OBESITY STUDIES

Sleep Disturbance and Changes in Energy Intake and Body Composition During Weight Loss in the POUNDS Lost Trial

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To examine associations between sleep disturbance and changes in weight and body composition and the mediating role of changes of appetite and food cravings in the Preventing Overweight Using Novel Dietary Strategies (POUNDS Lost) 2-year weight-loss diet intervention trial, this study included 810 overweight or obese individuals with baseline sleep disturbance assessment who were randomly assigned one of four diets varying in macronutrient composition. Changes in body weight and fat distribution were assessed by DEXA and computed tomography during the 2-year intervention. Participants were asked to provide sleep disturbance levels (no, slight, moderate, or great) at baseline and to recall their sleep disturbances since last visit at 6, 12, 18, and 24 months. Weight loss during the first 6 months was followed by 1.5 years of steady weight regain. Participants with greater sleep disturbance from baseline to 6 months showed significant losses of body weight (P_{trend} <0.001) and waist circumference (P_{trend} = 0.002) at 6 months, after multivariate adjustment. Compared with individuals without sleep disturbance at all from baseline to 6 months, those with slight, moderate, or great sleep disturbance showed an elevated risk of failure to lose weight (−5% or more loss) at 6 months, when the maximum weight loss was achieved, with an odds ratio of 1.24 (95% CI 0.87, 1.78), 1.27 (95% CI 0.75, 2.13), or 3.12 (95% CI 1.61, 6.03), respectively. In addition, we observed that the repeatedly measured levels of sleep disturbance over 2 years were inversely associated with the overall weight loss rate (weight changes per 6 months) (P_{trend} <0.001). Further, sleep disturbances during weight loss from baseline to 6 months and weight regain from 6 months to 24 months were significantly predictive of total fat, total fat mass percent, and trunk fat percent changes during the 2 years. Our results also indicated that food cravings for carbohydrates/starches, fast food fats, and sweets; cravings, prospective consumption, hunger of appetite measurements; and dietary restraint, disinhibition, and hunger subscales measured at 6 months significantly mediated the effects of sleep disturbance on weight loss. In conclusion, our results suggested that more severe sleep disturbance during weight loss was associated with an elevated risk of failure to lose weight during the dietary intervention. Food cravings and eating behaviors may partly mediate these associations.

The rapidly developing obesity epidemic, which has been implicated in the development of cardiovascular diseases and type 2 diabetes (1), has posed a great challenge to public health. Diet and lifestyle modifications are among the major interventional approaches in obesity management. Even though various dietary interventions successfully induce weight loss among participants who are overweight or obese, a proportion of the participants failed to lose body weight or to maintain initial weight loss (2), indicating considerable interindividual variability. Several potential mechanisms, such as differences in compliance to the interventions, markers of dietary protein intake, and genetic heterogeneity, have been proposed to explain such variability (3–6), but there is still a gap in understanding

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other behavioral factors that may also account for these observations.

Compelling evidence has shown that sleep duration and sleep quality play a pivotal role in regulating body weight and fat distribution (7–11). However, whether sleep behaviors affect weight loss and maintenance in response to various calorie-restricted diets remains unclear. Several previous interventions tested the impact of curtailing sleep on body weight and body composition during diet-induced weight loss, but mixed results hindered the interpretations of these associations (12–19). Interpretation of many of these studies is limited by their short duration of intervention, lack of generalizability, lack of repeated measurements, missing information on important covariates, and small sample size. Thus, an investigation on the relation between sleep behavior and long-term weight loss and fat distribution is needed. Notably, a number of causal pathways linking short sleep duration with obesity have been discussed in a systematic review, such as appetite and food cravings (11,20,21). However, no study has comprehensively assessed whether these changes mediate the effects of sleep behavior and weight loss in the context of long-term dietary weight-loss interventions.

In the current study, we investigated whether sleep disturbance, defined as disorders of initiation, maintenance of sleep, disruptions of circadian rhythms, excessive somnolence, and dysfunctions associated with sleep, sleep stages, or partial arousals (22) were associated with weight loss, weight regain, and changes in body fat weight and body fat distribution in a 2-year randomized dietary intervention study called Preventing Overweight Using Novel Dietary Strategies (POUNDS Lost).

RESEARCH DESIGN AND METHODS

Study Participants

The POUNDS Lost study was a 2-year randomized study of diet intervention, in which 811 participants who were overweight or obese were randomly assigned to one of four energy-reduced diets consisting of different composition of macronutrients (fat, protein, and carbohydrate) to compare their effects on body weight (23). Two diets were low in fat (20%), and the other two were high in fat (40%). There were also two diets that differed in protein, one with average protein (15%) and the other high protein (25%), constituting a 2-by-2 factorial design. The two high-fat diets were also low-carbohydrate diets, in which the energy derived from carbohydrate was 35% and 45%, respectively. Each participant's caloric prescription represented a deficit of 750 kcal/day from measured resting energy expenditure (REE) at baseline. Participants with diabetes, unstable cardiovascular disease, use of medications that affected body weight, and insufficient motivations were ineligible for the POUNDS Lost trial. Fifty percent of the total individuals were randomly selected to undergo DEXA scans at baseline, after 6 months, and 2 years (24). Of those with DEXA scans, 50% had abdominal fat measured by computed tomography (CT). We used a cutoff of 5% of initial body weight to define successful weight losers (25,26). According to the U.S. Food and Drug Administration, the lower bound of weight loss to reach clinically meaningful health benefits is 5% of body weight (27). In brief, most weight loss was observed after 6 months of diet intervention, with 421 individuals losing >5%. Gradual weight regain occurred from 6 to 24 months. No difference of weight loss was detected comparing four diet groups.

In POUNDS Lost, there were 810 participants with baseline assessment of sleep disturbance. Of those, 511 had complete assessments of sleep disturbance every 6 months over 2 years (see missing patterns of sleep disturbances in Supplementary Table 1). The protocol was approved by the Institutional Review Board at Harvard T.H. Chan School of Public Health, Brigham and Women's Hospital, and the Pennington Biomedical Research Center of the Louisiana State University System, as well as by a data and safety monitoring board appointed by the National Heart, Lung, and Blood Institute. All participants provided written informed consent.

Measurements of Sleep Disturbances

The information on sleep disturbances were self-reported. The standardized questionnaires about symptoms and medical reporting, including sleep disturbances, were administered by interviewers at baseline and every 6 months in the 2-year study period. Participants were asked to provide their baseline sleep disturbance information and to recall their levels of sleep disturbance since last visit at 6 months, 12 months, 18 months, and 24 months. Disturbance in sleep was rated in four categories from "not at all," "slight amount," "moderate amount," to "great amount." All interviewers received standardized training, and possible responses were read to the participants verbatim. The questionnaires about symptoms and medical reporting are included in the Supplementary Material.

Measurements of Body Composition and Adiposity

Height was measured at the baseline examination. Body weight and waist circumference were assessed in the morning before breakfast at baseline and every 6 months during the intervention. Participants' body weights were collected by calibrated hospital scales and waist circumferences using a nonstretchable tape measure, 4 cm above the iliac crest. BMI was calculated as weight in kilograms divided by the square of height in meters. The DEXA scan was conducted using a Hologic QDR 4500A (Hologic) after an overnight fast; total fat mass, total lean mass, whole body total fat mass percentage, and trunk fat percentage were measured at baseline, 6 months, and 24 months during the intervention. CT scans were performed, and total adipose tissue mass, visceral adipose tissue mass, deep subcutaneous adipose tissue mass, and superficial adipose tissue mass within the abdomen were assessed by standard methods at baseline, 6 months, and 24 months. Measurements of REE were performed for all trial participants at baseline, 6, and

24 months. Details of the assessment of REE have been reported previously (28).

Measurements of Appetite, Food Cravings, and Other Eating Behaviors

The Food Craving Inventory (FCI) is a 33-item, self-administrated tool to obtain how often the individual experiences craving. A Likert scale between 1 and 5 was used to describe levels of craving for particular foods, where 1 = never, 2 = rarely, 3 = sometimes, 4 = often, and 5 = always (29). There are also five subscales in the FCI, including high-fat foods (i.e., steak, fried fish, and fried chicken), sweets (e.g., cake, cookies, chocolate, and candy), carbohydrates/starches (i.e., rolls, baked potato, pasta, and cereal), fast-food fats (i.e., pizza, hamburgers, French fries, and chips), and fruits/vegetables.

Appetites of participants were acquired by using a motivation-to-eat visual analog scale (VAS) at baseline, 6 months, and 24 months (30,31), which has four questions: *1*) how strong is your desire to eat? ("very weak" to "very strong" to assess craving); *2*) how hungry do you feel? ("not hungry at all" to "as hungry as I've ever felt" to assess hunger); *3*) how full do you feel? ("very full" to "not full at all" to assess fullness); and *4*) how much food do you think you could eat? ("nothing at all" to "a large amount" to assess prospective consumption).

While fasting, participants completed the questionnaires before breakfast, between 0700 and 0900 h on a weekly basis, by placing a cursor on the 100-mm VASs to assess craving, hunger, fullness, and prospective consumption. Higher scores indicate greater levels. A total appetite score was calculated as appetite score = (craving + hunger + [100 − fullness] + prospective consumption)/4 at each visit time (30,32). The reliability and validity of the VASs have been reported previously (33).

The Three-Factor Eating Questionnaire (TFEQ) is a self-report measure consisting of 51 yes/no questions to evaluate cognitive restraint, disinhibition (susceptibility to overeating), and perceived hunger (34).

Dietary restraint refers to the intent to diet, intent to monitor, and regulate food intake (21 items). The disinhibition scale assesses uncontrolled eating in response to different stimuli, such as in the presence of palatable foods or emotional clues (16 items). The perceived hunger scale measures the tendency to eat in response to the subjective sense of hunger (14 items). Higher scores reflect higher levels of cognitive restraint, disinhibition, and perceived hunger.

Other Covariates

The Baecke questionnaire was used to assess physical activity (35). Levels of physical activity were indicated by physical activity score, calculated based on physical activity at work, sport during leisure time, and other physical activity during leisure time.

Statistical Analysis

The primary outcomes of interest in this study were: *1*) weight loss at 6 months and overall weight loss rate (weight change per 6 months) over 2 years; *2*) weight regain rate (weight change per 6 months) from 6 months to 2 years; and *3*) changes of body composition and fat distribution from baseline to 6 months and 6 months to 2 years.

Participants in the intervention achieved a maximum weight loss of 6.2% (−5.75 kg) at 6 months. After 6 months, most of them tended to regain weight and end up with an overall weight loss of 3.5% (−3.31 kg) at 2 years. Therefore, we categorized the study period from months 0 to 6 as weight loss period and months 6 to 24 as weight regain period. All statistical analysis are performed as post hoc analysis of the data collected from POUNDS Lost trial.

Multivariate-adjusted models controlling age, sex, ethnicity, diet intervention, BMI, and physical activity were used to assess the relationship between sleep disturbance from baseline to 6 months and weight loss at 6 months. Respective outcome traits at previous visits were further adjusted to test the association between sleep disturbance and changes in body composition and adiposity. In addition, we conducted analyses to examine the effect of sleep disturbances on weight changes (0–24 months and 6–24 months) using the generalized estimating equation (GEE), with a first-order autoregressive matrix. Sleep disturbance assessed at 6, 12, 18, and 24 months as well as weight changes at 6, 12, 18, and 24 months were included in the GEE models. The least squares (LS) means of weight loss rate according to levels of sleep disturbance were calculated. Tests for linear trend were conducted by including an ordinal variable of sleep disturbance in the model. To investigate the impact of sleep disturbance from baseline to 6 months on successful weight loss at 6 months, we further performed a logistic regression to calculate odds ratios (ORs) and 95% CIs for a failure of achieving successful weight loss.

The magnitude of mediation by psychologic and behavioral factors was assessed by calculating change of β coefficient for sleep disturbance comparing two generalized linear models predicting weight loss: *1*) adjusting for age, sex, ethnicity, diet, BMI, and physical activity; and *2*) further adjusting for each of the potential mediating factors individually. Due to power consideration and significant linear trend, sleep disturbance was coded as an ordinal variable in the generalized linear model. Also, we combined "slight" and "moderate" sleep disturbance levels, as their effects on weight change at 6 months are not significantly distinct in a sensitivity analysis (Table 2). The 95% CIs for the change of β coefficient between the two models were calculated using bootstrap methods with 1,000 replications.

A two-sided $P < 0.05$ was considered statistically significant. All statistical analyses were performed with SAS software, version 9.4 (SAS Institute Inc., Cary, NC).

Table 1—Characteristics of study participants according to sleep disturbance at the baseline examination

Outcomes	Not at all (*n* = 462)	Slight (*n* = 236)	Moderate (*n* = 95)	Great (*n* = 17)	*P**
Age (years)	50.56 (9.03)	51.24 (9.34)	51.45 (9.80)	50.13 (8.83)	0.70
Male	187 (40.48)	71 (30.08)	35 (36.84)	3 (17.65)	0.02
High-fat diet	230 (49.78)	118 (50.00)	49 (51.58)	8 (47.06)	0.98
BMI (kg/m^2)	32.74 (3.79)	32.57 (4.07)	32.97 (3.45)	31.94 (5.00)	0.82
Body weight (kg)	93.43 (15.66)	91.67 (15.74)	93.91 (13.54)	89.98 (19.82)	0.81
Waist circumference (cm)	104.08 (12.86)	101.90 (13.64)	104.27 (11.41)	101.01 (16.69)	0.79
Resting metabolic rate (kcal/24 h)	1,564.29 (305.23)	1,521.42 (294.12)	1,547.67 (269.88)	1,522.53 (379.28)	0.67
Respiratory quotient	0.84 (0.04)	0.84 (0.04)	0.85 (0.05)	0.83 (0.05)	0.34
Physical activity score	1.59 (0.11)	1.57 (0.11)	1.57 (0.11)	1.54 (0.13)	0.23
Body fat composition (%)					
Whole-body total fat mass	37.04 (6.89)	37.30 (6.67)	36.69 (6.60)	40.26 (8.62)	0.49
Trunk fat	38.11 (6.04)	37.85 (5.57)	38.12 (5.93)	38.60 (11.56)	0.31
Body fat distribution (kg)					
DSAT	5.85 (1.63)	5.49 (1.74)	5.84 (1.81)	5.33 (1.65)	0.60
SAT mass	11.31 (2.66)	10.46 (2.26)	11.22 (2.84)	12.21 (6.05)	0.23
VAT mass	5.57 (2.54)	5.36 (2.65)	5.06 (2.17)	4.21 (2.02)	0.35
TAT mass	16.98 (3.99)	15.92 (4.01)	16.30 (3.84)	17.00 (8.54)	0.42
Dietary intake/day					
Energy (kcal)	1,949.40 (530.33)	1,994.09 (625.48)	1,973.77 (639.97)	1,983.88 (411.48)	0.34
Protein (%)	18.15 (3.35)	17.90 (3.19)	18.29 (3.79)	16.10 (2.78)	0.39
Fat (%)	36.93 (5.69)	36.87 (6.43)	36.81 (6.02)	37.97 (5.60)	0.94
Carbohydrate (%)	44.78 (7.62)	44.91 (7.60)	44.89 (7.18)	46.05 (7.84)	0.99

Data are mean (SD) or *n* (%) unless otherwise indicated. DSAT, deep subcutaneous adipose tissue; SAT, superficial adipose tissue; TAT, total adipose tissue by CT; VAT, visceral adipose tissue. **P* value adjusted for age, sex, and ethnicity.

Data and Resource Availability

The data sets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request. No applicable resources were generated or analyzed during the current study.

RESULTS

Table 1 presents the baseline characteristics of study participants. Mean (SD) value for age was 50.9 (9.2) and 32.7 (3.9) kg/cm^2 for BMI. Of the 810 participants, 79% were White, and 68% possessed a college degree or higher. The prevalence of no, slight, moderate, and great sleep disturbance were 57%, 29%, 12%, and 2%, respectively. Compared with females, male participants were less likely to have sleep disturbance (P = 0.02). No significant differences were observed for age, sex, race, BMI, weight, physical activity, REE, and diet intervention allocation across different levels of sleep disturbance. A total of 511 (63%) participants completed all the five assessments (baseline, 6 months, 12 months, 18 months, and 24 months) of sleep disturbance and weight changes during the 2-year intervention (Supplementary Table 1). Among them, 221 (43%), 206 (40%), 228 (45%), and 212 (41%) participants' levels of sleep disturbance at 6, 12, 18, and 24 months, respectively, were different from previous measurements.

During the weight loss period, we found that higher levels of sleep disturbance from baseline to 6 months were significantly associated with less weight loss at 6 months after adjustment for covariates (P_{trend} <0.001) (Table 2). A similar linear trend was observed for waist circumference. However, among successful weight losers who lost at least 5% of their initial weight at 6 months, no statistically significant association was detected between repeated measurements of sleep disturbance and body weight or waist circumference changes for 6 months during the weight regain period. For the entire 2-year period, repeated measures of sleep disturbance were significantly related with the overall rate of changes in body weight (P_{trend} <0.001) and waist circumference (P_{trend} ≤0.001) (weight change per 6 months; waist circumference change per 6 months). Participants suffering from higher levels of sleep disturbance lost significantly less weight and waist circumference over the 2-year trial. The trajectories of changes in body weight and waist circumference according to sleep disturbance among all participants over 2 years are shown in Fig. 1.

We then investigated whether sleep disturbance from baseline to 6 months was significantly predictive of failure of weight loss at 6 months (Fig. 2). Among 810 participants, 48% (389 of 810) failed to lose at least 5% of their initial weight. Compared with individuals without sleep disturbance at all from baseline to 6 months, those with slight, moderate, or great sleep disturbance showed an elevated risk of failure to lose weight, with ORs of 1.24 (95% CI 0.87, 1.78), 1.27 (95% CI 0.75, 2.13), or 3.12

Table 2—Changes in body weight and waist circumference for 6 months according to sleep disturbances

Outcomes	Not at all	Slight	Moderate	Great	P_{trend}
0–6 months					
Δ weight (kg)					
Model 1*	−6.06 (0.58)	−4.81 (0.63)	−4.74 (0.75)	−2.41 (0.93)	<0.001
Model 2†	−6.14 (0.57)	−4.83 (0.62)	−4.79 (0.73)	−2.15 (0.91)	<0.001
Δ WC (cm)					
Model 1*	−6.17 (0.63)	−5.66 (0.68)	−5.39 (0.80)	−3.42 (1.00)	0.005
Model 2†	−6.26 (0.62)	−5.69 (0.66)	−5.45 (0.79)	−3.15 (0.98)	0.002
0–24 months					
Δ weight (kg)					
Model 3‡	−1.00 (0.23)	−0.53 (0.24)	−0.22 (0.30)	0.39 (0.33)	<0.001
Model 4‖	−1.01 (0.24)	−0.54 (0.25)	−0.22 (0.31)	0.43 (0.37)	<0.001
Δ WC (cm)					
Model 3‡	−1.43 (0.26)	−1.05 (0.26)	−0.89 (0.32)	−0.41 (0.38)	0.002
Model 4‖	−1.44 (0.27)	−1.07 (0.27)	−0.88 (0.32)	−0.36 (0.38)	0.001
6–24 months among those with successful weight loss (*n* = 421)					
Δ weight (kg)					
Model 3‡	0.82 (0.33)	0.79 (0.32)	1.40 (0.41)	1.10 (0.42)	0.14
Model 4‖	0.88 (0.32)	0.86 (0.31)	1.43 (0.40)	1.07 (0.41)	0.20
Model 5¶	0.87 (0.32)	0.84 (0.31)	1.39 (0.41)	1.02 (0.42)	0.24
Δ WC (cm)					
Model 3‡	0.11 (0.36)	0.38 (0.37)	0.93 (0.46)	0.38 (0.52)	0.06
Model 4‖	0.16 (0.35)	0.45 (0.36)	0.95 (0.45)	0.33 (0.51)	0.08
Model 5¶	0.15 (0.35)	0.45 (0.36)	0.94 (0.45)	0.32 (0.51)	0.09

Data are LS means (SE). Δ weight and Δ WC were calculated as the changes for 6 months. Tests for linear trend across categories of sleep disturbance were performed by modeling an ordinal variable for each sleep category. Δ WC, change in waist circumference. *Model 1: generalized linear model adjusted for age, sex, ethnicity, diet, BMI, and the respective variable (except for the outcome Δ weight) at the previous assessment. †Model 2: further adjusted for physical activity score at baseline. ‡Model 3: †GEE assuming first-order autoregressive adjusted for age, sex, ethnicity, visit, diet, BMI, and the respective variable (except for the outcome Δ weight) at the previous assessment. ‖Model 4: further adjusted for physical activity score at baseline. ¶Model 5: further adjusted for initial weight loss at 6 months.

(95% CI 1.61, 6.03), respectively. We also conducted a sensitivity analysis for those who lost at least 10% of their initial weight in 6 months. In comparison with no sleep disturbance at all, the ORs of weight-loss failure at 6 months were 1.59 (95% CI 1.08, 2.32), 2.01(95% CI 1.11, 3.65), and 4.00 (95% CI 1.68, 9.48) for those with slight, moderate, or great sleep disturbance, respectively.

In addition, greater sleep disturbance from baseline to 6 months was significantly associated with less decrease in total fat, total fat mass percentage, and trunk fat percentage, in the weight loss period (P_{trend} = 0.02, 0.04, and 0.05, respectively). Significant associations were also observed in weight regain period between sleep disturbance recalled at 24 months and body composition (P_{trend} = 0.02, <0.01, and <0.01, respectively) (Fig. 3 and Supplementary Table 2). The associations were more significant during the weight regain period. Interestingly, participants with moderate or great sleep disturbance showed an increased level of total fat mass percent and trunk fat percent, compared with baseline (the LS means of total fat mass percent change was 0.44 for moderate sleep disturbance and 0.65 for severe sleep disturbance; trunk fat percent change was 0.02 for moderate amount and 0.38 for severe sleep disturbance). No significant association was detected between sleep disturbance and less adiposity, possibly due to reduced statistical power (*n* = 107).

We further investigated whether measures of appetite and food cravings at 6 months might mediate the relationship between sleep disturbance and weight loss from baseline to 6 months (Table 3). When food craving subscales from the FCI were further adjusted, the largest indirect effect was observed by craving for carbohydrates/starches, craving for fast-food fats, and craving for sweets (β = −0.09, −0.06, and −0.06, respectively). These medications are significant under the 95% confidence level. Additionally, appetite measurements using VAS ratings were also examined. Cravings, prospective consumption, and hunger scores showed significantly indirect effects and were associated with less weight changes in the weight-loss period ($P < 0.05$ for all). Similarly, inclusion of dietary restraint, disinhibition, and hunger in the model significantly reduced the strength of the relationship between sleep and weight loss by 16% ([−1.06 + 0.89]/−1.06), 29% ([−1.06 + 0.75]/−1.06), and 23% ([−1.06 + 0.82]/ −1.06), respectively ($P < 0.05$ for all). The combined psychologic and behavioral factors (total food craving index, appetite score, dietary restraint, disinhibition, and hunger) mediated up to 42% (−0.44/−1.06) of the total effect from sleep disturbance to weight loss. By combining the categories "slight" and

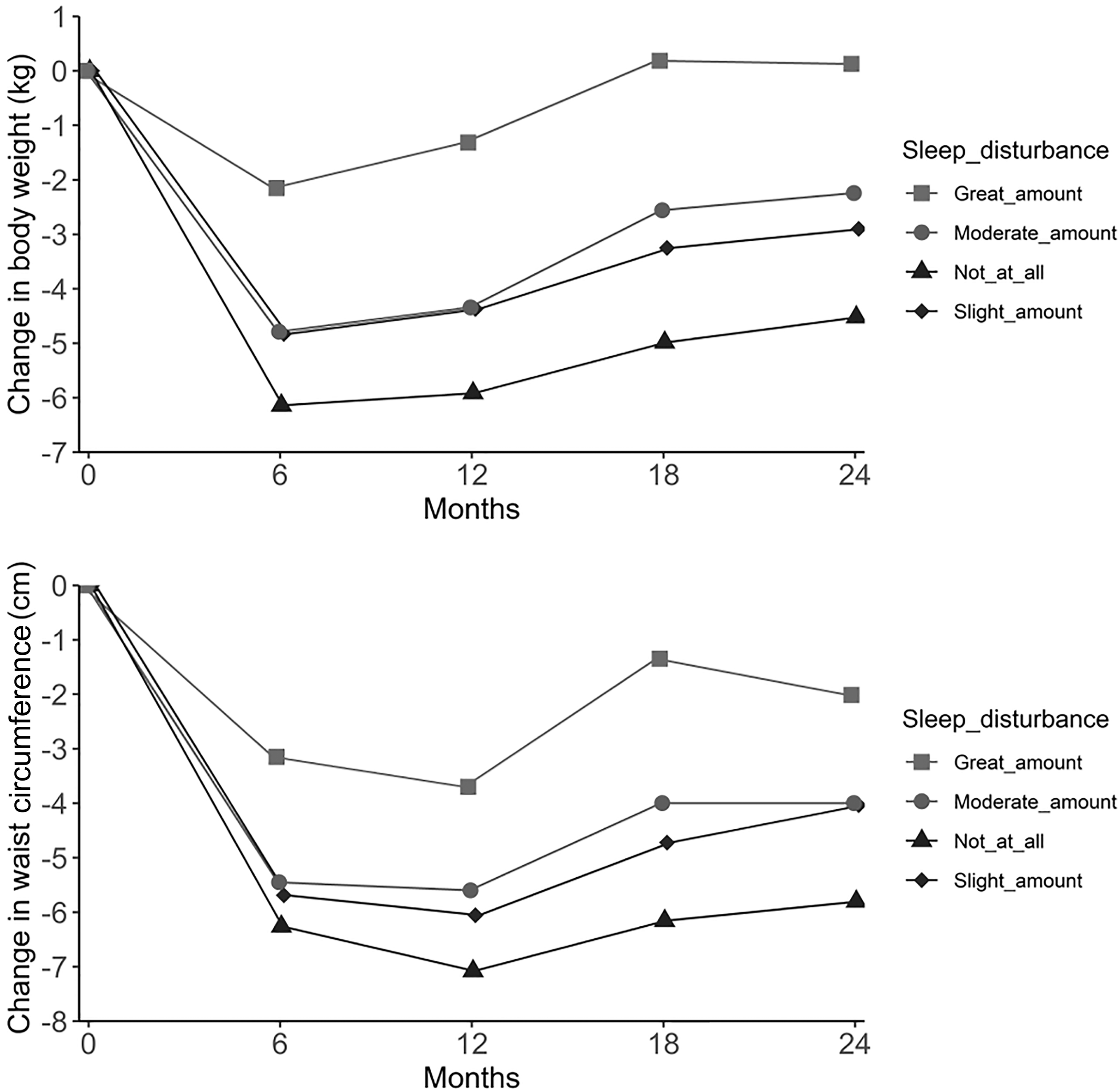

Figure 1—Trajectory of changes in body weight (kilograms) and waist circumference among all participants according to sleep disturbance over 2 years. Data were LS means, adjusted for age, sex, ethnicity, diet, BMI, physical activity score at baseline, and the respective variable (except for the outcome Δ weight) at the previous assessment.

"moderate" disturbance, the results were similarly significant in the main associations and mediation analyses.

DISCUSSION

In this 2-year dietary intervention among participants who were overweight or obese, we found that higher levels of sleep disturbance were significantly associated with less weight loss both at 6 months and over 24 months and elevated risk of failure to lose >5% of initial weight at 6 months. Further, we found that sleep disturbance predicted less loss and larger regains in body fat composition and fat distribution. Our results also indicated that food cravings for carbohydrates/starches, fast-food fats, and sweets, respectively; cravings, prospective consumption, and hunger of appetite measurements; and dietary restraint, inhibition, and hunger subscale mediated the effects of sleep disturbance on weight loss.

In our analysis, levels of sleep disturbance from baseline to 6 months were significantly predictive of risk of failure to lose weight at 6 months. Consistent with our findings, randomized trials focusing on sleep restriction have reported that longer sleep duration favored success

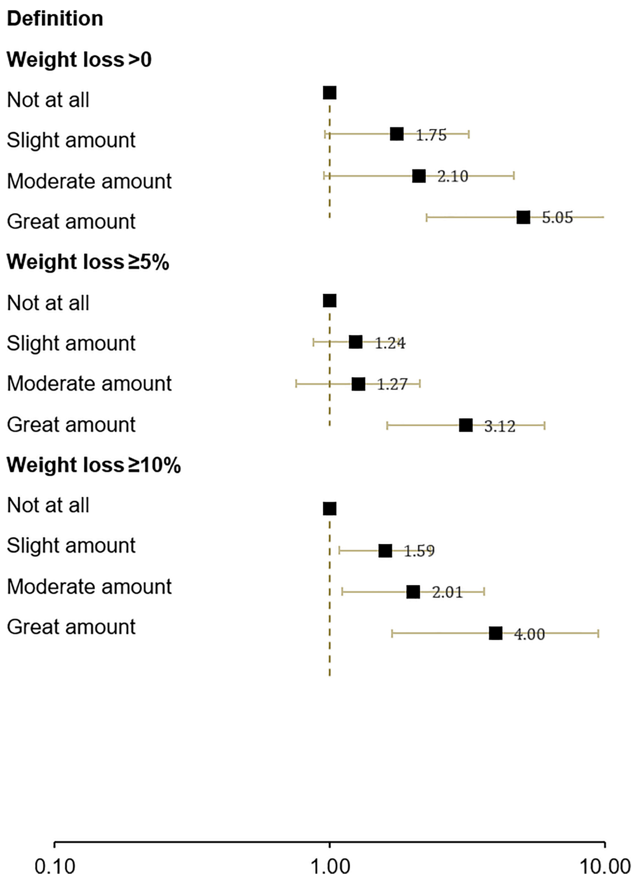

Figure 2—Probability of a failure of successful weight loss at 6 months according to sleep disturbance. ORs after adjustment for age, sex, ethnicity, baseline BMI, physical activity, and diet group. Successful weight loss is defined as weight loss >0%, ≥5%, and 10% of baseline body weight, respectively.

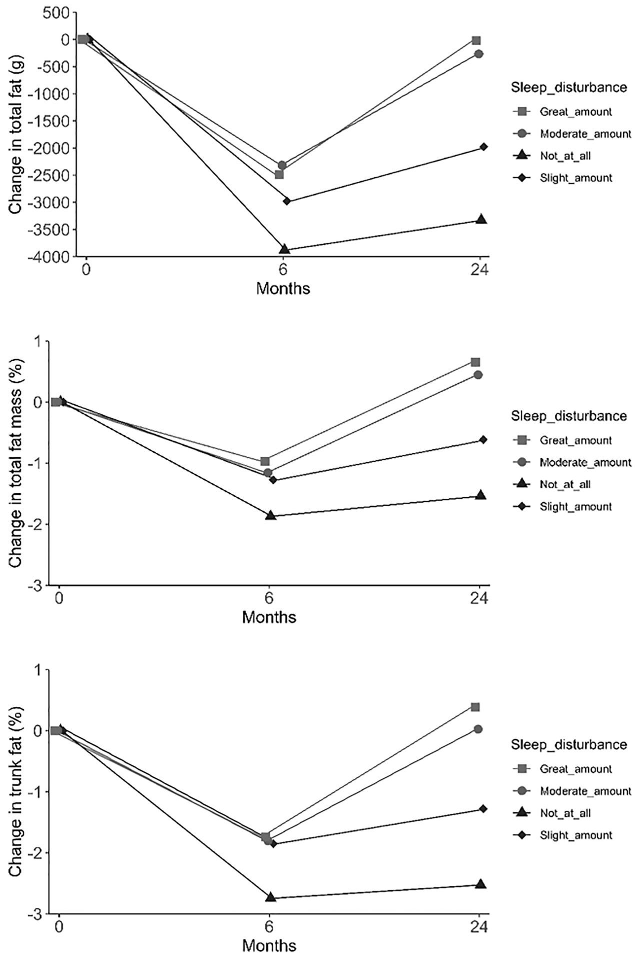

Figure 3—Trajectory of changes in total fat (grams), total fat mass (percentage), and trunk fat (percentage) among all participants according to sleep disturbance over 2 years. Data were LS means, adjusted for age, sex, ethnicity, diet, baseline physical activity, BMI, and the respective variable at previous visit.

of a calorie-restricted weight-loss diet (16,36,37). In contrast to our findings, however, some studies have reported no association between weight loss and sleep restriction among participants during caloric restriction (12,13,18). In another weight-loss intervention trial among 245 women who were obese or overweight, subjective sleep quality and sleep duration, rather than sleep disturbance, predicted success of weight loss at 6 months. These discrepancies may be attributed to varying sample size and different characteristics of study participants, including age, sex, baseline BMI, the extent of sleep disturbance, and adherence to caloric restriction.

Few studies have explored the impact of sleep on body composition and adiposity. In a short, 4-week, randomized crossover study, 10 adults who were overweight spent two 14-day periods in the laboratory with scheduled time-in-bed of 8.5 or 5.5 h/night in random order. After the intervention, the 5.5-h time-in-bed condition resulted in less loss of body fat compared with the 8.5-h time-in-bed condition (P = 0.043) (12). In another 9-month longitudinal study providing a calorie-restricted Mediterranean diet, 224 Caucasian women sleeping 6–8 or >8 h/day had an increased probability of losing fat mass than women who reported sleeping <6 h/day (OR 4.47 [95% CI 1.42, 14.04], P = 0.010; and OR 5.10 [95% CI 1.15, 22.70], P = 0.032, respectively) (17). Similarly, Wang et al. (13) observed that among 41 individuals, after an 8-week intervention, the calorie-restriction group without sleep restriction lost a greater percentage of fat mass within the total mass lost than the calorie-restriction group with sleep restriction (P = 0.016). A recent study conducted among British, Danish, and Portuguese adults suggested that maintaining a consistent sleep onset is associated with improved weight-loss maintenance and fat percentage (38).

To our knowledge, the current investigation was among the largest and longest studies that have examined the role of sleep disturbance on changes in body composition and adiposity during weight loss and weight regain in a controlled clinical trial. Consistently, we found that greater levels of sleep disturbance were related with lower losses in fat mass and fat mass percent at 6 months. Three recent cross-sectional studies reported an inverse

Table 3—Weight loss outcomes after respectively accounting for each mediator from 0 to 6 months (*n* = 648)

Effects	β (SE)*	
Total effect sleep disturbance → weight loss	**−1.06 (−1.51, −0.61)**	
Through mediation variables (analyzed respectively)	Direct effect, β (SE)*	Indirect effect through mediators, β (SE)*†
FCI		
Craving carbohydrates/starches	**−0.98 (0.23)**	**−0.09 (0.04)**
Craving fast-food fats	**−1.00 (0.23)**	**−0.06 (0.04)**
Craving fruits and vegetables	**−1.03 (0.23)**	−0.03 (0.03)
Craving high-fat foods	**−1.05 (0.24)**	−0.02 (0.03)
Craving sweets	**−1.00 (0.23)**	**−0.06 (−0.04)**
FCI total score	**−0.97 (0.24)**	**0.09 (0.05)**
Appetite		
Craving	**−0.98 (0.24)**	**−0.09 (0.04)**
Fullness	**−1.04 (0.23)**	−0.02 (0.02)
Prospective consumption	**−1.02 (0.23)**	**−0.04 (0.03)**
Hunger	**−0.97 (0.23)**	**−0.09 (0.04)**
Total appetite score	**−0.91 (0.23)**	**−0.15 (0.06)**
TFEQ		
Cognitive restraint of eating subscale	**−0.89 (0.22)**	**−0.17 (0.08)**
Disinhibition subscale	**−0.75 (0.23)**	**−0.31 (0.09)**
Hunger subscale	**−0.82 (0.23)**	**−0.24 (0.07)**
FCI total score plus appetite score plus TFEQ	**−0.62 (0.22)**	**−0.44 (0.12)**

Data in boldface are statistically significant mediation effects with 95% confidence. *Adjusted for age, sex, ethnicity, diet, physical activity score, and baseline BMI. Sleep disturbance is coded as an ordinal variable (0, 1, 2, or 3), indicating no, slight, moderate, and great sleep disturbance. †Indirect effect calculated through bootstrap. SEs are reported.

association between sleep problems and trunk fat measurements (39–41). Our analysis extended those findings by showing similar patterns for trunk fat percent in a longitudinal weight loss intervention. Moreover, during the period of weight regain, participants with greater sleep disturbance tended to regain more fat mass, fat mass percentage, and trunk fat.

These findings were partly explained by changes of respiratory quotient toward less oxidation of fat among participants with greater levels of sleep disturbance, suggesting less utilization of fat (12,13). Consistent with past findings of sleep curtailment with elevated ghrelin (42,43), a 24-h experimental study among healthy young men indicated that sleep inhibited the acylation of ghrelin (44). Acylated ghrelin was considered as the only bioactive form of ghrelin (45). Compelling evidence from both animal and human studies has demonstrated its effects to stimulate appetite, promote accumulation of fat, and increase glucose release by hepatocytes to support the availability of fuel to glucose-dependent tissues (46–50). Taken together, we speculate that sleep may interfere with fat metabolism, regardless of baseline weight. Further studies are warranted to investigate the mechanisms underlying our findings.

Mediation analysis suggests that the effects of sleep disturbance may be mediated by change in food cravings, hunger, and appetite (51–54). Our results about food cravings measurements are in concordance with research stating that sleep was inversely associated with cravings for sweets, carbohydrates/starches, and fat (20,51,55). The mediation effect of cravings for carbohydrates/starches is the strongest among the FCI, suggesting that interventions targeting low carbohydrate/starches intake, such as reducing the availability and variety of carbohydrates, may benefit weight loss among people with sleep disturbance (56). Few studies have examined dietary restraint, disinhibition, and their mechanisms relating to sleep disturbance to increased BMI. Dietary restraint and disinhibition are significant predictors of successful weight loss and weight regain after weight-loss regimes (57–59). Aligning with our results, researchers have suggested a significant indirect relationship between sleep quality and BMI via disinhibition in a cross-sectional study (60). Our study further showed the consistency in a longitudinal intervention. Disinhibition refers to the tendency to overeat under circumstances such as being presented with an array of palatable foods or under emotional distress. It has been consistently associated with weight change and showed stronger mediations in contrast to other factors (61). Our findings suggested that to improve disinhibited eating is particularly important for weight-loss interventions among the obese or overweight population with sleep disturbance, like cognitive therapy (62) or use of sibutramine (63). When controlling for all factors noted earlier, the overall mediation effect accounted for 44% of the total effect. However, the direct association between sleep disturbance and weight loss still remained significant, suggesting that partial mediation was present, and further researches about other underlying mechanism are clearly warranted.

Our study has several strengths. We conducted our analysis in thus far the largest and longest weight-loss dietary intervention trial, which could alleviate the potential influences by unknown confounders. Moreover, repeated measures of sleep disturbance improved the validity of our analysis.

Sleep disturbance may be improved after the initiation of a calorie-restricted diet (64,65). Misclassification may be a threat to study validity, if only a baseline assessment is performed. Repeated measurements of sleep disturbance, body weight, body composition, adiposity, and potential mediators, as done in this study, could increase our statistical power and help capture the differences during weight loss and weight regain. Furthermore, a bidirectional relationship may exist between successful weight loss and sleep traits (66). The interpretation of our findings was facilitated by the longitudinal setting. Lastly, the randomized controlled design and validated measurement tools (15,29) would add robustness to our mediation analysis.

However, the results of this study must be interpreted in light of several limitations. First, sleep disturbance was self-reported and retrospectively collected during the diet intervention trial from 2003 to 2007, when objectively measured sleep traits like use of a tracking sensor were unavailable. In addition, secondary data do not allow us to explore different domains of sleep patterns separately (67).

Furthermore, compared with characteristics of a general population of the U.S. in the National Health and Nutrition Examination Survey, the homogeneity among our participants (White, well-educated, nonsmoker, etc.) might undermine the generalizability of our findings.

In conclusion, in this long-term calorie-restricted dietary intervention trial, higher levels of sleep disturbance were significantly associated with less weight loss at 6 months and over the entire 2 years. Changes in body composition and adiposity during weight loss and weight regain were predicted by sleep disturbance. In addition, changes in appetite and food cravings partly mediated the effects of sleep disturbance on weight loss.

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