2011;50:833-838.

9. de Jonge L, Zhao X, Mattingly MS, Zuber SM, Piaggi P, Csako G, Cizza G, Group NSES. Poor sleep quality and sleep apnea are associated with higher resting energy expenditure in obese individuals with short sleep duration. *J Clin Endocrinol Metab* 2012;97:2881-2889.

10. Fekete K, Boutou AK, Pitsiou G, Chavouzis N, Pataka A, Athanasiou I, Ilonidis G, Kontakiotis T, Argyropoulou P, Kioumis I. Resting energy expenditure in OSAS: the impact of a single CPAP application. *Sleep Breath* 2015 [Epub ahead of print]

11. Lin CC, Chang KC, Lee KS. Effects of treatment by laser-assisted uvuloplasty on sleep energy expenditure in obstructive sleep apnea patients. *Metabolism* 2002;51:622-627.

12. Vasquez MM, Goodwin JL, Drescher AA, Smith TW, Quan SF. Associations of dietary intake and physical activity with sleep disordered breathing in the Apnea Positive Pressure Long-term Efficacy Study (APPLES). *J Clin Sleep Med* 2008;4:411-418.

13. Beebe DW, Miller N, Kirk S, Daniels SR, Amin R. The association between obstructive sleep apnea and dietary choices among obese individuals during middle to late childhood. *Sleep Med* 2011;12:797-799.

14. Galli G, Piaggi P, Mattingly MS, de Jonge L, Courville AB, Pinchera A, Santini

F, Csako G, Cizza G. Inverse relationship of food and alcohol intake to sleep measures in obesity. *Nutr Diabetes* 2013;3:e58.

15. Smith SS, Waight C, Doyle G, Rossa KR, Sullivan KA. Liking for high fat foods in patients with obstructive sleep apnoea. *Appetite* 2014;78:185-192.

16. Redenius R, Murphy C, O'Neill E, Al-Hamwi M, Zallek SN. Does CPAP lead to change in BMI? *J Clin Sleep Med* 2008;4:205-209.

17. Quan SF, Budhiraja R, Clarke DP, Goodwin JL, Gottlieb DJ, Nichols DA, Simon RD, Smith TW, Walsh JK, Kushida CA. Impact of treatment with continuous positive airway pressure (CPAP) on weight in obstructive sleep apnea. *J Clin Sleep Med* 2013;9:989-993.

18. Keenan BT, Maislin G, Sunwoo BY, Arnardottir ES, Jackson N, Olafsson I, Juliusson S, Schwab RJ, Gislason T, Benediktsdottir B, Pack AI. Obstructive sleep apnoea treatment and fasting lipids: a comparative effectiveness study. *Eur Respir J* 2014;44:405-414.

19. Drager LF, Brunoni AR, Jenner R, Lorenzi-Filho G, Bensenor IM, Lotufo PA. Effects of CPAP on body weight in patients with obstructive sleep apnoea: a meta-analysis of randomised trials. *Thorax* 2014;70:258-264.

20. West SD, Kohler M, Nicoll DJ, Stradling JR. The effect of continuous positive airway pressure treatment on physical activity in patients with obstructive sleep apnoea: a randomised controlled trial. *Sleep Med* 2009;10:1056-1058.

21. Batool-Anwar S, Goodwin JL, Drescher AA, Baldwin CM, Simon RD, Smith TW, Quan SF. Impact of CPAP on activity patterns and diet in patients with obstructive sleep apnea (OSA). *J Clin Sleep Med* 2014;10:465-472.

22. Bamberga M, Rizzi M, Gadaleta F, Grechi A, Baiardini R, Fanfulla F.

Relationship between energy expenditure, physical activity and weight loss during CPAP treatment in obese OSA subjects. *Respir Med* 2015;109:540-545.

23. Tachikawa R, Ikeda K, Matsumoto T, Hamada S, Azuma M, Murase K, Tanizawa K, Inouchi M, Oga T, Inagaki N, Mishima M, Chin. K. Effects of CPAP on energy balance in patients with obstructive sleep apnea [abstract]. *Eur Respir J* 2015;46:PA2371.

24. Berry RB, Budhiraja R, Gottlieb DJ, Gozal D, Iber C, Kapur VK, Marcus CL, Mehra R, Parthasarathy S, Quan SF, Redline S, Strohl KP, Davidson Ward SL, Tangredi MM, American Academy of Sleep Medicine. Rules for scoring respiratory events in sleep: Update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. *J Clin Sleep Med* 2012;8:597-619.

25. Compher C, Frankenfield D, Keim N, Roth-Yousey L, Evidence Analysis Working Group. Best practice methods to apply to measurement of resting metabolic rate in adults: a systematic review. *J Am Diet Assoc* 2006;106:881-903.

26. Kobayashi S, Murakami K, Sasaki S, Okubo H, Hirota N, Notsu A, Fukui M, Date C. Comparison of relative validity of food group intakes estimated by comprehensive and brief-type self-administered diet history questionnaires against 16 d dietary records in Japanese adults. *Public Health Nutr* 2011;14:1200-1211.

27. Kobayashi S, Honda S, Murakami K, Sasaki S, Okubo H, Hirota N, Notsu A, Fukui M, Date C. Both comprehensive and brief self-administered diet history questionnaires satisfactorily rank nutrient intakes in Japanese adults. *J Epidemiol* 2012;22:151-159.

28. Inoue K, Maeda N, Kashine S, Fujishima Y, Kozawa J, Hiuge-Shimizu A,

Okita K, Imagawa A, Funahashi T, Shimomura I. Short-term effects of liraglutide on visceral fat adiposity, appetite, and food preference: a pilot study of obese Japanese patients with type 2 diabetes. *Cardiovasc Diabetol* 2011;10:109.

29. Japan Society for the Study of Obesity. Clinical guidelines for the treatment of obesity. *Himan Kenkyu* 2006;12.

30. Garatachea N, Torres Luque G, Gonzalez Gallego J. Physical activity and energy expenditure measurements using accelerometers in older adults. *Nutr Hosp* 2010;25:224-230.

31. Van Remoortel H, Raste Y, Louvaris Z, Giavedoni S, Burtin C, Langer D, Wilson F, Rabinovich R, Vogiatzis I, Hopkinson NS, Troosters T, consortium PR. Validity of six activity monitors in chronic obstructive pulmonary disease: a comparison with indirect calorimetry. *PLoS One* 2012;7:e39198.

32. Chaput JP, Despres JP, Bouchard C, Tremblay A. The association between short sleep duration and weight gain is dependent on disinhibited eating behavior in adults. *Sleep* 2011;34:1291-1297.

33. Garaulet M, Ortega FB, Ruiz JR, Rey-Lopez JP, Beghin L, Manios Y, Cuenca-Garcia M, Plada M, Diethelm K, Kafatos A, Molnar D, Al-Tahan J, Moreno LA. Short sleep duration is associated with increased obesity markers in European adolescents: effect of physical activity and dietary habits. The HELENA study. *Int J Obes (Lond)* 2011;35:1308-1317.

34. Markwald RR, Melanson EL, Smith MR, Higgins J, Perreault L, Eckel RH, Wright KP, Jr. Impact of insufficient sleep on total daily energy expenditure, food intake, and weight gain. *Proc Natl Acad Sci U S A* 2013;110:5695-5700.

35. Calvin AD, Carter RE, Adachi T, Macedo PG, Albuquerque FN, van der Walt C,

Bukartyk J, Davison DE, Levine JA, Somers VK. Effects of experimental sleep restriction on caloric intake and activity energy expenditure. *Chest* 2013;144:79-86.

36. Tschop M, Weyer C, Tataranni PA, Devanarayan V, Ravussin E, Heiman ML. Circulating ghrelin levels are decreased in human obesity. *Diabetes* 2001;50:707-709.

37. Cummings DE, Weigle DS, Frayo RS, Breen PA, Ma MK, Dellinger EP, Purnell JQ. Plasma ghrelin levels after diet-induced weight loss or gastric bypass surgery. *N Engl J Med* 2002;346:1623-1630.

38. Hansen TK, Dall R, Hosoda H, Kojima M, Kangawa K, Christiansen JS, Jorgensen JO. Weight loss increases circulating levels of ghrelin in human obesity. *Clin Endocrinol (Oxf)* 2002;56:203-206.

39. Geliebter A, Gluck ME, Hashim SA. Plasma ghrelin concentrations are lower in binge-eating disorder. *J Nutr* 2005;135:1326-1330.

40. Maffei M, Halaas J, Ravussin E, Pratley RE, Lee GH, Zhang Y, Fei H, Kim S, Lallone R, Ranganathan S, et al. Leptin levels in human and rodent: measurement of plasma leptin and ob RNA in obese and weight-reduced subjects. *Nat Med* 1995;1:1155-1161.

41. Rosenbaum M, Nicolson M, Hirsch J, Murphy E, Chu F, Leibel RL. Effects of weight change on plasma leptin concentrations and energy expenditure. *J Clin Endocrinol Metab* 1997;82:3647-3654.

42. McLean JA, Barr SI, Prior JC. Cognitive dietary restraint is associated with higher urinary cortisol excretion in healthy premenopausal women. *Am J Clin Nutr* 2001;73:7-12.

43. Bedford JL, Prior JC, Barr SI. A prospective exploration of cognitive dietary restraint, subclinical ovulatory disturbances, cortisol, and change in bone density over

two years in healthy young women. *J Clin Endocrinol Metab* 2010;95:3291-3299.

44. Munzer T, Hegglin A, Stannek T, Schoch OD, Korte W, Buche D, Schmid C, Hurny C. Effects of long-term continuous positive airway pressure on body composition and IGF1. *Eur J Endocrinol* 2010;162:695-704.

45. Chirinos JA, Gurubhagavatula I, Teff K, Rader DJ, Wadden TA, Townsend R, Foster GD, Maislin G, Saif H, Broderick P, Chittams J, Hanlon AL, Pack AI. CPAP, weight loss, or both for obstructive sleep apnea. *N Engl J Med* 2014;370:2265-2275.

46. Chin K, Shimizu K, Nakamura T, Narai N, Masuzaki H, Ogawa Y, Mishima M, Nakamura T, Nakao K, Ohi M. Changes in intra-abdominal visceral fat and serum leptin levels in patients with obstructive sleep apnea syndrome following nasal continuous positive airway pressure therapy. *Circulation* 1999;100:706-712.

47. Trenell MI, Ward JA, Yee BJ, Phillips CL, Kemp GJ, Grunstein RR, Thompson CH. Influence of constant positive airway pressure therapy on lipid storage, muscle metabolism and insulin action in obese patients with severe obstructive sleep apnoea syndrome. *Diabetes Obes Metab* 2007;9:679-687.

48. Harsch IA, Schahin SP, Radespiel-Troger M, Weintz O, Jahreiss H, Fuchs FS, Wiest GH, Hahn EG, Lohmann T, Konturek PC, Ficker JH. Continuous positive airway pressure treatment rapidly improves insulin sensitivity in patients with obstructive sleep apnea syndrome. *Am J Respir Crit Care Med* 2004;169:156-162.

49. Dorkova Z, Petrasova D, Molcanyiova A, Popovnakova M, Tkacova R. Effects of continuous positive airway pressure on cardiovascular risk profile in patients with severe obstructive sleep apnea and metabolic syndrome. *Chest* 2008;134:686-692.

50. Hoyos CM, Killick R, Yee BJ, Phillips CL, Grunstein RR, Liu PY. Cardiometabolic changes after continuous positive airway pressure for obstructive sleep

apnoea: a randomised sham-controlled study. *Thorax* 2012;67:1081-1089.

51. Harsch IA, Konturek PC, Koebnick C, Kuehnlein PP, Fuchs FS, Pour Schahin S, Wiest GH, Hahn EG, Lohmann T, Ficker JH. Leptin and ghrelin levels in patients with obstructive sleep apnoea: effect of CPAP treatment. *Eur Respir J* 2003;22:251-257.

52. Garcia JM, Sharafkhaneh H, Hirshkowitz M, Elkhatib R, Sharafkhaneh A. Weight and metabolic effects of CPAP in obstructive sleep apnea patients with obesity. *Respir Res* 2011;12:80.

53. Tomfohr LM, Edwards KM, Dimsdale JE. Is obstructive sleep apnea associated with cortisol levels? A systematic review of the research evidence. *Sleep Med Rev* 2012;16:243-249.

54. Sanchez-de-la-Torre M, Mediano O, Barcelo A, Pierola J, de la Pena M, Esquinas C, Miro A, Duran-Cantolla J, Agusti AG, Capote F, Marin JM, Montserrat JM, Garcia-Rio F, Barbe F. The influence of obesity and obstructive sleep apnea on metabolic hormones. *Sleep Breath* 2012;16:649-656.

Figure legends

Figure 1. Flowchart of the study.

AHI: apnea-hypopnea index, CPAP: continuous positive airway pressure, OSA: obstructive sleep apnea

Figure 2. Comparison between weight gainers and non-weight gainers.

A) Basal metabolic rate, B) Physical activity, C) Total caloric intake, D) Plasma cortisol, E) Plasma Leptin, F) Plasma acylated ghrelin. Vertical bars represent mean ± standard error.

AC: activity counts, BMR: basal metabolic rate

Figure 3. Radar chart for changes in eating behavior scores in the weight gainers (A) and non-weight gainers (B). Scores were significantly higher in the weight gainers than the non-weight gainers at baseline, CPAP initiation, and 3-mo follow-up ($p < 0.001$, two-way ANOVA).

Scores were expressed as a percentage of the maximum possible score for each category.

$^{*}p < 0.05$ for the intra-category difference during the study period

$^{1}p < 0.05$ vs. the other group at baseline

$^{2}p < 0.05$ vs. the other group at CPAP initiation

$^{3}p < 0.05$ vs. the other group at 3-month follow-up

Table 1. Participant's characteristics according to body weight change

Characteristics	All participants (n = 63)	Weight gainers* (n = 33)	Non-weight gainers* (n = 30)	P value
Age, years	60.6 ± 10.0	59.8 ± 8.8	61.5 ± 11.3	0.518
Male sex	51 (81%)	25 (76%)	26 (87%)	0.344
Body weight, kg	77.8 ± 12.6	77.6 ± 11.1	78.0 ± 14.3	0.921
ΔBody weight, kg	0.4 ± 2.2	2.1 ± 1.3	-1.4 ± 1.5	< 0.001
Body mass index, kg/m^2	27.9 ± 3.8	28.0 ± 3.3	27.9 ± 4.4	0.973
Fat mass, kg	24.4 ± 7.8	24.8 ± 6.7	23.9 ± 8.9	0.659
Fat-free mass, kg	53.4 ± 8.3	52.8 ± 7.7	54.0 ± 9.0	0.595
Neck circumference, cm	39.9 ± 3.5	39.7 ± 3.4	40.1 ± 3.8	0.648
Waist circumference, cm	95.8 ± 8.6	96.0 ± 7.5	95.6 ± 9.8	0.851
Hypertension	50 (79%)	26 (79%)	24 (80%)	0.905
Dyslipidemia	41 (66%)	19 (58%)	22 (73%)	0.190
Diabetes mellitus	15 (24%)	8 (24%)	7 (23%)	0.933
Current smoking	14 (22%)	4 (12%)	10 (33%)	0.068
ESS	8.7 ± 5.3	9.1 ± 5.4	8.2 ± 5.2	0.502
AHI, events/h	42.2 ± 19.9	46.1 ± 20.2	38.0 ± 19.0	0.070
Lowest SpO_2, %	76.5 ± 8.3	75.8 ± 6.1	77.3 ± 10.3	0.494
Mean SpO_2, %	93.0 ± 3.2	93.2 ± 2.5	92.8 ± 3.9	0.699
Time of SpO_2 <90%, %	16.8 ± 20.3	18.0 ± 19.8	15.6 ± 21.1	0.429
Average CPAP use, min/day	268 ± 98	277 ± 102	257 ± 94	0.386
Percent days of CPAP use >4 h, %	61.5 ± 29.0	65.0 ± 28.2	57.8 ± 30.0	0.299

AHI: apnea hypopnea index, CPAP: continuous positive airway pressure, ESS: Epworth Sleepiness Scale

*Weight gainers denote participants who gained weight at the 3-mo follow-up compared to baseline, and non-weight gainers denote those in whom body weight decreased or did not change.

Table 2. Changes in parameters related to energy metabolism before and after CPAP therapy

Variables	Baseline	CPAP initiation*	3-mo follow-up	P value
Indirect calorimetry				
Basal metabolic rate, kcal/day	1584 ± 261	1561 ± 252	1508 ± 258†	<0.001
Respiratory quotient	0.86 ± 0.08	0.86 ± 0.09	0.85 ± 0.07	0.404
Physical activity				
Physical activity, activity counts/min	185 ± 80		184 ± 65	0.952
Energy/nutrition intake				
Total caloric intake, kcal/day	2018 ± 509	1906 ± 488	1982 ± 462	0.076
Energy, protein, %	15.8 ± 3.4	15.4 ± 2.9	15.7 ± 3.3	0.525
Energy, fat, %	26.7 ± 6.2	26.2 ± 4.6	27.4 ± 6.3	0.209
Energy, carbohydrate , %	52.7 ± 8.7	53.2 ± 8.1	51.8 ± 8.4	0.245
Anthropometric parameters				
Body weight, kg	77.8 ± 12.6	77.6 ± 12.5	78.2 ± 12.3‡	0.010
Fat mass, kg	24.4 ± 7.8	24.3 ± 8.0	24.4 ± 7.9	0.840
Fat-free mass, kg	53.4 ± 8.3	53.3 ± 8.3	53.8 ± 8.6	0.061
Muscle mass, kg	29.7 ± 5.1	29.7 ± 5.1	29.9 ± 5.2	0.253

Hormones				
Cortisol, μg/dL	14.7 ± 3.9	15.3 ± 3.2	14.5 ± 3.4	0.363
Plasma norepinephrine, pg/mL	242 ± 125	230 ± 128	213 ± 101	0.240
Urine norepinephrine, μg/gCr	102 ± 53	107 ± 59	96 ± 41	0.273
IGF-1, ng/mL	130 ± 37	134 ± 33	138 ± 37[§]	0.004
Leptin, ng/mL	15.0 ± 7.8	16.1 ± 9.6	16.3 ± 10.2	0.078
Acylated ghrelin, fmol/mL	7.1 ± 5.7	7.0 ± 6.3	6.7 ± 6.6	0.766
Des-acyl ghrelin, fmol/mL	36.9 ± 23.7	35.0 ± 19.7	35.2 ± 21.0	0.199
Sleep parameters				
Total sleep time, min	372 ± 82	383 ± 80	398 ± 66	0.068
Sleep stage 1/2, %	84.4 ± 6.9	78.0 ± 8.1[‖]	77.0 ± 7.5[‖]	<0.001
Sleep stage 3/4, %	1.2 ± 2.3	2.9 ± 4.6[§]	2.8 ± 5.2[¶]	0.004
Sleep REM , %	14.6 ± 6.3	19.0 ± 6.5[‖]	20.1 ± 5.7[‖]	<0.001
AHI, events/h	42.2 ± 19.9	5.6 ± 6.2[‖]	3.9 ± 3.7[‖]	<0.001
Time of SpO_2 <90 %, %	16.8 ± 20.3	0.6 ± 1.8[‖]	0.7 ± 3.5[‖]	<0.001

AHI: apnea-hypopnea index, IGF-1: insulin-like growth factor-1, REM: rapid eye movement

[*]Values in anthropometric and energy/nutrition intake parameters represent assessments just before CPAP therapy. Other values represent those measured after 1 night of CPAP therapy.

[†]p <0.001 vs. baseline, p <0.01 vs. CPAP initiation

‡p <0.05 vs. CPAP initiation

§p <0.01 vs. baseline

‖p <0.001 vs. baseline

¶p <0.05 vs. baseline

Table 3. Stepwise linear regression model for predicting ΔBMR after 1 night or 3 mo of CPAP therapy

Variables*	After 1 night of CPAP		After 3 mo of CPAP	
	β	P value	β	P value
ΔFat-free mass, kg	0.26	0.024		
ΔUrine norepinephrine, %†	0.28	0.015	0.22	0.071
Baseline AHI, events/h	-0.35	0.002		
% days of CPAP use >4 h, %			-0.27	0.027
Model R^2 (adjusted R^2)	0.28 (0.24)		0.13 (0.10)	

AHI: apnea-hypopnea index, β: standardized partial regression coefficient, BMR: basal metabolic rate, CPAP: continuous positive airway pressure

*Other potential covariates included age, sex, body mass index, Δfat mass (kg), Δplasma cortisol (μg/dL), Δplasma norepinephrine (pg/mL), and Δleptin (ng/mL)

†Change rate (%) was calculated as (values after 1 night or 3 mo of CPAP - baseline value) / baseline value x 100

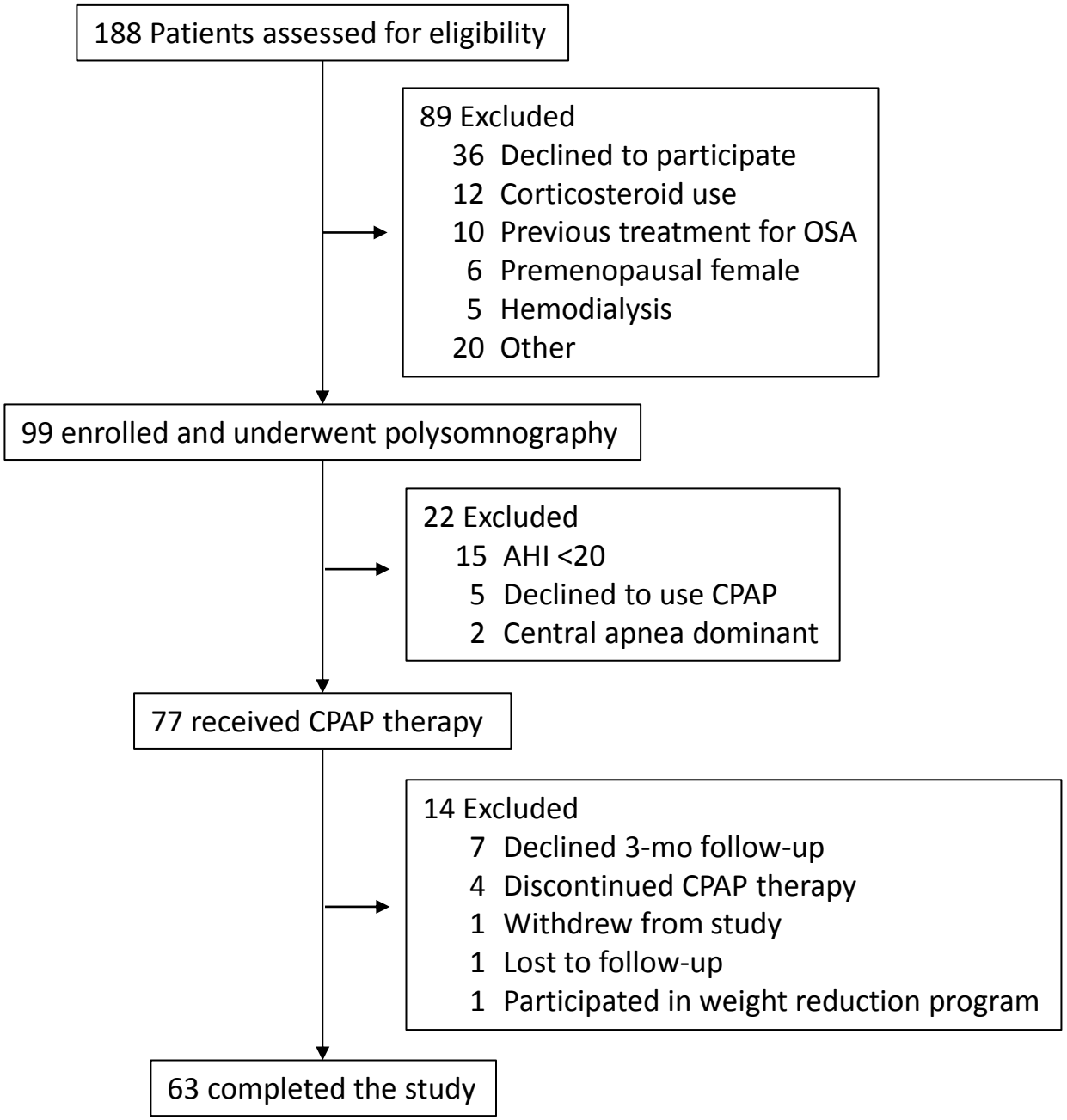
Table 4. Stepwise linear regression model for predicting ΔBMI after 3 mo of CPAP therapy

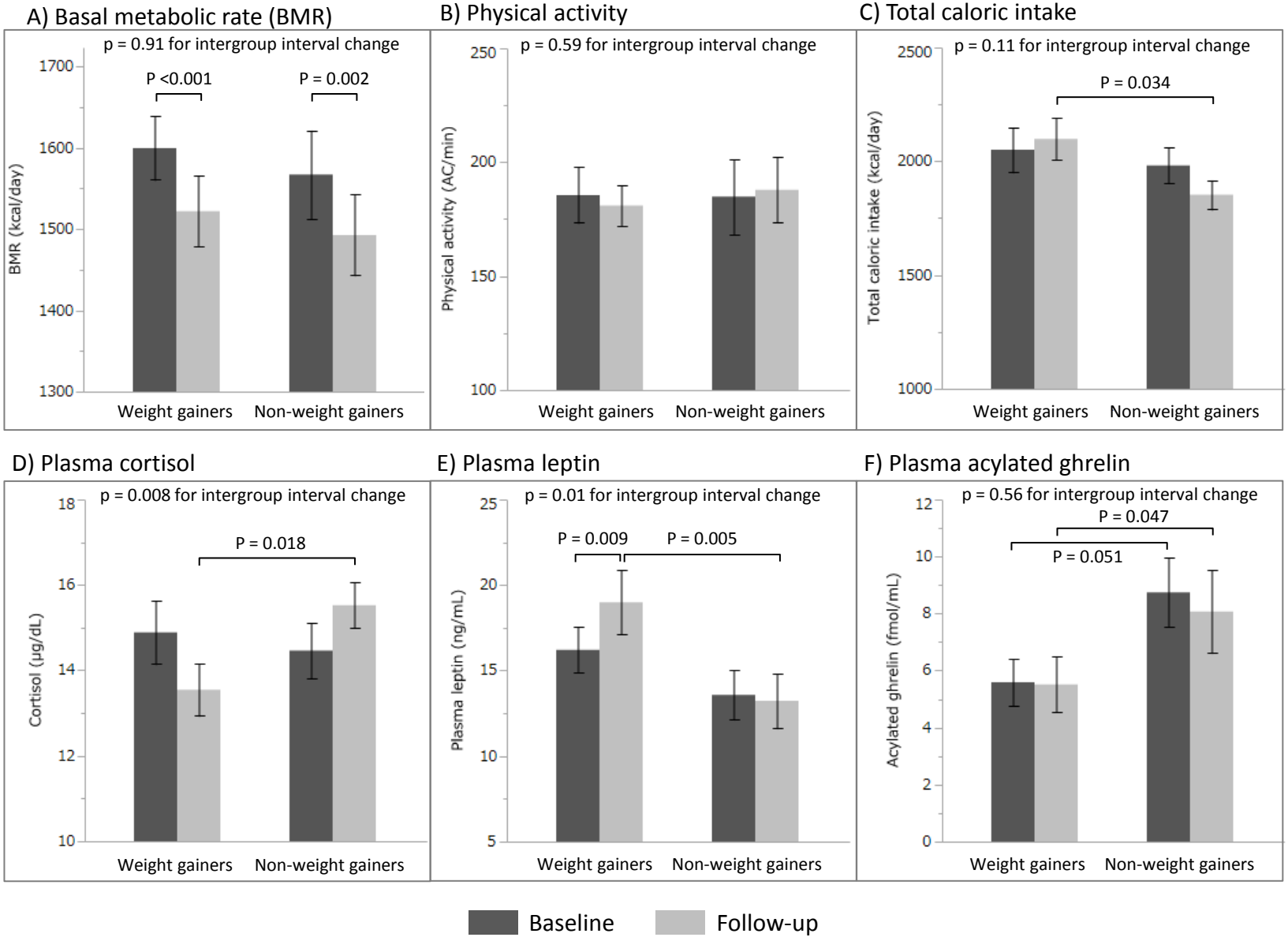
Variables*	β	P value
Age, years	-0.29	0.021
Male sex	-0.33	0.004
BMI, kg/m^2	-0.30	0.017
Current smoking	-0.30	0.009
ΔCortisol, μg/dL	-0.26	0.020
ΔTotal caloric intake, kcal/day	0.29	0.009
Model R^2 (adjusted R^2)	0.38 (0.31)	

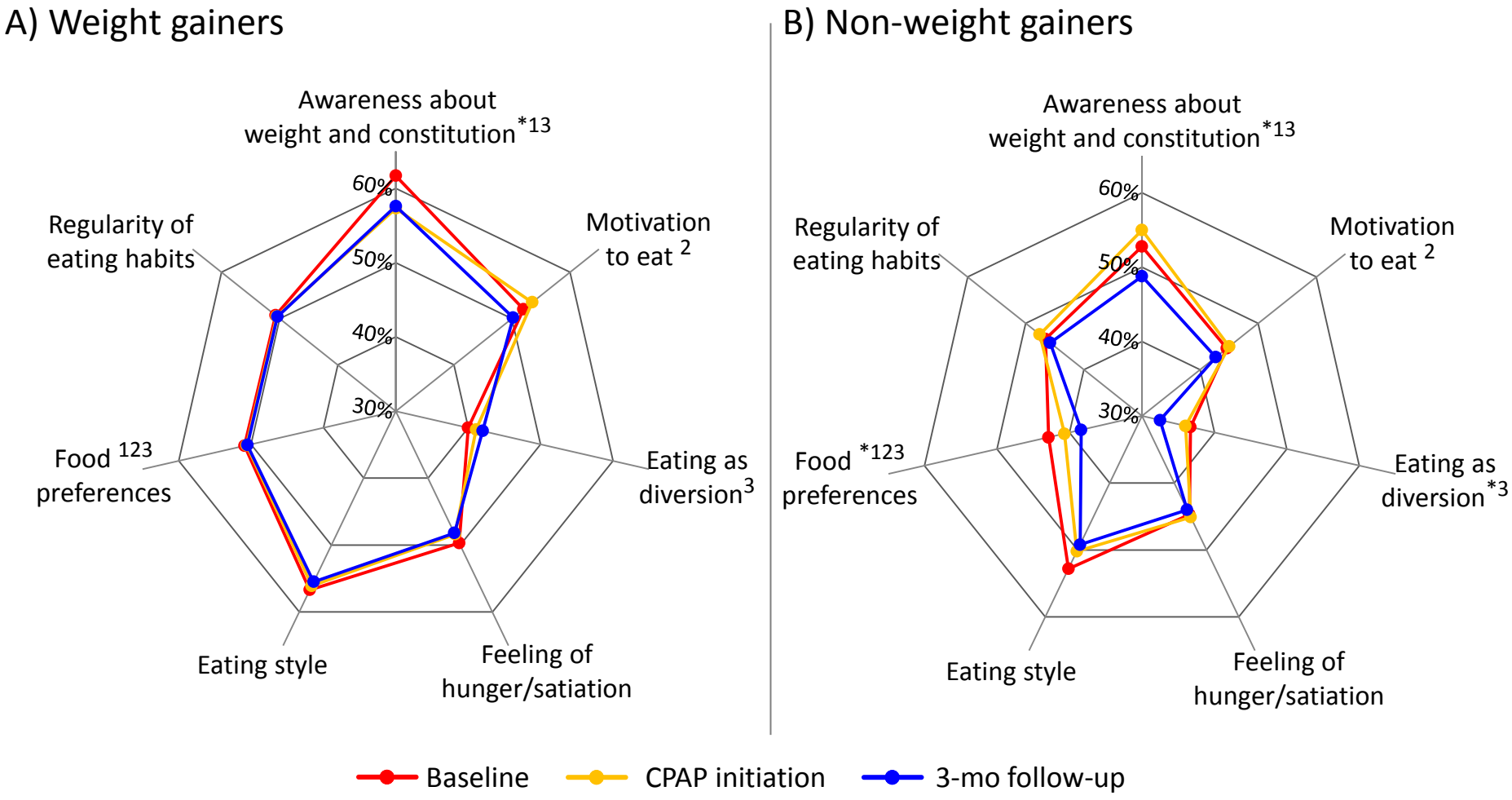
β: standardized partial regression coefficient, BMI: body mass index

*Other potential covariates included age, Δbasal metabolic rate (kcal/day), Δphysical activity (activity count/min), Δinsulin-like growth factor-1 (ng/mL), Δacylated ghlerin (fmol/mL), baseline apnea-hypopnea index, and % of days of CPAP use >4 h.

Figure 1


188 Patients assessed for eligibility
89 Excluded
36 Declined to participate
12 Corticosteroid use
10 Previous treatment for OSA
6 Premenopausal female
5 Hemodialysis
20 Other
99 enrolled and underwent polysomnography
22 Excluded
15 AHI <20
5 Declined to use CPAP
2 Central apnea dominant
77 received CPAP therapy
14 Excluded
7 Declined 3-mo follow-up
4 Discontinued CPAP therapy
1 Withdrew from study
1 Lost to follow-up
1 Participated in weight reduction program
63 completed the study


A) Basal metabolic rate (BMR)
p = 0.91 for intergroup interval change
P <0.001
P = 0.002
BMR (kcal/day)
1700
1600
1500
1400
1300
Weight gainers
Non-weight gainers
B) Physical activity
p = 0.59 for intergroup interval change
Physical activity (AC/min)
250
200
150
100
Weight gainers
Non-weight gainers
C) Total caloric intake
p = 0.11 for intergroup interval change
P = 0.034
Total caloric intake (kcal/day)
2500
2000
1500
1000
Weight gainers
Non-weight gainers
D) Plasma cortisol
p = 0.008 for intergroup interval change
P = 0.018
Cortisol (µg/dL)
18
16
14
12
10
Weight gainers
Non-weight gainers
E) Plasma leptin
p = 0.01 for intergroup interval change
P = 0.009
P = 0.005
Plasma leptin (ng/mL)
25
20
15
10
5
Weight gainers
Non-weight gainers
F) Plasma acylated ghrelin
p = 0.56 for intergroup interval change
P = 0.047
P = 0.051
Acylated ghrelin (fmol/mL)
12
10
8
6
4
2
0
Weight gainers
Non-weight gainers
Baseline
Follow-up


A) Weight gainers
B) Non-weight gainers
Awareness about weight and constitution *13
Motivation to eat 2
Eating as diversion 3
Feeling of hunger/satiation
Eating style
Food 123 preferences
Regularity of eating habits
60%
50%
40%
30%
Awareness about weight and constitution *13
Motivation to eat 2
Eating as diversion *3
Feeling of hunger/satiation
Eating style
Food *123 preferences
Regularity of eating habits
60%
50%
40%
30%
Baseline
CPAP initiation
3-mo follow-up