Brief Communication: Sleep Curtailment in Healthy Young Men Is Associated with Decreased Leptin Levels, Elevated Ghrelin Levels, and Increased Hunger and Appetite

Karine Spiegel, PhD; Esra Tasali, MD; Plamen Penev, MD, PhD; and Eve Van Cauter, PhD

Background: **Total sleep deprivation in rodents and in humans has been associated with hyperphagia. Over the past 40 years, self-reported sleep duration in the United States has decreased by almost 2 hours.**

Objective: **To determine whether partial sleep curtailment, an increasingly prevalent behavior, alters appetite regulation.**

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

Setting: **Clinical Research Center, University of Chicago, Chicago, Illinois.**

Patients: **12 healthy men (mean age [±SD], 22 ± 2 years; mean body mass index [±SD], 23.6 ± 2.0 kg/m^2).**

Measurements: **Daytime profiles of plasma leptin and ghrelin levels and subjective ratings of hunger and appetite.**

Intervention: **2 days of sleep restriction and 2 days of sleep extension under controlled conditions of caloric intake and physical activity.**

Results: **Sleep restriction was associated with average reductions in the anorexigenic hormone leptin (decrease, 18%; $P = 0.04$), elevations in the orexigenic factor ghrelin (increase, 28%; $P < 0.04$), and increased hunger (increase, 24%; $P < 0.01$) and appetite (increase, 23%; $P = 0.01$), especially for calorie-dense foods with high carbohydrate content (increase, 33% to 45%; $P = 0.02$).**

Limitations: **The study included only 12 young men and did not measure energy expenditure.**

Conclusions: **Short sleep duration in young, healthy men is associated with decreased leptin levels, increased ghrelin levels, and increased hunger and appetite.**

Ann Intern Med. 2004;141:846-850. www.annals.org

For author affiliations, see end of text.

See editorial comment on pp 885-886.

Sleep plays an important role in energy balance. In rodents, food shortage or starvation results in decreased sleep (1), and, conversely, total sleep deprivation leads to marked hyperphagia (2). Leptin and ghrelin are peripheral signals that contribute to the central regulation of food intake. Leptin, a hormone released by the adipocytes, provides information about energy status to hypothalamic regulatory centers (3). In humans, circulating leptin levels rapidly decrease or increase in response to acute caloric shortage or surplus, respectively (4). These changes in leptin levels have been associated with reciprocal changes in hunger (4). Ghrelin, a peptide produced predominantly by the stomach, is also involved in energy balance regulation, but, in contrast to the anorexigenic effects of leptin, ghrelin stimulates appetite (5). It has been proposed that leptin and ghrelin "represent the 'yin–yang' of one regulatory system that has developed to inform the brain about the current energy balance state" (6).

Over the past 40 years, sleep duration in the U.S. population has decreased by 1 to 2 hours (7–10). The proportion of young adults sleeping fewer than 7 hours per night has more than doubled between 1960 and 2001–2002 (from 15.6% to 37.1%) (7–10). The effect of sleep curtailment on the control of appetite and food intake is not known. Because of the well-documented associations between sleep and food intake (1, 2), we sought to determine whether sleep duration influences the daytime profiles of leptin and ghrelin.

METHODS

Participants

Twelve healthy men (mean age [±SD], 22 ± 2 years]; mean body mass index [±SD], 23.6 ± 2.0 kg/m^2) who did not smoke or take any medications participated in the study. All of the men were within 10% of ideal body weight and had regular nocturnal time in bed of 7 to 9 hours. We excluded persons who had traveled across time zones less than 4 weeks before the study.

Experimental Protocol

The Institutional Review Board of the University of Chicago approved the protocol, and we obtained written informed consent from all participants. During the week preceding each study, we asked participants not to deviate from a fixed time in bed (11:00 p.m. to 7:00 a.m.) by more than 30 minutes. Naps were not allowed.

The men participated in 2 studies that were conducted in a randomized order, were spaced at least 6 weeks apart, and were performed in the Clinical Research Center at the University of Chicago, Chicago, Illinois. Six of the 12 men first performed the study with restricted time in bed, and the remaining 6 men first performed the study with extended time in bed. Average weight did not change over the time period separating the 2 study conditions (75.2 kg in the sleep restriction condition vs. 75.4 kg in the sleep extension condition; $P > 0.2$). We obtained blood samples at 20-minute intervals from 8:00 a.m. to 9:00 p.m. after 2 consecutive nights of 10 hours in bed (10:00 p.m. to 8:00

a.m.; sleep extension) and after 2 consecutive nights of 4 hours in bed (1:00 a.m. to 5:00 a.m.; sleep restriction). Sleep was recorded every night. For both extension and restriction conditions, each overnight stay began at 7:00 p.m. with a standard hospital dinner, and the first overnight stay ended after breakfast, which was served at 8:00 a.m. We instructed the participants not to deviate from their usual eating habits between breakfast and dinner, but caloric intake was not otherwise monitored. Participants were readmitted in the early evening and, after receiving a standard hospital dinner at 7:00 p.m., remained at bed rest. At 8:00 a.m. after the second night, the participants' caloric intake was kept constant to avoid meal-related fluctuations of hunger and satiety and consisted of an intravenous glucose infusion at a constant rate of 5 g/kg of body weight every 24 hours. There was no other source of calories. Every hour from 9:00 a.m. to 9:00 p.m., the men completed validated visual analogue scales (0 to 10 cm) for hunger (11) and appetite for various food categories (12). To assess hunger, we asked participants to mark their response to the question "How hungry do you feel right now?" on a 10-cm scale (with "not at all hungry" on the left and "extremely hungry" on the right). To assess appetite, we asked participants to mark their response to how much they would enjoy eating foods from 7 different food categories on a 10-cm scale (with "not at all" on the left and "very much" on the right). They were asked to provide a score based only on their appetite at the moment, without concern for calories, fat, or a healthy diet. The food categories were sweets (such as cake, candy, cookies, ice cream, and pastry); salty foods (such as chips, salted nuts, pickles, and olives); starchy foods (such as bread, pasta, cereal, and potatoes); fruits and fruit juices; vegetables; meat, poultry, fish, and eggs; and dairy products (such as milk, cheese, and yogurt).

Assays

We measured serum leptin levels in all samples by using a human leptin radioimmunoassay kit (Linco Research, St. Charles, Missouri) with a sensitivity of 0.5 ng/mL and an intra-assay coefficient of variation of 8.3%. In 9 of the 12 participants, we also measured total ghrelin levels at hourly intervals by radioimmunoassay (Linco Research) with a sensitivity of 0.5 ng/mL and an intra-assay coefficient of variation of 7.9%.

Statistical Analysis

We performed paired comparisons by using the Wilcoxon matched-pairs signed-rank test. We calculated correlations by using the Spearman coefficient. The mean relative changes in leptin, ghrelin, hunger, and appetite between extended sleep (the reference category) and restricted sleep were calculated by using the ratios of the corresponding individual data and then deriving the mean across all individuals.

Context

Studies in animals and humans suggest that sleep duration is an important regulator of metabolism.

Contribution

In this study, 12 young, healthy, normal-weight men exhibited reductions in the satiety hormone leptin, increases in the hunger hormone ghrelin, and increases in hunger after 2 nights of only 4 hours of sleep compared with after 2 nights of 10 hours of sleep.

Implications

Inadequate sleep seems to influence the hormones that regulate satiety and hunger in a way that could promote excess eating.

–The Editors

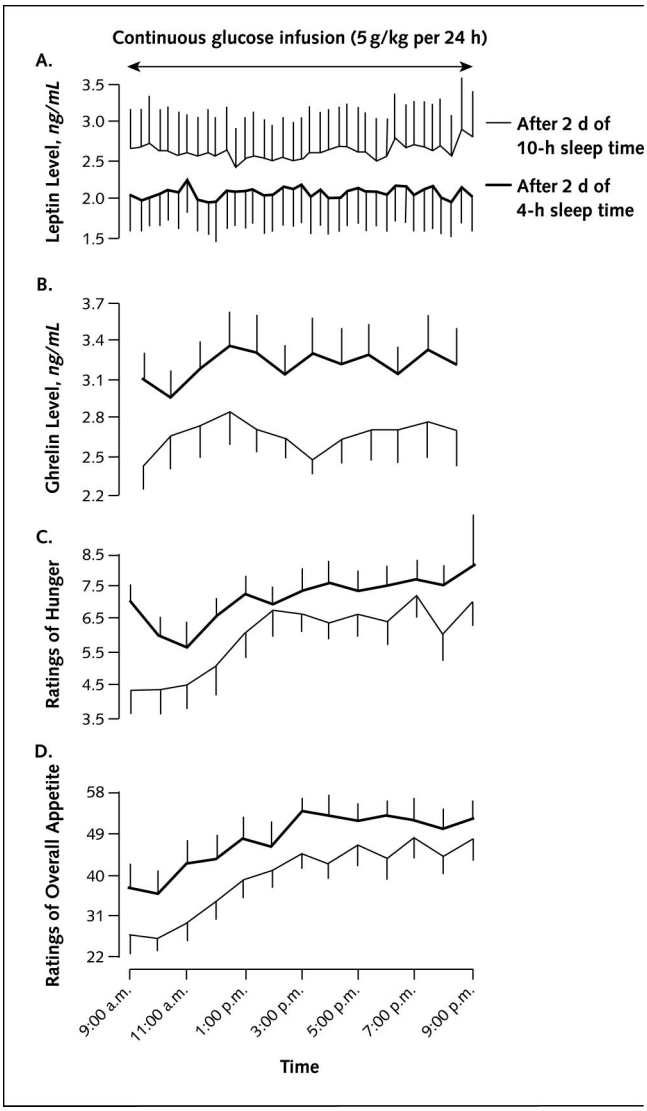
Role of the Funding Sources

This work was partially supported by grants from the National Institutes of Health, the European Sleep Research Society, the Belgian Fonds de la Recherche Scientifique Médicale, the University of Chicago Diabetes Research and Training Grant, and The University of Chicago General Clinical Research Center. The funding sources had no role in the design, conduct, and reporting of the study or in the decision to submit the manuscript for publication.

RESULTS

Leptin levels were stable across the daytime period under both sleep conditions, which was consistent with the fact that calories were exclusively delivered in the form of a constant glucose infusion. Average total sleep time was 9 hours and 8 minutes when the men spent 10 hours in bed and 3 hours and 53 minutes when the men spent 4 hours in bed ($P < 0.01$). When spending 4 hours in bed, the participants had mean leptin levels that were 18% lower (2.1 ng/mL vs. 2.6 ng/mL; $P = 0.04$) (**Figure 1**, *part A*) and mean ghrelin levels that were 28% higher (3.3 ng/mL vs. 2.6 ng/mL; $P = 0.04$) (**Figure 1**, *part B*) than when the participants spent 10 hours in bed. The ratio of the concentrations of orexigenic ghrelin to anorexigenic leptin increased by 71% (CI, 7% to 135%) with 4 hours in bed compared with 10 hours in bed. Sleep restriction relative to sleep extension was associated with a 24% increase in hunger ratings on the 10-cm visual analogue scale ($P < 0.01$) and a 23% increase in appetite ratings for all food categories combined ($P = 0.01$) (**Figure 1**, *parts C and D*, and **Table 1**). The increase in appetite tended to be greatest for calorie-dense foods with high carbohydrate content (sweets, salty foods, and starchy foods: increase, 33% to 45%; $P = 0.06$) (**Table 1**). The increase in appetite for fruits and vegetables was less consistent and of lesser magnitude (increase, 17% to 21%) (**Table 1**). Appetite for

Figure 1. **Effect of sleep duration on daytime leptin levels, ghrelin levels, hunger, and appetite.**



A. Mean (±SE) daytime (9:00 a.m. to 9:00 p.m.) profiles of leptin after 2 days with 4 hours in bed or 2 days with 10 hours in bed. Mean leptin levels were 18% lower when sleep was restricted. **B.** Mean (±SE) daytime (9:00 a.m. to 9:00 p.m.) profiles of ghrelin from 9 of the 12 participants after 2 days with 4 hours in bed or 2 days with 10 hours in bed. Mean ghrelin levels were 28% higher in the afternoon and early evening (12:00 noon to 9:00 p.m.) when sleep was restricted. **C** and **D**. Ratings of hunger (*C*) (0- to 10-cm visual analogue scale) and overall appetite (*D*) (0- to 70-cm visual analogue scale) after 2 days with 4 hours in bed or 2 days with 10 hours in bed. When sleep was restricted, ratings of hunger and overall appetite increased by 24% and 23%, respectively.

protein-rich nutrients (meat, poultry, fish, eggs, and dairy foods) was not significantly affected by sleep duration (**Table 1**). When we considered the changes in ghrelin and leptin in an integrated fashion by calculating the ghrelin-to-leptin ratio, the increase in hunger was proportional to the increase in ghrelin-to-leptin ratio ($r = 0.87$) (**Figure 2**). Almost 70% of the variance in increased hunger could be accounted for by the increase in the ghrelin-to-leptin ratio.

DISCUSSION

We observed that sleep duration may affect the circulating levels of neuroendocrine factors that regulate hunger and appetite. Two days with 4 hours of time in bed each night were associated with an 18% decrease in the levels of the anorexigenic hormone leptin. By comparison, 3 days of underfeeding by approximately 900 calories per day in healthy lean volunteers has been reported to result in a decrease of leptin levels averaging 22% (4). Sleep curtailment was also associated with an almost 28% increase in daytime levels of the orexigenic factor ghrelin. The reciprocal changes in leptin and ghrelin that we observed in response to sleep restriction were associated with a 24% increase in hunger and a 23% increase in appetite. Appetite for calorie-dense nutrients with high carbohydrate content, including sweets, salty snacks, and starchy foods, increased by 33% to 45%. In contrast, appetite for fruits, vegetables, and high-protein nutrients was less affected. The increase in hunger during sleep restriction was strongly correlated with the increase in the ghrelin-to-leptin ratio.

Our study involved intensive physiologic monitoring under laboratory conditions in a relatively small group of normal young men and will need to be replicated in a larger sample. In addition, because age and sex may affect neuroendocrine regulation of appetite (3, 5), our findings may not readily apply to women and older adults. Recent findings from a population study involving 1030 persons are, however, in complete agreement with our observations (13). In that study, restricted duration of sleep was associated with reduced leptin levels, increased ghrelin levels, and elevated body mass index (13).

The alterations in appetite regulation that we observed after sleep restriction may reflect a normal adaptation to the increased caloric need associated with extended wakefulness. Our experimental protocol was designed to keep energy intake and activity levels as constant as possible, and the extra hours of wakefulness during sleep restriction were spent lying in bed or sitting in a comfortable armchair. Although several studies have indicated that differences in energy expenditure between sleeping in bed compared with quiet wakefulness are very small, if at all detectable (14, 15), it is not known whether sleep deprivation increases the energy requirements of maintaining wakefulness. In studies in rats in which the disk over water method achieved total sleep deprivation, researchers observed a marked increase in energy expenditure that resulted in overall weight loss despite increased food intake (2). However, an increased energy demand is an intrinsic feature of this method of sleep deprivation, which involves forced locomotion and repeated water immersions. Careful studies of energy balance in sleep-restricted humans under comfortable sedentary conditions will be necessary to determine whether increased hunger will result in excessive food intake and weight gain.

The causes of decreased leptin levels and increased

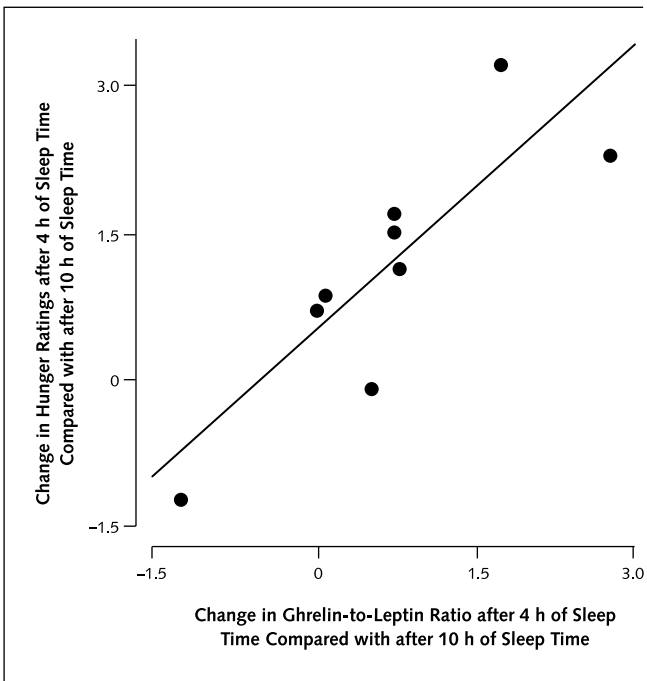
Table. **Average Ratings of Appetite after 2 Days of Sleep Restriction or Sleep Extension**

Food Category*	Ratings for 10 h in Bed (n = 12)	Ratings for 4 h in Bed (n = 12)	*P* Value	Change, %
Sweets (cake, candy, cookies, ice cream, and pastry)	5.4	6.6	0.03	33
Salty food (chips, salted nuts, pickles, and olives)	5.0	6.7	0.02	45
Starchy food (bread, pasta, cereal, and potatoes)	5.9	7.4	0.03	33
Fruits and fruit juices	6.4	7.2	0.07	17
Vegetables	5.6	6.6	0.02	21
Meat, poultry, fish, and eggs	5.9	6.9	0.11	21
Dairy (milk, cheese, and yogurt)	5.5	6.4	>0.2	19
Overall appetite†	39.7	47.7	0.01	23

* Each category is rated on a 0- to 10-cm visual analogue scale.
† Rated on a 0- to 70-cm visual analogue scale.

ghrelin levels in a state of sleep loss remain to be determined. We have previously shown that 6 days of sleep restriction in healthy adults resulted in an increase in cardiac sympathovagal balance (16). Some, but not all, studies have indicated that sleep loss is associated with increased sympathetic nervous system outflow (17). Because leptin release is inhibited by sympathetic nervous system activity (18), decreased leptin levels, in the presence of a sleep debt, may result from an inhibitory effect of increased sympathetic outflow. Increased cardiac sympathovagal balance could also reflect decreased vagal activity, which could explain increased ghrelin levels. Several studies have shown that the vagus has a negative influence on ghrelin (5, 19, 20).

Figure 2. **Association between the change in hunger ratings and the change in ghrelin-to-leptin ratio during the 12:00 noon to 9:00 p.m. time period when sleep is restricted as compared with extended.**



The changes in hunger ratings and in ghrelin-to-leptin ratio were calculated as the values obtained after 4 hours in bed minus the values obtained after 10 hours in bed. For each of these variables, negative values were obtained when the variable measured after 10 hours in bed was higher than when measured after 4 hours in bed. The Spearman coefficient was 0.87 and the *P* value was 0.01.

Sleep loss due to voluntary curtailment of time in bed has become a hallmark of modern society. Self-reported sleep duration in the United States has decreased by 1 to 2 hours during the second half of the 20th century (7–10). The proportion of young adults sleeping 8 to 8.9 hours per night has decreased from 40.8% in 1960 to 23.5% in 2001–2002 (8–10). During the same time period, the incidence of obesity has nearly doubled (21). Three epidemiologic studies have found a relationship between higher body mass index and shorter sleep duration (13, 22, 23). This epidemiologic evidence, together with our experimental findings that sleep restriction affects leptin levels, ghrelin levels, hunger, and appetite, suggests that additional studies should examine the possible role of chronic sleep curtailment as a previously unrecognized risk factor for obesity.

From University of Chicago, Chicago, Illinois, and Université Libre de Bruxelles, Brussels, Belgium.

Acknowledgment: The authors thank Paul Rue for performing the leptin assays, Miho Yoshida for performing the ghrelin assays, and Kristen Knutson for providing statistical assistance. The authors also thank the volunteers for their participation in this demanding study and the nursing staff of the University of Chicago General Clinical Research Center for their expert assistance.

Grant Support: In part by grants from the National Institutes of Health (DK-41814, AG-11412, and HL-72694), from the European Sleep Research Society, from the Belgian Fonds de la Recherche Scientifique Médicale (FRSM-3.4583.02), from the University of Chicago Diabetes Research and Training Grant (NIH DK-20595), and from The University of Chicago General Clinical Research Center (NIH MO1-RR-00055).

Potential Financial Conflicts of Interest: None disclosed.

Requests for Single Reprints: Eve Van Cauter, PhD, Department of Medicine, MC 1027, University of Chicago, 5841 South Maryland Avenue, Chicago, IL 60637.

Current author addresses and author contributions are available at www.annals.org.

References

1. **Danguir J, Nicolaidis S.** Dependence of sleep on nutrients' availability. Physiol Behav. 1979;22:735-40. [PMID: 225752]

2. **Everson CA, Bergmann BM, Rechtschaffen A.** Sleep deprivation in the rat: III. Total sleep deprivation. Sleep. 1989;12:13-21. [PMID: 2928622]

3. **Ahima RS, Saper CB, Flier JS, Elmquist JK.** Leptin regulation of neuroendocrine systems. Front Neuroendocrinol. 2000;21:263-307. [PMID: 10882542]

4. **Chin-Chance C, Polonsky KS, Schoeller DA.** Twenty-four-hour leptin levels respond to cumulative short-term energy imbalance and predict subsequent intake. J Clin Endocrinol Metab. 2000;85:2685-91. [PMID: 10946866]

5. **van der Lely AJ, Tschop M, Heiman ML, Ghigo E.** Biological, physiological, pathophysiological, and pharmacological aspects of ghrelin. Endocr Rev. 2004; 25:426-57. [PMID: 15180951]

6. **Muccioli G, Tschop M, Papotti M, Deghenghi R, Heiman M, Ghigo E.** Neuroendocrine and peripheral activities of ghrelin: implications in metabolism and obesity. Eur J Pharmacol. 2002;440:235-54. [PMID: 12007539]

7. **Kripke DF, Simons RN, Garfinkel L, Hammond EC.** Short and long sleep and sleeping pills. Is increased mortality associated? Arch Gen Psychiatry. 1979; 36:103-16. [PMID: 760693]

8. **National Sleep Foundation.** 2000 "Sleep in America" Poll. Washington, DC: National Sleep Foundation; 2000.

9. **National Sleep Foundation.** 2001 "Sleep in America" Poll. Washington, DC: National Sleep Foundation; 2001.

10. **National Sleep Foundation.** 2002 "Sleep in America" Poll. Washington, DC: National Sleep Foundation; 2001.

11. **Stubbs RJ, Hughes DA, Johnstone AM, Rowley E, Reid C, Elia M, et al.** The use of visual analogue scales to assess motivation to eat in human subjects: a review of their reliability and validity with an evaluation of new hand-held computerized systems for temporal tracking of appetite ratings. Br J Nutr. 2000;84: 405-15. [PMID: 11103211]

12. **Fernstrom MH, Krowinski RL, Kupfer DJ.** Appetite and food preference in depression: effects of imipramine treatment. Biol Psychiatry. 1987;22:529-39. [PMID: 3580430]

13. **Taheri S, Lin L, Austin D, Young T, Mignot E.** Short sleep duration is associated with reduced leptin, elevated ghrelin, and increased body mass index (BMI) [Abstract]. Sleep. 2004;27(Abstr Suppl):A146-7.

14. **Seale JL, Conway JM.** Relationship between overnight energy expenditure and BMR measured in a room-sized calorimeter. Eur J Clin Nutr. 1999;53:107-11. [PMID: 10099943]

15. **Zhang K, Sun M, Werner P, Kovera AJ, Albu J, Pi-Sunyer FX, et al.** Sleeping metabolic rate in relation to body mass index and body composition. Int J Obes Relat Metab Disord. 2002;26:376-83. [PMID: 11896493]

16. **Spiegel K, Leproult R, Van Cauter E.** Impact of sleep debt on metabolic and endocrine function. Lancet. 1999;354:1435-9. [PMID: 10543671]

17. **Irwin M, Thompson J, Miller C, Gillin JC, Ziegler M.** Effects of sleep and sleep deprivation on catecholamine and interleukin-2 levels in humans: clinical implications. J Clin Endocrinol Metab. 1999;84:1979-85. [PMID: 10372697]

18. **Rayner DV, Trayhurn P.** Regulation of leptin production: sympathetic nervous system interactions. J Mol Med. 2001;79:8-20. [PMID: 11327106]

19. **Sugino T, Yamaura J, Yamagishi M, Kurose Y, Kojima M, Kangawa K, et al.** Involvement of cholinergic neurons in the regulation of the ghrelin secretory response to feeding in sheep. Biochem Biophys Res Commun. 2003;304:308-12. [PMID: 12711315]

20. **Heath RB, Jones R, Frayn KN, Robertson MD.** Vagal stimulation exaggerates the inhibitory ghrelin response to oral fat in humans. J Endocrinol. 2004; 180:273-81. [PMID: 14765979]

21. **Flegal KM, Carroll MD, Ogden CL, Johnson CL.** Prevalence and trends in obesity among US adults, 1999-2000. JAMA. 2002;288:1723-7. [PMID: 12365955]

22. **Kripke DF, Garfinkel L, Wingard DL, Klauber MR, Marler MR.** Mortality associated with sleep duration and insomnia. Arch Gen Psychiatry. 2002;59: 131-6. [PMID: 11825133]

23. **Vioque J, Torres A, Quiles J.** Time spent watching television, sleep duration and obesity in adults living in Valencia, Spain. Int J Obes Relat Metab Disord. 2000;24:1683-8. [PMID: 11126224]

Current Author Addresses: Dr. Spiegel: Laboratoire de Physiologie, Centre d'Etude des Rythmes Biologiques (CERB), Université Libre de Bruxelles, Campus Hôpital Erasme–CPI 604, 808, Route de Lennik, B-1070 Brussels, Belgium.
Drs. Tasali, Penev, and Van Cauter: Department of Medicine, MC 1027, University of Chicago, 5841 South Maryland Avenue, Chicago, IL 60637.

Author Contributions: Conception and design: K. Spiegel, E. Van Cauter.
Analysis and interpretation of the data: K. Spiegel, E. Tasali, P. Penev, E. Van Cauter.
Drafting of the article: K. Spiegel, E. Tasali, E. Van Cauter.
Critical revision of the article for important intellectual content: E. Tasali, P. Penev, E. Van Cauter.
Final approval of the article: K. Spiegel, E. Tasali, P. Penev, E. Van Cauter.
Provision of study materials or patients: E. Van Cauter.
Statistical expertise: E. Van Cauter.
Obtaining of funding: K. Spiegel, E. Van Cauter.
Administrative, technical, or logistic support: E. Van Cauter.
Collection and assembly of data: K. Spiegel, E. Tasali, E. Van Cauter.