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Insufficient Sleep Undermines Dietary Efforts to Reduce Adiposity

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Background: Sleep loss can modify energy intake and expenditure.

Objective: To determine whether sleep restriction attenuates the effect of a reduced-calorie diet on excess adiposity.

Design: Randomized, 2-period, 2-condition crossover study.

Setting: University clinical research center and sleep laboratory.

Patients: 10 overweight nonsmoking adults (3 women and 7 men) with a mean age of 41 years (SD, 5) and a mean body mass index of 27.4 kg/m^2 (SD, 2.0).

Intervention: 14 days of moderate caloric restriction with 8.5 or 5.5 hours of nighttime sleep opportunity.

Measurements: The primary measure was loss of fat and fat-free body mass. Secondary measures were changes in substrate utilization, energy expenditure, hunger, and 24-hour metabolic hormone concentrations.

Results: Sleep curtailment decreased the proportion of weight lost as fat by 55% (1.4 vs. 0.6 kg with 8.5 vs. 5.5 hours of sleep opportunity, respectively; $P = 0.043$) and increased the loss of fat-free body mass by 60% (1.5 vs. 2.4 kg; $P = 0.002$). This was accompanied by markers of enhanced neuroendocrine adaptation to caloric restriction, increased hunger, and a shift in relative substrate utilization toward oxidation of less fat.

Limitation: The nature of the study limited its duration and sample size.

Conclusion: The amount of human sleep contributes to the maintenance of fat-free body mass at times of decreased energy intake. Lack of sufficient sleep may compromise the efficacy of typical dietary interventions for weight loss and related metabolic risk reduction.

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Mammalian sleep is closely integrated with the regulation of energy balance and metabolic survival of the organism (1). Compared with the robust catabolic effects of sleep deprivation in rodents (2, 3), the increase in energy expenditure in sleep-deprived humans is much smaller (4, 5). Nevertheless, emerging data suggest that lack of sufficient sleep may modify the human neuroendocrine response to reduced food intake and adversely affect the metabolic effects of caloric restriction. Studies in volunteers who slept short versus long hours show that sleep curtailment was accompanied by increased hunger; higher circulating concentrations of the orexigenic hormone, ghrelin; and reduced concentrations of the anorexigenic hormone, leptin, when their caloric intake during the testing period was restricted to about 20 kcal/kg of body weight per day (intravenous glucose infusion, 5 g/kg per 24 hours) (6), but not when they were in positive energy balance (5, 7).

Many people today are overweight or obese, and diet-induced weight loss is a widely used strategy to reduce the health risks associated with excess adiposity. The neuroendocrine changes associated with sleep curtailment in the presence of caloric restriction (6), however, suggest that lack of sufficient sleep may compromise the efficacy of commonly used dietary interventions in such persons. For instance, higher ghrelin concentrations may facilitate the retention of fat (8–10), and increased hunger could compromise adherence to caloric restriction. We tested the hypothesis that recurrent bedtime restriction can attenuate the effect of a reduced-calorie diet on excess adiposity, enhance subjective hunger, and modify 24-hour serum leptin and acylated ghrelin concentrations in overweight persons. Because sleep loss may affect several neuroendocrine signals involved in the control of substrate utilization, we also examined the changes in circulating cortisol, epinephrine, norepinephrine, thyroid, and growth hormone concentrations.

METHODS

Study Participants

Sedentary nonsmokers aged 35 to 49 years with a body mass index of 25 to 32 kg/m^2 and self-reported sleep from 6.5 to 8.5 hours per day were recruited through local newspaper advertisements. We conducted the study from July 2003 to July 2008 in parallel with other experiments in our laboratory (5) aimed at exploring the effects of sleep loss on human energy metabolism. Persons were excluded if they had self-reported sleep problems (Pittsburgh Sleep Quality Index score >10), night work, variable sleep habits, or

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Context

Decreased sleep time has been suggested as contributing to obesity.

Contribution

Ten healthy adults were randomly assigned to sleep either 5.5 hours or 8.5 hours each night in conjunction with moderate caloric restriction. They were monitored in a closed clinical research environment. Compared with participants who slept 8.5 hours per night, participants who slept only 5.5 hours lost less body fat and more fat-free body mass, and had less favorable changes in metabolic hormones and in substrate and energy utilization. In addition, participants in the shorter sleep group perceived greater hunger than participants in the longer sleep group.

Implication

Sleep restriction may attenuate the effects of caloric restriction.

—The Editors

habitual daytime naps; physically demanding occupations or regular exercise schedules; depressed mood (Center for Epidemiologic Studies Depression Scale score >15); excessive intake of alcohol (>14 drinks/wk for men or >7 drinks/wk for women) or caffeine (>300 mg/d); smoked; used prescription medications or over-the-counter drugs affecting sleep or metabolism; or had abnormal findings on medical history, physical examination, and laboratory screening tests (including a 75-g oral glucose challenge and 1 night of full polysomnography). We only studied nonpregnant women, and data collection was scheduled during the first half of their menstrual cycle. Twelve participants (5 women and 7 men) were enrolled, and 10 of them completed the study. One woman withdrew after completing the first half of the study to start a new job. The participation of a second woman was stopped by the research team after she experienced palpitations during the period of combined caloric and sleep restriction and electrocardiography showed episodic premature atrial contractions in the absence of serum electrolyte abnormalities. Of the remaining 3 women and 7 men, 3 were white, 4 were black, and 3 were Hispanic. All volunteers gave written informed consent and were paid for their participation. The University of Chicago Institutional Review Board approved the study protocol.

Experimental Protocol

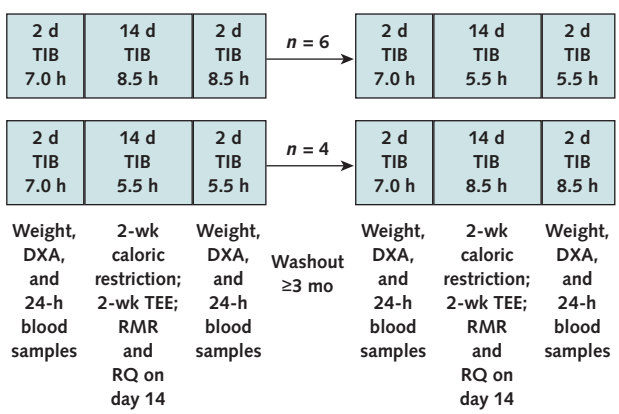
Figure 1 shows the study protocol. Participants spent two 14-day periods in the laboratory with scheduled time in bed of 8.5 or 5.5 hours per night in random order at least 3 months apart (mean time between treatments was 7 months [SD, 3]). To modify overnight sleep duration without changes in circadian phase, the usual going-to-bed and getting-out-of-bed times of the participants were moved proportionally closer together or further apart. Order of treatment was determined by using random-number tables. Six participants were studied in the 8.5-hour time-in-bed condition first, and 4 participants started with the 5.5-hour time-in-bed condition first (**Appendix Table 1**, available at www.annals.org). Sleep was recorded every night (Neurofax-1100, Nihon-Kohden, Foothill Ranch, California), and no daytime naps were allowed.

Food Intake and Energy Expenditure

During each 14-day intervention period, participants consumed the same individualized diet, with caloric content restricted to 90% of their resting metabolic rate at the time of screening. Daily calories were divided among breakfast (25%, 8:00 to 9:00), lunch (30%, 12:30 to 13:30), dinner (35%, 18:30 to 19:30), and an evening snack (10%, 21:00). This weight-reducing diet was supplemented with a daily multivitamin plus minerals (Theragran-M, Walgreens, Deerfield, Illinois) and 325 mg of ferrous sulfate. Food was weighed before and after each meal to determine actual consumption (Nutritionist-IV, Axxya Systems, Stafford, Texas).

Participants spent their waking hours indoors engaged in home office–type work or leisure activities (5). Total energy expenditure plays an important role in the control of energy balance and has 3 principal components: resting metabolic rate under basal conditions (the energy expenditure of a person resting in bed awake and in the fasting state); thermic effect of food (the energy expenditure associated with the digestion, absorption, metabolism and storage of food, equal to approximately 10% of total energy expenditure); and physical activity–related energy expenditure (the energy expended in all volitional and nonvolitional daily activities). In parallel studies with ad libitum food intake (5), exposure to this same laboratory environment was accompanied by sedentary levels of physical ac-

Figure 1. **Study protocol.**



DXA was used to measure body composition, RMR and RQ assessed body composition by indirect calorimetry, and TEE was measured by using doubly-labeled water. DXA = dual-energy x-ray absorptiometry; RMR = resting metabolic rate; RQ = respiratory quotient; TEE = total energy expenditure; TIB = time in bed.

tivity corresponding to total energy expenditure equal to about 1.5 times the resting metabolic rate of the study participants (25th percentile physical activity level), regardless of the presence or absence of sleep loss. Total energy expenditure of study participants was measured by doubly labeled water (5) during each 14-day treatment period, and individual respiratory quotients (RQs) and total body water changes derived from the individual food quotients and changes in body composition were assessed during the measurement period (11). On the last day of each dietary intervention, resting metabolic rate and RQ were measured by indirect calorimetry under fasting conditions and for 4 hours after breakfast, and the thermic effect of food was calculated, as described elsewhere (5). Technical problems caused loss of resting metabolic rate data from 1 participant during the 5.5-hour time-in-bed condition. The RQ values of this participant were imputed by using the means of the other participants. Hunger was measured daily before each meal and at 22:30 by using 10-cm visual analogue scales (12). Results were averaged to generate individual 24-hour hunger scores. Treatment-related changes were determined by subtracting the 2-day mean hunger score before each intervention from the daily hunger scores during the study.

Body Weight and Composition and Hormone Measurements

Before and after each treatment, participants remained at rest for 48 hours with identical caloric intake, including oral and intravenous doses of glucose at 9:00 (the results of these glucose tolerance tests will be reported elsewhere) and the same carbohydrate-rich meals at 14:00 and 19:00 (13). Time in bed during this 48-hour period was 7 hours per night before and 8.5 or 5.5 hours per night after each 14-day intervention to match the assigned sleep condition (**Figure 1**). We assessed fasting body weight and adiposity in the morning of the first day. Fat-free body mass was calculated as the difference between body weight measured by scale (Scale-Tronix, Wheaton, Illinois) and body fat measured by dual-energy x-ray absorptiometry (Lunar Prodigy, Lunar, Madison, Wisconsin). During the last 24 hours of this 2-day period, blood was sampled every 30 minutes starting at 20:00. We measured serum leptin and acylated ghrelin concentrations by radioimmunoassay (Linco Research, St. Charles, Missouri), and cortisol and growth hormone concentrations were measured by chemiluminescent enzyme immunoassay (Immulite 2000, Diagnostic Products, Los Angeles, California). We measured plasma epinephrine and norepinephrine by using high-pressure liquid chromatography (13). Twenty-four hour serum thyroid-stimulating hormone and free thyroxine concentrations were analyzed only at the end of each intervention (Immulite 2000, Diagnostic Products). Serum triiodothyronine and reverse serum triiodothyronine were measured in 7 of 10 participants who had sufficient residual serum pooled from 3 to 4 fasting morning samples.

Statistical Analysis

Body weight and composition before and mean sleep variables during each intervention were compared by using paired *t* tests. To control for differences in baseline body composition, the effect of the 5.5-hour versus 8.5-hour time-in-bed condition (a fixed factor) on the loss of fat and fat-free body mass as main outcome measures of this study was evaluated by using mixed linear models with the treatment period as a repeated measure, initial fat and fat-free body mass as time-varying covariates, and participants as a random factor. Similar mixed-model analyses controlling for order of treatment and differences in fat and fat-free body mass were used to explore the effects of sleep restriction on ancillary measures, such as resting metabolic rate, RQ, hunger, leptin, ghrelin, and other metabolic hormones that can be influenced by changes in body composition. Statistical analyses were done with SPSS, version 17.0 (SPSS, Chicago, Illinois). Results are reported as means (SDs).

Role of the Funding Source

The National Institutes of Health funded this study. The funding source had no role in the design of the study, analysis and interpretation of the data, writing of the manuscript, or the decision to submit the manuscript for publication.

RESULTS

Study participants had a mean age of 41 years (SD, 5), self-reported habitual sleep duration of 7.7 hours per day (SD, 0.7), Center for Epidemiologic Studies Depression Scale score of 4 (SD, 5), Pittsburgh Sleep Quality Index score of 3 (SD, 2), sleep respiratory disturbance index of 3 events per hour (SD, 3), and resting metabolic rate of 1624 kcal/d (SD, 210). Mean sleep duration was reduced by 131 min/d (SD, 30) from 7 hours 25 minutes (SD, 32) during the 8.5-hour time-in-bed condition to 5 hours 14 minutes (SD, 6) during the 5.5-hour time-in-bed condition ($P < 0.001$) (**Table**). When time in bed was restricted to 5.5 hours, participants went to bed later (0:43 [SD, 37] vs. 23:23 [SD, 43]) and got up earlier (6:14 [SD, 36] vs. 7:52 [SD, 45]). The **Table** summarizes the body weight and composition of the participants before each treatment. Participants consumed similar amounts of energy (1447 [SD, 227] vs. 1450 kcal/d [SD, 236]) during the 8.5-hour and 5.5-hour time-in-bed conditions, which as intended were considerably lower than their corresponding doubly-labeled water–based measures of total energy expenditure (2136 [SD, 342] vs. 2139 kcal/d [SD, 393]). Carbohydrate, fat, and protein contributed 48% (SD, 1), 34% (SD, 1), and 18% (SD, 1) of energy during each study period. Both treatments were accompanied by similar weight loss (approximately 3 kg [**Table**]); however, more than half of the weight loss during the 8.5-hour time-in-bed condition and only one quarter of the weight loss during the 5.5-hour time-in-bed condition was fat (55% reduction in fat

Table. **Sleep and Reduction in Body Weight and Adiposity***

Characteristic	8.5-h TIB	5.5-h TIB	Difference†	*P* Value
Baseline				
Body weight, *kg*	82.0 (11.2)	80.5 (10.3)	−1.5 (2.1)	0.057
Body mass index, kg/m^2	27.5 (2.2)	27.1 (2.0)	−0.5 (0.7)	0.069
Body fat, *kg*	26.4 (6.4)	25.0 (6.3)	−1.4 (1.6)	0.022
Fat-free body mass, *kg*	55.6 (11.5)	55.5 (11.2)	−0.1 (0.7)	0.84
Mean 14-d sleep measurements				
Total sleep time, *h:min*	7:25 (0:32)	5:14 (0:06)	−2:11 (0:30)	<0.001
Sleep efficiency, *%*	87 (6)	95 (2)	8 (5)	0.001
Sleep onset latency, *min*	21 (9)	7 (4)	−14 (6)	<0.001
TIB scored as wake, *min*	66 (31)	16 (5)	−50 (29)	<0.001
Stage 1 sleep, *min*	29 (10)	12 (3)	−17 (9)	<0.001
Stage 2 sleep, *min*	264 (37)	180 (42)	−84 (36)	<0.001
Slow-wave sleep (stages 3 and 4), *min*	43 (28)	46 (34)	3 (24)	0.66
REM sleep, *min*	108 (22)	76 (13)	−32 (16)	<0.001
			β-Coefficient (95% CI)	
End of treatment				
Weight loss, *kg*	2.9 (1.4)	3.0 (1.0)	0.2 (−0.2 to 0.7)‡	0.24
Loss of fat-free mass, *kg*	1.5 (1.3)	2.4 (1.4)	1.0 (0.4 to 1.5)‡	0.002
Loss of fat, *kg*	1.4 (0.9)	0.6 (0.6)	−0.7 (−1.4 to −0.03)‡	0.043
Weight loss as fat, *%*	56 (35)	25 (24)	−31 (−49 to −12)‡	0.004
Fasting RQ	0.80 (0.04)	0.83 (0.04)	0.03 (0.01 to 0.06)§	0.042
Postprandial RQ (4-h mean)	0.80 (0.04)	0.83 (0.05)	0.03 (0.002 to 0.06)‡	0.038
RMR, *kcal/d*	1505 (262)	1391 (180)	−147 (−253 to −41)§	0.010

REM = rapid eye movement; RMR = resting metabolic rate; RQ = respiratory quotient; TIB = time in bed.
* Data are presented as means (SDs).
† Paired *t* test comparisons.
‡ β-Coefficient for the effect of sleep restriction (5.5-h vs. 8.5-h TIB) and its 95% CI are based on a mixed linear model controlling for crossover study design; treatment period was the repeated measure, and baseline fat and fat-free body mass were the time-varying covariates.
§ Effect of sleep restriction in a mixed linear model controlling for treatment period and body composition at the end of each intervention.

loss, 1.4 [SD, 0.9] vs. 0.6 kg [SD, 0.6] for the 8.5 vs. 5.5-hour sleep opportunity; $P = 0.043$) (**Table** and **Figure 2**). Instead, sleep restriction resulted in considerably increased loss of fat-free body mass compared with the 8.5-hour time-in-bed condition (60% increase in fat-free weight loss, 1.5 [SD, 1.3] vs. 2.4 kg [SD, 1.4] for the 8.5 vs. 5.5-hour sleep opportunity; $P = 0.002$) (**Table** and **Figure 2**).

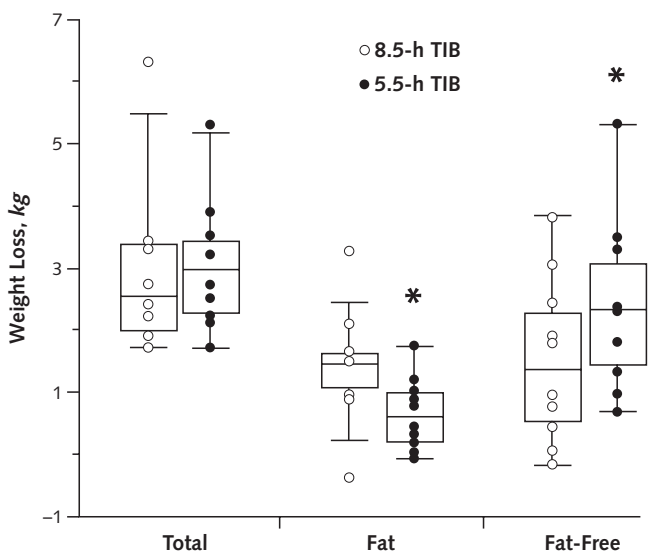
The differential loss of fat and fat-free mass between the 2 sleep conditions was accompanied by changes in several secondary end points, including increased hunger during the period of sleep restriction (−0.1 [SD, 1.2] vs. 0.7 cm [SD, 1.2] for the mixed linear model; $P = 0.043$ during the 8.5 vs. 5.5-hour sleep opportunity), as well as higher fasting and postprandial RQ (**Table** and **Figure 3**) and 24-hour acylated ghrelin concentrations (**Appendix Figure** and **Appendix Table 2**, available at www.annals.org) at the end of the 5.5-hour time-in-bed condition ($P = 0.04$ for each measure). In contrast, resting metabolic rate ($P = 0.01$; **Table**) and 24-hour plasma epinephrine concentrations ($P = 0.005$; **Appendix Table 2**) were lower at the end of the 5.5-hour compared with the 8.5-hour time-in-bed condition. Leptin concentrations declined in parallel with the loss of weight and adiposity ($P = 0.001$; **Appendix Figure 1**) without a significant independent effect of sleep loss (**Appendix Table 2**). There were no differences in the fractional thermic effect of food (10.2% [SD, 7.5] vs. 12.8% [SD, 6.7]) and the 24-hour norepinephrine, cortisol, growth hormone, and thyroid hormone concentrations at the end of the 8.5-hour versus the 5.5-hour time-in-bed condition (**Appendix Table 2**).

DISCUSSION

We examined whether experimental sleep restriction, designed to approximate the short sleep times of a growing number of persons in modern society, may compromise the effect of reduced-calorie diets on excess adiposity. The proportion of body weight lost as fat during the 8.5-hour time-in-bed condition (56%) is consistent with other published short-term observations (14); however, the combination of energy and sleep restriction in overweight adults resulted in a modified state of negative energy balance characterized by decreased loss of fat and considerably increased loss of fat-free body mass (**Table** and **Figure 2**). Although rodent studies have established that sleep deprivation can have considerable catabolic effects that resemble protein malnutrition (2), so far the possibility that sleep loss may have a similar negative effect in humans has not received much attention. One study found that 1 to 2 nights of total sleep deprivation was accompanied by elevated 24-hour urinary nitrogen excretion (15), but the effects of reduced sleep duration have not been tested. Our experimental data now indicate that sleep plays an important role in the preservation of human fat-free body mass during periods of reduced caloric intake.

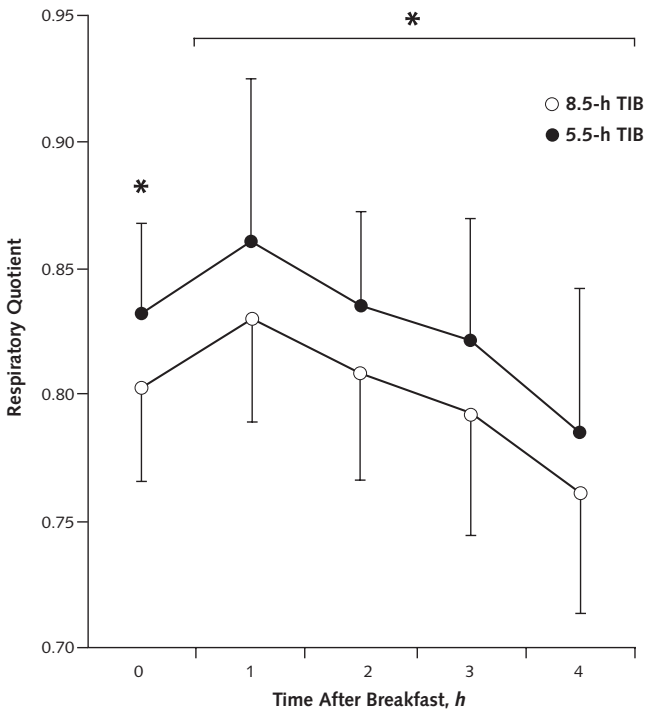
In addition to its clinically relevant primary outcome measures, this study examined an ancillary set of mostly research-oriented metabolic end points that have been hypothesized to reflect important mechanistic relationships between sleep and human energy metabolism (6). The difference in RQ (**Figure 3**) between the 2 treatments suggests that sleep loss was accompanied by changes in substrate utilization, which is in good agreement with the observed sparing of body fat. Serum concentrations of acylated ghrelin also increased during the short-sleep condition (**Appendix Table 2**), which resembled the changes in total ghrelin associated with caloric restriction and acute sleep deprivation (6). Acylated ghrelin has been shown to reduce energy expenditure, stimulate hunger and food intake, promote retention of fat, and increase hepatic glucose production to support the availability of fuel to glucose-dependent tissues (8–10, 16). In our experiment, sleep restriction was accompanied by a similar pattern of increased hunger and elevated fasting and postprandial RQ values consistent with reduced relative oxidation of fat (**Figure 3**). Of importance, sleep restriction was not accompanied by higher 24-hour concentrations of catabolic hormones, such as serum cortisol, serum triiodothyronine and free thyroxine, and plasma catecholamines (**Appendix Table 2**). Together, these results suggest that the loss of sleep at times of limited food intake amplifies the pattern of ghrelin-associated changes in human hunger, glucose and fat utilization, and energy metabolism. Thus, the increased loss of fat-free body mass during the short-sleep condition of our study may be due to increased conversion of body protein into glucose to support the more prolonged metabolic needs of the waking brain and other glucose-dependent tissues (17). Although this hypothesis is compatible with the energy-saving and restorative functions of mammalian sleep (1), it remains untested and requires more detailed human studies.

Figure 2. **Changes in body weight and composition.**



Box plots show weight loss and its composition during the 8.5-h and 5.5-h TIB conditions (n = 10). TIB = time in bed.
* Significant difference in loss of fat (P = 0.043) and fat-free body mass (P = 0.002) between the 2 sleep conditions after study period (initial vs. crossover) and pretreatment body composition were controlled for.

Figure 3. **Respiratory quotient.**



Mean respiratory quotient is shown under fasting conditions (time 0) and during 4 consecutive 1-h intervals after breakfast at the end of the 8.5-h and 5.5-h TIB conditions (n = 10). Error bars indicate SDs. TIB = time in bed.
* Significant difference in fasting (P = 0.042) and 4-h postprandial respiratory quotient (P = 0.038) after study period and body composition at the end of each intervention were controlled for.

The reduced loss of fat during the short-sleep condition implies a difference in the balance of energy intake and expenditure between the 2 treatments. On the basis of energy conversion factors of 9.46 and 4.32 kcal/g of lost fat and protein (11) and 21% protein content of fat-free body mass, the estimated energy deficit during the 5.5-hour time-in-bed condition was about 520 kcal/d compared with about 920 kcal/d during the 8.5-hour time-in-bed condition. Because caloric intake was nearly identical, these calculations suggest that the energy expenditure of the participants during the 5.5-hour versus 8.5-hour time-in-bed condition was reduced by about 400 kcal/d. Using doubly-labeled water, we did not detect a change in total energy expenditure, as suggested by the differential loss of body fat between the 2 sleep conditions. Unfortunately, the larger-than-anticipated variance of the total energy expenditure data makes interpretation of these results difficult. Our

initial power calculations were based on previous work showing that the SD for within-participant change in total energy expenditure by doubly-labeled water was 140 kcal/d. This would have given us 80% power to detect a change in total energy expenditure between the 2 sleep conditions of 392 kcal/d. However, the observed SD in our study was 340 kcal/d. As a result, the CIs for total energy expenditure measured by doubly-labeled water include the change that would be required to explain the differences in the composition of weight loss between the 2 treatments (about 400 kcal/d). The high SD may have resulted from the lower total energy expenditure during this inpatient weight-loss study protocol and variation in physical activity between visits. The strongest difference between treatments was the increased loss of fat-free mass during the 5.5-hour time-in-bed condition (**Table** and **Figure 2**), which has the weakest relationship to energy balance because lean tissue is mostly water and has low energy density. Because there is also variation in the measurement of change in body composition, the actual difference in total energy expenditure between the 2 sleep conditions may lie somewhere between 400 kcal/d, as suggested by the difference in fat loss, and the absence of change in total energy expenditure as measured with doubly-labeled water.

Ongoing depletion of energy stores in humans is accompanied by metabolic, neuroendocrine, and behavioral compensations to produce opposing decreases in resting metabolic rate and nonresting energy expenditure (18–22). Of note, the resting metabolic rate was significantly lower at the end of the 5.5-hour versus 8.5-hour time-in-bed condition. This decrease in resting metabolic rate was greater than expected on the basis of the observed loss of fat and fat-free body mass alone (**Table**) and could contribute to the decrease in estimated energy expenditure during the period of combined caloric and sleep restriction (18–20). A greater decline in adrenomedullary activity (**Appendix Table 2**) (21) and energy expenditure in activities of daily living (7, 19, 22) could also enhance the development of a more thrifty phenotype in the presence of sleep loss. The fat-derived hormone, leptin, plays a key role in the metabolic and neuroendocrine adaptations to weight loss (20) and, in previous experiments, short-term sleep restriction was accompanied by lower 24-hour plasma concentrations of leptin (6, 23). However, our study and other controlled studies (5, 7, 24, 25) did not find a significant independent effect of sleep loss on 24-hour leptin levels, suggesting that acuity of exposure to sleep and caloric restriction may be important determinants of any such change (3).

In a broader context, our results shed new light on the paradoxical association of human obesity with the loss of the most energy-efficient and sedentary human behavior: sleep (26). Our data suggest that insufficient sleep may compromise the maintenance of fat-free body mass and promote retention of fat when people aim to reestablish their usual weight after life events associated with excessive food intake and increased adiposity. The enhanced metabolic, neuroendocrine, and behavioral compensation in the form of increased hunger and reduced energy expenditure that develop in response to combined caloric and sleep restriction can disrupt adherence to a lower-energy diet and promote efficient weight regain once it is discontinued. However, because of the high cost and technical difficulty of such experiments, our discussion is based on the detailed laboratory evaluation of a small number of participants during a limited period. Additional studies are needed to examine the longer-term effects of sleep loss on body composition, energy metabolism, and substrate utilization in weight-reduced persons.

In summary, exposure of overweight middle-aged adults to 2 weeks of combined energy and sleep restriction produced a catabolic state characterized by reduced loss of body fat and increased loss of fat-free body mass, accompanied by increased hunger and changes in energy expenditure and the neuroendocrine control of substrate utilization. These results highlight the importance of human sleep for maintenance of fat-free body mass during periods of reduced energy intake and suggest that insufficient sleep may compromise several factors that contribute to the efficacy of and adherence to dietary energy-restriction strategies for metabolic risk reduction.

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Reproducible Research Statement: *Study protocol, statistical code, and data set:* Available from Dr. Penev (e-mail, ppenev@medicine.bsd.uchicago.edu).

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Appendix Table 1. Individual Changes in Body Weight and Composition

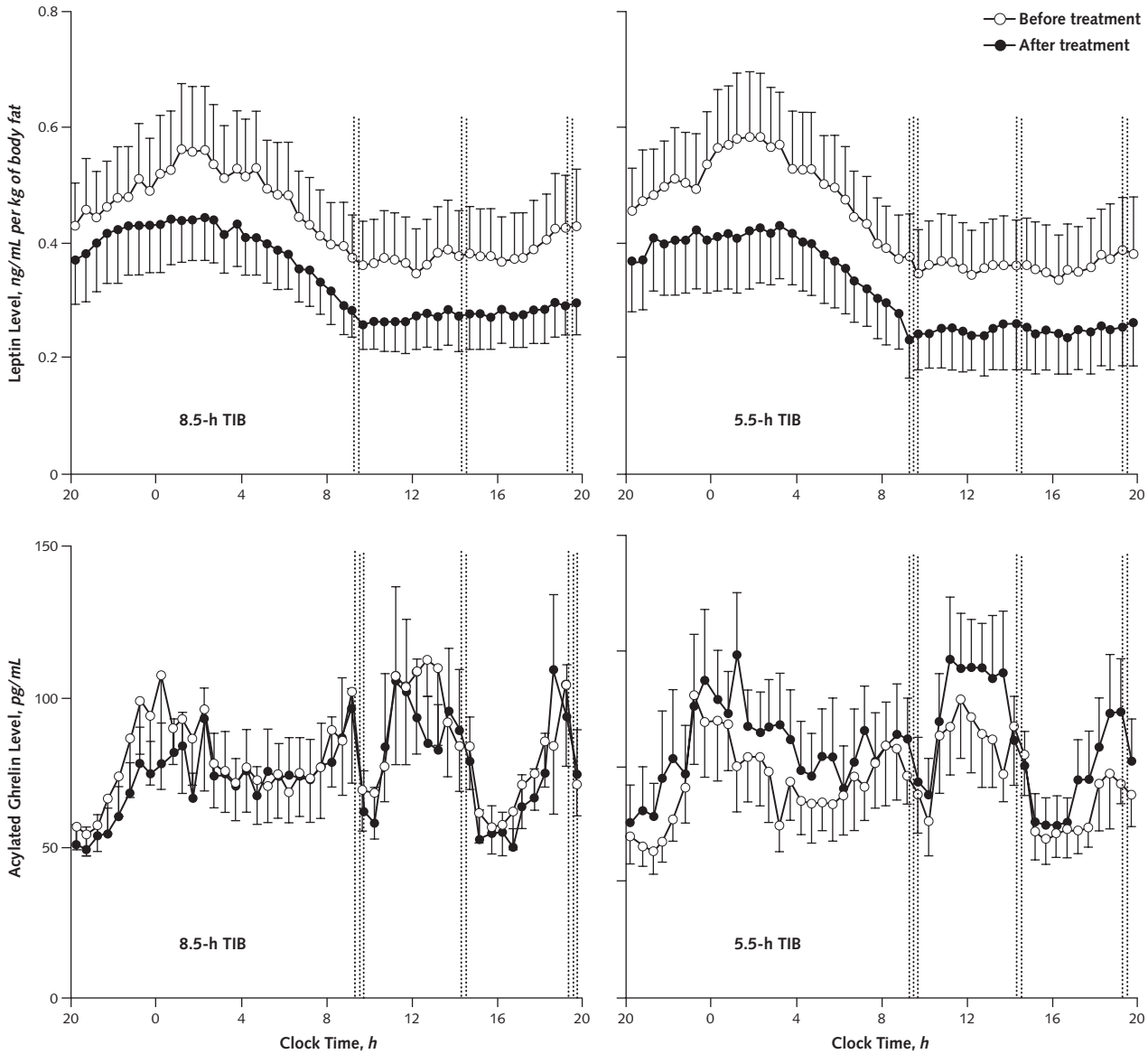
Participant	Sex	Treatment Order*	Body Weight, *kg*						Body Fat, *kg*		
			8-5 h TIB			5.5-h TIB			8-5 h TIB		
			Before Treatment	After Treatment	Change	Before Treatment	After Treatment	Change	Before Treatment	After Treatment	Change
1	Male	8.5 h	83.0	81.1	−1.9	81.4	78.7	−2.7	21.7	20.3	−1.5
2	Male	5.5 h	87.2	85.0	−2.2	87.4	84.2	−3.2	20.8	19.3	−1.5
3	Male	8.5 h	76.9	73.5	−3.4	74.4	71.9	−2.5	17.0	15.5	−1.5
4	Female	5.5 h	73.8	72.1	−1.7	74.0	72.3	−1.7	34.3	32.7	−1.6
5	Male	8.5 h	75.5	73.1	−2.4	72.6	70.4	−2.2	25.9	24.4	−1.5
6	Male	8.5 h	102.1	95.8	−6.3	97.5	92.2	−5.3	31.9	28.7	−3.3
7	Male	5.5 h	84.7	81.4	−3.3	85.2	81.3	−3.9	22.1	21.2	−0.9
8	Male	5.5 h	97.4	94.0	−3.4	94.4	91.2	−3.2	35.2	35.6	0.4
9	Female	8.5 h	67.2	65.3	−1.9	69.4	67.3	−2.1	30.6	28.5	−2.1
10	Female	8.5 h	72.4	69.7	−2.7	69.1	65.6	−3.5	24.9	23.9	−0.9

TIB = time in bed.
* In the 8.5-h TIB treatment order, the participant completed the 8.5-h TIB condition first; in the 5.5-h TIB treatment order, the participant completed the 5.5-h TIB condition first.

Appendix Table 1—Continued

Body Fat, *kg*			Fat-Free Mass, *kg*					
5.5-h TIB			8-5 h TIB			5.5-h TIB		
Before Treatment	After Treatment	Change	Before Treatment	After Treatment	Change	Before Treatment	After Treatment	Change
20.7	19.0	−1.7	61.3	60.8	−0.4	60.7	59.7	−1.0
20.8	20.0	−0.8	66.4	65.7	−0.7	66.6	64.2	−2.4
14.9	14.7	−0.2	59.9	58.0	−1.9	59.5	57.2	−2.3
34.5	33.5	−1.0	39.5	39.4	−0.1	39.5	38.8	−0.7
23.9	23.0	−0.9	49.6	48.7	−0.9	48.7	47.4	−1.3
27.5	27.5	0.0	70.2	67.1	−3.0	70.0	64.7	−5.3
22.2	21.7	−0.4	62.7	60.2	−2.4	63.0	59.6	−3.5
32.9	32.9	0.1	62.2	58.4	−3.8	61.5	58.3	−3.3
31.0	30.7	−0.3	36.6	36.8	0.2	38.4	36.6	−1.8
21.8	20.6	−1.2	47.5	45.7	−1.8	47.3	45.0	−2.3

Appendix Figure. **Selected metabolic hormone profiles.**



Error bars indicate SEs. Vertical dotted lines indicate times of controlled calorie intake. TIB = time in bed. **Top.** Mean 24-h serum leptin levels before and after the 8.5-h and 5.5-h TIB conditions (n = 10). **Bottom.** Mean 24-h serum acylated ghrelin levels before and after the 8.5-h and 5.5-h TIB conditions (n = 10).

Appendix Table 2. Metabolic Hormone Measurements*

Hormone Measurement	Pretreatment Value		End-of-Treatment Value	
	8.5-h TIB	5.5-h TIB	8.5-h TIB	5.5-h TIB
24-h serum leptin, *μg/L*	13.1 (10.2)	12.4 (9.5)	9.7 (7.2)	9.1 (9.2)
24-h acylated ghrelin, *ng/L*	81 (50)	73 (38)	75 (40)	84 (47)†
24-h serum growth hormone, *μg/L*	0.88 (0.49)	0.79 (0.34)	0.81 (0.38)	0.95 (0.47)
24-h plasma epinephrine, *pmol/L*	129 (38)	136 (58)	140 (45)	114 (30)‡
24-h plasma norepinephrine, *pmol/L*	1171 (589)	1291 (829)	1161 (512)	1104 (481)
24-h serum cortisol, *nmol/L*	196 (21)	198 (25)	190 (22)	193 (23)
24-h serum TSH, *mU/L*	–	–	1.2 (0.6)	1.2 (0.5)
24-h serum free T_4				
pmol/L	–	–	16.1 (1.2)	16.5 (1.2)
ng/dL	–	–	1.25 (0.10)	1.28 (0.10)
Serum T_3, *nmol/L*	–	–	1.89 (0.18)	1.95 (0.24)

T_3 = triiodothyronine; T_4 = thyroxine; TIB = time in bed; TSH = thyroid-stimulating hormone.
* Data are presented as means (SDs).
† $P = 0.039$.
‡ $P = 0.005$. Effect of sleep restriction at the end of the 5.5-h vs. 8.5-h time-in-bed condition, based on a mixed linear model controlling for crossover study design (treatment period) and final body composition.