Insufficient sleep predicts poor weight loss maintenance after one year

Bogh, Adrian F.; Jensen, Simon B K; Juhl, Christian R; Janus, Charlotte; Sandsdal, Rasmus M; Lundgren, Julie R; Noer, Mikkel H.; Vu, Nhu Q.; Fiorenza, Matteo; Stallknecht, Bente M; Holst, Jens J.; Madsbad, Sten; Torekov, Signe S.

Published in:
Sleep

DOI:
10.1093/sleep/zsac295

Publication date:
2023

Document version
Publisher's PDF, also known as Version of record

Document license:
CC BY-NC

Citation for published version (APA):
Insufficient sleep predicts poor weight loss maintenance after 1 year

Adrian F. Bogh1,†, Simon B. K. Jensen1,†, Christian R. Juhl1, Charlotte Janus1, Rasmus M. Sandsdal1,†, Julie R. Lundgren1, Mikkel H. Noer1,†, Nhu Q. Vu1,†, Matteo Fiorenza1, Bente M. Stallknecht1, Jens J. Holst1,2, Sten Madsbad3 and Signe S. Torekov1,*

1Department of Biomedical Sciences, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark, 2Novo Nordisk Foundation Center for Basic Metabolic Research, University of Copenhagen, Copenhagen, Denmark and 3Department of Endocrinology, Hvidovre University Hospital, Copenhagen, Denmark

†These authors contributed equally to the work.

*Corresponding author. Signe S. Torekov, Department of Biomedical Sciences, University of Copenhagen, Panum Rm. 12 4 6, Blegdamsvej 3B, DK-2200 Copenhagen N, Denmark. Email: torekov@sund.ku.dk

Abstract

Study Objectives: Insufficient sleep may attenuate weight loss, but the role of sleep in weight loss maintenance is unknown. Since weight regain after weight loss remains a major obstacle in obesity treatment, we investigated whether insufficient sleep predicts weight regain during weight loss maintenance.

Methods: In a randomized, controlled, two-by-two factorial study, 195 adults with obesity completed an 8-week low-calorie diet and were randomly assigned to 1-year weight loss maintenance with or without exercise and liraglutide 3.0 mg/day or placebo. Sleep duration and quality were measured before and after the low-calorie diet and during weight maintenance using wrist-worn accelerometers (GENEActiv) and Pittsburgh Sleep Quality Index (PSQI). To test associations between insufficient sleep and weight regain, participants were stratified at randomization into subgroups according to sleep duration (</=6 h/night) or sleep quality (PSQI score ≤/>5).

Results: After a diet-induced 13.1 kg weight loss, participants with short sleep duration at randomization regained 5.3 kg body weight (p = .0008) and had less reduction in body fat percentage compared with participants with normal sleep duration (p = .007) during the 1-year weight maintenance phase. Participants with poor sleep quality before the weight loss regained 3.5 kg body weight compared with good quality sleepers (p = .010). During the weight maintenance phase, participants undergoing liraglutide treatment displayed increased sleep duration compared with placebo after 26 weeks (5 vs. −15 min/night) but not after 1 year. Participants undergoing exercise treatment preserved the sleep quality improvements attained from the initial weight loss.

Conclusions: Short sleep duration or poor sleep quality was associated with weight regain after weight loss in adults with obesity.

Key words: sleep duration; sleep quality; weight loss maintenance; obesity; exercise; GLP-1 receptor agonist

Graphical Abstract

Insufficient sleep predicts poor weight loss maintenance after one year

Objective

Population and intervention

Findings

Measurements and outcomes

Conclusion

Short sleep duration or poor sleep quality was associated with weight regain after weight loss in adults with obesity
Introduction

Sleep disturbances are prevalent in modern society. Objective assessments of sleep duration indicate that 22%-53% of adults across various nationalities sleep less than 6 h/night [1, 2]. This contrasts with the 7-9 h/night of sleep recommended for adults according to The National Sleep Foundation, The American Thoracic Society, and The American Academy of Sleep Research and Sleep Research Society [3-5]. Short sleep duration, defined as less than 6 h/night, is associated with all-cause mortality, cardiovascular diseases, hypertension, diabetes, and obesity [6, 7], and is therefore clinically relevant. Sleep restriction causes metabolic and behavioral changes that seem to affect glucose metabolism, increase appetite and energy intake [8, 9], and decrease physical activity [10, 11], suggesting that short sleep duration may contribute to the development of obesity.

Few longitudinal studies have examined associations between insufficient sleep and change in weight during weight loss interventions. One study found objective short sleep duration to be associated with less reduction in waist circumference compared with adequate sleepers after 12 months [12]. During a 2-year diet intervention, greater sleep disturbances were associated with less weight loss and decreased odds of achieving ≥5% weight loss after 6 months [13]. For women participating in a weight loss intervention, longer subjective sleep duration and better sleep quality, as measured by the Pittsburgh Sleep Quality Index (PSQI), were associated with an increased likelihood of weight loss success [14]. In a study combining questionnaire and accelerometer data to produce an overall sleep health score, better sleep health was associated with greater weight loss during a behavioral weight loss intervention [15]. Insufficient sleep may affect adherence to physical and dietary recommendations, ultimately reducing the effectiveness of such interventions to reduce body weight [16].

One major obstacle in treating obesity is that weight regain often occurs after weight loss [17]. In this context, it is understudied whether insufficient sleep impacts weight loss maintenance after an initial weight loss. While some studies have indicated that insufficient sleep can hinder the maintenance of weight loss [18-20], a methodological limitation of these studies is that they rely solely on self-reported measures of sleep duration and quality, which introduces self-reporting bias. This is often seen in the discrepancy between objective and subjective sleep measures [21, 22] and it is unclear whether subjective and objective sleep measures capture equivalent features or assess different sleep phenomena [23].

Physical activity and weight loss are considered beneficial for sleep. Regular exercise has been shown to improve total sleep duration, time spent in deep sleep, and self-reported sleep quality [24]. However, most exercise studies are short term, and the benefits of exercise on sleep after weight loss have not been investigated.

Glucagon-like peptide-1 receptor agonists (GLP-1 RA) inhibit appetite and lower body weight [25] and may, therefore, also improve sleep. However, despite the increasing use of GLP-1 RA in the treatment of obesity, data on their effect on sleep is limited. In a 32-week study including patients with obstructive sleep apnea, the GLP-1 RA liraglutide 3.0 mg did not affect sleep duration, measured by polysomnography, but improved sleep apnea severity [26]. In patients with type 2 diabetes, liraglutide decreased daytime sleepiness [27]. Whether GLP-1 RA improves sleep during weight loss maintenance in patients with obesity has not been investigated.

The present study is based on data from the S-LiTE randomized, controlled trial [28, 29]. Using repeatedly measured accelerometer (objective) and self-reported (subjective) sleep data from 195 adults with obesity, the primary aim of the present study was to investigate associations between short sleep duration or poor sleep quality and weight regain after weight loss. Second, we investigated the effects of exercise and liraglutide on sleep duration and sleep quality during weight loss maintenance.

Methods

Trial design

We analyzed data from the S-LiTE randomized, controlled trial, which was conducted from August 2016 to November 2019 at Hvidovre Hospital and University of Copenhagen, Denmark (EudraCT number, 2015-005585-32; ClinicalTrials.gov number, NCT04122716). The primary and secondary outcomes (change in body weight and fat percentage), and the study protocol have been published previously [28, 29]. The trial followed the principles of the Declaration of Helsinki and Good Clinical Practice guidelines and was approved by the local ethics committee (H-16027082) and the Danish Medicines Agency. Participants provided written informed consent prior to inclusion.
Participants followed a low-calorie diet (800 kcal/day, Cambridge Weight Plan) for eight weeks prior to randomization. Those who lost at least 5% of initial weight were randomized, stratified according to age (<40 years) and sex, in a two-by-two factorial design to a 52-week weight maintenance phase with or without exercise and liraglutide 3.0 mg/day or placebo. Investigators and participants were blinded regarding placebo versus liraglutide assignments.

Study population
Eligible participants were adults (18–65 years of age) with obesity (BMI 32–43 kg/m²). Exclusion criteria included any known serious chronic illnesses such as diabetes type 1 and 2 (a full list is available with the protocol [28]).

Interventions
Participants randomized to exercise were encouraged to attend two weekly supervised sessions of 45 min duration along with two weekly sessions of 30 min performed individually. The supervised sessions involved interval-based spinning and circuit training. The individual sessions comprised aerobic exercise, mostly in the form of cycling, rowing, running, brisk walking, and active commuting. During all sessions, a sports watch with heart rate monitor (Polar A300) was worn to ensure protocol adherence during exercise volume. Participants who were not randomized to exercise were instructed to maintain habitual physical activity.

Liraglutide or volume-matched placebo was injected subcutaneously with an initial dose of 0.6 mg/day with weekly increments of 0.6 mg until 3.0 mg/day or the highest dose at which participants did not have unacceptable adverse events.

To support weight maintenance after weight loss, all participants attended monthly consultations with weighing and dietetic support in accordance with recommendations from the Danish authorities.

Sleep assessment
Accelerometer and data processing
The GENEActiv (Activinsights Ltd., Cambridgeshire, UK), a triaxial, wrist-worn accelerometer was used to obtain objective sleep parameters. Assessing sleep with accelerometer is less invasive and more applicable when used for consecutive days compared with “gold standard” polysomnography [30]. Participants were instructed to wear the accelerometer on their non-dominant wrist for 24 h/day for seven consecutive days on five occasions: before (week −8) and after (week 0) the low-calorie diet, week 13, week 26, and end of intervention (week 52). During these periods, participants kept a sleep log, including bedtime and get-up time. Sample frequency was set to 75 Hz, and the raw accelerometer data were processed using the R-package GGIR (version 1.11) [31]. Sleep duration was calculated from accumulated data of sustained inactivity, defined as time periods of minimum 5 minutes with less than five degrees change in wrist angle in the nocturnal window (time between bedtime and get-up time) [32]. Sleep efficiency was calculated as the percentage time in bed where the individual was sleeping: total sleep/total bedtime × 100. Sedentary time was calculated using a cut-off of <40 milligravity (m, 1 g = 9.81 m/s²) [33]. Accelerometer non-wear time was estimated as previously described [34]. Files with data available for less than 16 h/day on three consecutive days were excluded from the analyses.

Self-reported sleep quality and duration
Subjective sleep quality was assessed using a Danish version of the PSQI [35]. Participants filled out the questionnaire before (week −8) and after (week 0) the low-calorie diet and at the end of intervention (week 52). The questionnaire consists of 19 questions regarding a variety of factors related to sleep quality in the past month prior to questionnaire completion. These questions are combined into seven component scores, each ranging from 0 to 3, with 0 indicating no difficulty and 3 indicating severe difficulty. The seven components are: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. All component scores are then added together, yielding a PSQI global score ranging from 0 to 21. The higher the score, the worse the subjective sleep quality. A global score of >5 has high diagnostic sensitivity and specificity in distinguishing between poor and good sleepers [35]. A meta-analysis of 37 studies showed strong validity and reliability of the PSQI, suggesting the instrument works as intended [36]. To further investigate which parts of sleep quality that were affected by treatment and which parts that could potentially predict weight loss and weight maintenance, the PSQI components were calculated into its three factors: sleep efficiency (comprising the sleep duration and habitual sleep efficiency components), perceived sleep quality (comprising the components subjective sleep quality, sleep latency, and sleeping medication use), and daily disturbances (comprising sleep disturbances and daytime dysfunction) [37]. This three-factor scoring model has shown to be statistically favored over the PSQI global score to reflect the response to the PSQI questionnaire [37, 38]. Self-reported sleep duration was assessed via PSQI through the following question (translated from Danish to English): "During the past month, how many hours of actual sleep did you get per night? (The number of hours of sleep may be different from the actual number of hours spent in bed)."

Body composition
Dual-energy X-ray absorptiometry (Hologic Discovery, Bedford) scans were performed before (week −8) and after (week 0) the low-calorie-diet, and at week 52, to measure total fat and lean mass. Total body fat percentage was calculated as fat mass (kg)/body weight (kg) × 100.

Measurement of circulating leptin, soluble leptin receptor, and the free leptin index
Plasma leptin was measured by radioimmunoassay (Merck KGaA, Damstadt, Germany). Plasma soluble leptin receptor was measured by ELISA (R&D Systems Inc., Minneapolis, MN). The free leptin index was calculated as leptin concentration/soluble leptin receptor concentration × 100 [39].

Statistical analysis
To test the hypothesis that short sleep duration is associated with weight gain after weight loss, participants were stratified into subgroups according to their objective sleep duration at randomization (after the low-calorie diet): short sleep duration (<6 h/night) and normal sleep duration (≥6 h/night). The <6 h/night cutoff was chosen because it is a prevalent sleep behavior when assessed with accelerometry [1, 2]. Less than 6 h/night has frequently been used in previous studies to identify short sleepers [40–42]. Furthermore, sleeping <6 h/night has in epidemiological studies consistently been associated with adverse health outcomes, such as all-cause mortality, diabetes, cardiovascular diseases, hypertension, and obesity [6, 7], and is thus clinically relevant.
Change in weight was analyzed using a linear mixed model with time, sleep duration (<26 h/night), time × sleep duration interaction, sex, age group (<40 years or ≥40 years), intervention group, and time × intervention group interaction included as fixed effects. Model specifications included an unstructured covariance and a repeated effect for time on participant level. The effect of short sleep on change in body composition was also investigated. As sleep apnea is a potential confounder in sleep research, we performed sensitivity analyses excluding participants with potential obstructive sleep apnea. Following an approach previously used [43, 44], potential obstructive sleep apnea was defined as either loud snoring more than 2 nights/week or respiratory pauses during sleep at least 1–2 times/week.

To further explore the impact of sleep quality and duration on weight loss and weight maintenance, we performed multiple linear regression analyses with change in weight or fat percentage as dependent variable and values of the sleep quality factors (sleep efficiency, perceived sleep quality, and daily disturbances), PSQI global score, or sleep duration as explanatory variable, together with age group, sex, and baseline weight/fat percentage value. Sleep values before the low-calorie diet were used in the analyses of changes in outcomes during the low-calorie diet. For analyses of changes during weight maintenance, sleep values from after the low-calorie diet were used, and intervention group was included as covariate in the model.

Based on the PSQI global score, we stratified participants into poor (>5) and good sleep quality (≤5). Using this method, we investigated whether poor sleep quality would predict the magnitude of weight loss during the low-calorie diet and changes in weight during 1-year weight maintenance.

Finally, to investigate the effects of exercise and liraglutide on sleep during weight loss maintenance, we tested exercise groups versus non-exercising control groups and the liraglutide groups versus placebo groups using linear mixed models with time, treatment group, time × treatment group, sex, and age group as fixed effects. All analyses were performed in the intention-to-treat population, which included all randomized participants. Per-protocol analyses were also performed, which included participants with adequate adherence to the study interventions. For exercise interventions, this was defined as completing ≥75% of WHO’s minimum recommendations on physical activity for health in adults: at least 150 min/week of moderate-intensity aerobic physical activity, 75 min/week of vigorous-intensity aerobic physical activity, or an equivalent combination of both [45]. For study medication, adequate adherence was defined as having administered ≥75% of the study medication use (comprising the PSQI components subjective sleep quality, sleep latency, and sleep medication use) the corresponding weight loss was 0.35 kg less (p = .033) (Table 1).

Results

Study flow

A flow chart of study participants with available data and reasons for missing accelerometer data is shown in Supplementary Figure S1. A total of 195 participants completed the low-calorie diet and underwent randomization. Of these, accelerometer data were available for 159 participants, and PSQI data were available for 187 participants. In total, 166 (85%) participants attended the final assessment of body weight (52 weeks after randomization), for which valid accelerometer data were available for 119 participants and a PSQI global score was available for 161 participants. Before the low-calorie diet, overall mean sleep duration was 6.07 ± 0.83 h/night as measured by accelerometer, mean self-reported sleep duration was 6.60 ± 1.05 h/night, and self-reported sleep quality (PSQI global score) was 6.1 ± 3.1, indicating poor sleep quality (>5) on average. Based on the PSQI data, 48 (24%) participants had potential sleep apnea before the low-calorie diet.

Impact of sleep on low-calorie diet-induced weight loss

The 8-week low-calorie diet induced a mean weight loss of 13.1 kg (95% CI = 12.4 to 13.7) and a mean decrease in fat percentage of 2.3 %–points (95% CI = 2.1 to 2.6) [29].

Multiple linear regression models showed that worse sleep quality was associated with less weight loss during the low-calorie diet (Table 1). For each increment in PSQI global score, the corresponding weight loss was 0.19 kg less (p = .022). Likewise, for each increment in the factor perceived sleep quality (comprising the PSQI components subjective sleep quality, sleep latency, and sleep medication use) the corresponding weight loss was 0.35 kg less (p = .033) (Table 1).

Results for participants categorized before the low-calorie diet with either short vs. normal sleep duration or poor vs. good sleep quality are shown in Supplementary Table S1. After the low-calorie diet, sleep duration, as measured by accelerometer, increased by 17 min/night (95% CI = 9 to 24). Self-reported sleep duration increased by 9 min/night (95% CI = 0 to 17), and sleep efficiency increased by 2.1% (95% CI = 1.3 to 3.0). PSQI global score decreased by −0.8 (95% CI = −1.2 to −0.4), indicating improved sleep quality. All the PSQI factors were improved; sleep efficiency (−0.24; 95% CI = −0.46 to −0.02), perceived sleep quality (−0.31; 95% CI = −0.51 to −0.11), and daily disturbances (−0.24; 95% CI = −0.36 to −0.11). Potential sleep apnea was detected in 24 (13%) of the study participants after the low-calorie diet.

Table 1. Associations between sleep habits and change in weight and body composition in response to 8-week low-calorie diet

<table>
<thead>
<tr>
<th></th>
<th>Objective sleep duration (h/night)</th>
<th>PSQI global score</th>
<th>Sleep efficiency</th>
<th>Perceived Sleep quality score</th>
<th>Daily disturbances</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ß (95% CI)</td>
<td>ß (95% CI)</td>
<td>ß (95% CI)</td>
<td>ß (95% CI)</td>
<td>ß (95% CI)</td>
</tr>
<tr>
<td>Δ Body weight, kg</td>
<td>0.03 (−0.64 to 0.70)</td>
<td>0.19 (0.03 to 0.35)</td>
<td>0.31 (−0.02 to 0.63)</td>
<td>0.35 (0.03 to 0.68)</td>
<td>0.23 (−0.33 to 0.78)</td>
</tr>
<tr>
<td>Δ Fat percentage, %–points</td>
<td>0.00 (−0.01 to 0.01)</td>
<td>0.02 (−0.06 to 0.10)</td>
<td>−0.02 (−0.19 to 0.14)</td>
<td>0.00 (−0.16 to 0.16)</td>
<td>0.26 (−0.01 to 0.53)</td>
</tr>
</tbody>
</table>

Data are presented as unstandardized regression coefficients (ß) (95% CI). Values in boldface indicate statistical significance. Sleep values were measured before the low-calorie diet. Objective sleep duration was measured by wrist-worn accelerometer. PSQI global score, sleep efficiency, perceived sleep quality and daily disturbances were all derived from the PSQI. Higher scores indicate worse sleep quality. Thus, a positive regression coefficient means less weight/fat percentage reduction with worse sleep quality.
Impact of sleep duration on weight loss maintenance

At randomization, immediately after the diet-induced weight loss, we identified 48 participants with short sleep duration, defined as accelerometer-measured mean sleep duration of <6 h/night. Conversely, 111 participants had a mean sleep duration of ≥6 h/night, which was characterized as normal sleep duration. Characteristics of short and normal sleepers at randomization are shown in Table 2. We assessed potential differences between participants with short and normal sleep duration in order to identify potential mechanisms underlying different weight trajectories. Short sleepers (mean sleep duration of 5.38 h/night) and normal sleepers (mean sleep duration of 6.80 h/night) had similar age and BMI, and there was an even distribution across the four randomization groups. We found that short sleepers spent 56 min (p = .001) more per day being sedentary. Short sleepers also tended to have a lower free leptin index, a measure of leptin bioavailability, compared with normal sleepers (−29%, p = .07).

After the 52-week weight maintenance phase, short sleepers regained body weight in contrast to normal sleepers who maintained weight loss (Figure 1A and Table 3). Furthermore, after 52 weeks, body fat percentage was decreased in normal sleepers compared with short sleepers (Figure 1B). This was mainly a result of fat mass loss in normal sleepers not seen in short sleepers (Table 3). Excluding participants with potential obstructive sleep apnea [n = 8 (17%) and n = 11 (10%) with short and normal sleep duration, respectively] did not change the outcome of these analyses (Supplementary Table S2). Linear regression analyses showed that for each hour increase in mean sleep duration after diet-induced weight loss, the change in body weight after 52 weeks was −1.7 kg (p = .073) while change in body fat percentage was −0.80 %-points (p = .026) (Table 4).

Impact of sleep quality on weight loss maintenance

At randomization, 73 participants were categorized as having poor sleep quality (PSQI global score > 5), and 114 participants had good sleep quality. Poor sleepers (mean PSQI global score of 8.2) and good sleepers (mean PSQI global score of 3.3) were similar with regards to age and BMI at randomization and were evenly distributed across randomization groups (Supplementary Table S3). The difference in weight change during weight maintenance was 1.5 kg (p = .27) and fat percentage by 0.1 %-points (p = .91) in favor of the good quality sleepers. A worse global PSQI score after diet-induced weight loss tended to be associated with weight regain (p = .052) and increased fat percentage (p = .087) during weight maintenance (Table 4).

When participants were categorized as having either good or poor sleep quality before the low-calorie diet (at study inclusion), good quality sleepers had a larger decrease in body weight (−3.5 kg; p = .010) and body fat percentage (−1.3 %-points; p = .018) during the study period as a whole (low-calorie diet + weight loss maintenance) compared with poor quality sleepers (Supplementary Table S4). Specifically, worse perceived sleep quality and higher daily disturbances were associated with less weight loss throughout the whole study period and daily disturbances were associated with attenuated fat loss (Supplementary Table S5).

Effects of weight loss maintenance with exercise on sleep

From randomization to week 52, weight loss was maintained for exercise groups compared with regain in the non-exercising control groups (Figure 2A). Accelerometer-measured sleep duration decreased in both the exercise and non-exercising groups, with no differences between groups (Figure 2B and Supplementary Table S6). Sleep efficiency also decreased in the exercise and non-exercising groups, calculated as (estimated ratio − 1) × 100.

Table 2. Characteristics of participants with short and normal sleep duration after low-calorie diet-induced weight loss

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Short sleep (n = 48)†</th>
<th>Normal sleep (n = 111)</th>
<th>Mean difference‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss during low-calorie diet, kg</td>
<td>−14.1 (−15.4 to −12.8)§</td>
<td>−12.9 (−13.7 to −12.0)†</td>
<td>−1.3 (−2.8 to 0.3)</td>
</tr>
<tr>
<td>Sleep duration, min/night</td>
<td>323 ± 26</td>
<td>408 ± 31</td>
<td>−85 (−95 to −75)</td>
</tr>
<tr>
<td>Male/female, n(%)</td>
<td>24/24 (50%/50%)</td>
<td>31/80 (28%/72%)</td>
<td>—</td>
</tr>
<tr>
<td>Age, years</td>
<td>45 ± 12</td>
<td>43 ± 11</td>
<td>1.4 (−2.6 to 5.3)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>32.8 ± 2.7</td>
<td>32.7 ± 3.0</td>
<td>0.1 (−0.9 to 1.1)</td>
</tr>
<tr>
<td>Fat mass, kg</td>
<td>37.5 ± 3.5</td>
<td>38.1 ± 7.5</td>
<td>−0.6 (−3.2 to 1.9)</td>
</tr>
<tr>
<td>Sedentary time, min/day</td>
<td>682 ± 104</td>
<td>626 ± 83</td>
<td>56 (26 to 87)</td>
</tr>
<tr>
<td>Leptin, ng/mL</td>
<td>19 (9, 33)†</td>
<td>22 (11, 34)‡</td>
<td>−13% (−35 to 18)‡</td>
</tr>
<tr>
<td>Soluble leptin receptor, ng/mL</td>
<td>21.4 ± 7.3</td>
<td>19.2 ± 7.1</td>
<td>2.2 (−0.5 to 5.0)</td>
</tr>
<tr>
<td>Free leptin index</td>
<td>102 (32, 161)†</td>
<td>126 (66, 214)‡</td>
<td>−29% (−51 to 3)‡</td>
</tr>
<tr>
<td>Potential, unidentified obstructive sleep apnea, n(%)§</td>
<td>8 (17%)</td>
<td>11 (10%)</td>
<td>—</td>
</tr>
<tr>
<td>Randomization group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo, n(%)</td>
<td>10 (21%)</td>
<td>29 (26%)</td>
<td>—</td>
</tr>
<tr>
<td>Exercise + placebo, n(%)</td>
<td>9 (19%)</td>
<td>34 (31%)</td>
<td>—</td>
</tr>
<tr>
<td>Liraglutide, n(%)</td>
<td>15 (31%)</td>
<td>22 (20%)</td>
<td>—</td>
</tr>
<tr>
<td>Exercise + liraglutide, n(%)</td>
<td>14 (29%)</td>
<td>26 (23%)</td>
<td>—</td>
</tr>
</tbody>
</table>

†Short sleep duration was defined as sleeping fewer than 6 h/night on average and normal sleep duration was defined as 6 h/night or above measured by wrist-worn accelerometry. Plus-minus values are observed means and standard deviation after the low-calorie diet (at week 0).
‡Mean difference with 95% confidence interval. Values in boldface indicate statistically significant differences between groups.
§These outcomes were initially analyzed on a log scale. For presentation, these outcomes were back-transformed and expressed as percentage difference between groups, calculated as (estimated ratio − 1) × 100.
¶Values are median and interquartile range.
§Potential, unidentified obstructive sleep apnea was based on the PSQI, defined as either loud snoring more than two nights per week or respiratory pauses during sleep at least 1–2 times per week.
non-exercise groups with no difference between the two groups (Supplementary Table S6). At week 52, the exercise groups maintained the increments in self-reported sleep quality attained from the low-calorie diet, whereas the non-exercise groups relapsed (Figure 2C). The factors that improved with exercise as compared with control were daily disturbances (p < .001) and perceived sleep quality (p = .05) (Supplementary Table S6). The per-protocol analyses supported the conclusions of the intention-to-treat analyses (Supplementary Table S7).

**Effect of weight loss maintenance with liraglutide on sleep**

For participants assigned to liraglutide groups, weight loss was maintained compared with regain in the placebo groups (Figure 3A). Liraglutide led to increased accelerometer-measured sleep duration compared with placebo after 26 weeks (5 vs. −15 min/night). However, at week 52, liraglutide groups decreased their sleep duration, and there was no difference compared with placebo (Figure 3B and Supplementary Table S8). Sleep efficiency...
decreased in the liraglutide and placebo groups, with no difference between the two groups (Supplementary Table S8). No significant difference in sleep quality was observed for the liraglutide groups compared with the placebo groups (Figure 3C and Supplementary Table S8). The per-protocol analyses supported the intention-to-treat analyses (Supplementary Table S9).

**Discussion**

We investigated the role of insufficient sleep during a low-calorie diet-induced weight loss and a subsequent 1-year weight maintenance period with exercise and/or liraglutide in adults with obesity. The primary finding was that short objective sleep duration was associated with weight regain and attenuated improvements in body composition 1 year after weight loss, independent of intervention allocation, age, and sex. Worse perceived sleep quality was associated with less weight loss during the low-calorie diet. A higher degree of self-reported daily disturbances, characterized by disturbed sleeping and daily dysfunction, was also associated with less reduction in body weight and fat percentage during the whole study period. Finally, exercise retained the low-calorie diet-induced improvements in sleep quality during weight maintenance, whereas liraglutide treatment initially increased sleep duration after weight loss.

We investigated the association between objectively measured sleep duration and change in weight and body composition during a weight loss maintenance intervention. The notion of short sleep duration as a risk factor for weight regain is supported by prospective cohort studies, linking short sleep duration to increased risk of developing obesity [46–48], as well as short-term sleep restriction studies showing increased energy intake [8, 9, 49–51] and attenuated fat loss during calorie restriction [52]. Here, we identify habitual sleep duration of less than 6 h/night as a significant risk factor for weight regain and attenuated fat loss during weight loss maintenance interventions with lifestyle and/or pharmacological treatment.

We observed no associations between short objective sleep duration and weight loss or changes in body composition during the 8-week low-calorie diet. This contrasts with previous studies showing blunted weight loss with short sleep duration during lifestyle interventions [12, 14, 15, 53]. This may be explained by the controlled setting of the low-calorie diet in the present study comprising total diet replacement and greater energy deficit, leaving less possibility for short sleep to affect energy balance and intervention adherence. Notably, worse perceived sleep quality was associated with less weight loss during the low-calorie diet, suggesting that even in this controlled setting, sleep may be important to consider for optimal success during dieting. In addition, participants who were categorized as poor-quality sleepers at the initiation of the study had less body weight and fat percentage reductions compared with participants with good quality sleep.

Higher ratings of sleep disturbances in our study were also associated with less weight loss and reduction in fat percentage during the whole study period. These findings agree with a recent study, where higher levels of self-reported sleep disturbances were associated with less weight loss and less body fat loss during a 2-year diet intervention [13]. Our results support the notion that insufficient sleep may counteract efforts to lose weight and maintain healthy weight after a diet-induced weight loss. Thus, characterization of sleep habits may be important for people initiating a weight loss program with lifestyle interventions and/or pharmaceutical treatment. In support, shifting self-reported sleep duration from short (<6 h/night) to a "healthy" length (7–8 h/night) was associated with lower gain of body weight and fat mass over a 6-year follow-up period, compared with short sleepers who maintained their short sleep duration [54]. In a 2-week, randomized, controlled trial, sleep hygiene counselling led to a 1.2 h/night increase in objective sleep duration in habitually sleep-curtailed adults with overweight [55]. This intervention resulted in reduced energy intake and body weight [55]. Future studies should investigate whether interventions targeting sleep habits can improve long-term weight outcomes in people with obesity and insufficient sleep engaging in weight loss or weight maintenance regimens.

The low-calorie diet-induced weight loss increased sleep duration and improved sleep quality. The latter was maintained by exercise. The benefits of exercise were driven by maintained improvements in the factors perceived sleep quality and daily disturbances, which worsened in the non-exercising groups during the weight maintenance phase. We did not observe any change in objective or subjective sleep duration with exercise compared with the control group. A study using polysomnography showed that 12 months of exercise resulted in less time spent in the early sleep stage 1 and a greater amount of time spent in the deeper stage 2 [56]. Thus, exercise may impact sleep stages rather than the total sleep duration. A meta-analysis showed a small beneficial effect of regular exercise on sleep duration and a moderate effect on sleep quality [24]. Our findings extend this notion to weight loss maintenance and support recommendations of regular physical activity to maintain and possibly improve sleep quality in adults with obesity after weight loss.

The increased sleep duration obtained from the low-calorie diet was maintained for the first 26 weeks in the liraglutide groups, but not after 52 weeks. In patients with obesity and obstructive sleep apnea, 32 weeks of liraglutide 3.0 mg/day did not affect sleep duration but led to reductions in sleep apnea severity [26]. Sleep duration was assessed by polysomnography in
In our study, no participants had a known clinical diagnosis of obstructive sleep apnea and sleep duration was assessed via accelerometers, which reflects an individual’s sleep in their habitual environment.

We explored putative correlates underlying differences between short and normal sleepers. We observed that short sleepers spent more time being sedentary during waking hours than normal sleepers. Since sedentary time is associated with obesity...
and lower active energy expenditure [58], this may increase body weight. Furthermore, short sleepers tended to have a lower free leptin index, a biomarker of leptin bioavailability, than normal sleepers. This finding suggests an association between sleep duration and the appetite-suppressing action of leptin and is in line with prior studies showing reduced leptin levels in response to sleep restriction [8, 59]. This may ultimately promote increased food intake.

Figure 3. Changes in (A) body weight, (B) sleep duration, and (C) sleep quality during a low-calorie diet (shaded area; week −8 to week 0) and during 1 year of weight maintenance with either liraglutide 3.0 mg (blue color; n = 98) or control (gray color; n = 98) in the intention-to-treat population. Values are estimated mean ± SE changes from week 0 (randomization). Values at randomization were set to 0. Between-group differences are estimated mean differences with 95% confidence intervals. Sleep quality was measured with the PSQI, with a lower score denoting better sleep quality. Sleep duration was measured by wrist-worn accelerometry.
A strength of this study is the use of objective and subjective sleep measures at multiple intervals during weight loss and 1-year weight loss maintenance. Another strength is the inclusion of body composition measures from dual-energy X-ray absorptiometry. Also, the randomized, controlled design preceded by a low-calorie diet allowed us to investigate associations between sleep and both weight loss and weight loss maintenance in the same population, whereas most studies within this area only have a weight loss phase [12–16, 52]. The study also has limitations. Sleep was a predefined exploratory endpoint in the study. Thus, objective sleep apnea, which is known to be an important confounder in sleep research, was not part of the inclusion or exclusion criteria. However, none of the participants had a known clinical obstructive sleep apnea diagnosis at inclusion. This finding agrees with the notion that the majority of people with obstructive sleep apnea are undiagnosed. Indeed, in previous assessments of obstructive sleep apnea in weight loss interventions, a high prevalence (36%–64%) was found in populations with overweight obesity without previously known sleep apnea [60–62]. In our study, we aimed to include a representative cohort of the population with obesity. We identified potential obstructive sleep apnea from the PSQI questions regarding snoring and breathing [43, 44]. Twenty-four percent of the study participants were identified as having potential sleep apnea at study inclusion, which may be an underestimation based on previous studies using clinical, diagnostic assessments of sleep apnea. Excluding participants categorized with potential obstructive sleep apnea from the analyses did not change the findings of our study. Thus, our observations of obesity and sleep seem to represent the general population with obesity, both with and without potential obstructive sleep apnea. Another limitation is that we cannot prove causal inferences that the observed differences in weight change between short and normal sleepers were directly attributable to sleep duration.

In summary, participants with objectively measured short sleep duration after a diet-induced weight loss had less success during weight loss maintenance than those with longer sleep duration. Worse sleep quality was associated with less weight loss during a low-calorie diet and subsequent weight maintenance. These findings indicate that insufficient sleep predicts weight regain during interventional efforts to maintain weight loss. Exercise maintained low-calorie diet-induced improvements in sleep quality during 1 year of weight loss maintenance, and liraglutide transiently increased sleep duration.

Supplementary material
Supplementary material is available at SLEEP online.

Acknowledgments
We thank all the participants in the S-LITE study. S.S.T., J.R.L., C.J., B.M.S., J.J.H., and S.M. designed the study. S.B.K.J., C.R.J., J.R.L., C.J., and R.M.S. contributed to data collection. A.F.B., S.B.K.J., and C.J. processed accelerometer data and performed statistical analyses. M.H.N., N.Q.V., and M.F. contributed to data collection and performed leptin and soluble leptin receptor analyses. A.F.B., S.B.K.J., and S.S.T. wrote the first draft of the manuscript. All authors contributed to subsequent drafts and interpretation of data.

Funding
The S-LITE study was funded by an Excellence grant (NNF16OC0019968) from the Novo Nordisk Foundation. Furthermore, grants were received from the Faculty of Health and Medical Sciences, University of Copenhagen, Helsefonden, Danish Diabetes Academy, and Department of Biomedical Sciences, University of Copenhagen. Novo Nordisk A/S supplied Saxenda (liraglutide) and placebo pens, and Cambridge Weight Plan supplied low-calorie meal replacement products and accelerometers. None of the mentioned partners participated in or influenced the study.

Disclosure Statement

Data Availability
The data underlying this article will be shared on reasonable request to the corresponding author.

References


