0021-972X/04/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 89(5):2119–2126

doi: 10.1210/jc.2003-031562

Adverse Effects of Modest Sleep Restriction on Sleepiness, Performance, and Inflammatory Cytokines

A. N. VGONTZAS, E. ZOUMAKIS, E. O. BIXLER, H.-M. LIN, H. FOLLETT, A. KALES, AND G. P. CHROUSOS

Sleep Research and Treatment Center, Department of Psychiatry (A.N.V., E.O.B., H.F., A.K.), and Health Evaluation Sciences (H.-M.L.), Pennsylvania State University College of Medicine, Hershey, Pennsylvania 17033; and Pediatric and Reproductive Endocrinology Branch, National Institutes of Health (E.Z., G.P.C.), Bethesda, Maryland 20892

Total sleep restriction in humans is associated with increased daytime sleepiness, decreased performance, and hormonal/metabolic disturbances. The effects of mild chronic sleep restriction that mimic real life are not known. To assess the effects of modest sleep restriction from 8 to 6 h/night for 1 wk, 25 young, healthy, normal sleepers (12 men and 13 women) were studied for 12 consecutive nights in the sleep laboratory. After 1 wk of sleep restriction, although subjects' nighttime sleep was deeper, subjects were significantly sleepier (multiple sleep latency test) and performed worse in four primary variables of psychomotor vigilance test (both $P < 0.01$). Furthermore, 24-h secretion of IL-6 was increased by 0.8 ± 0.3 pg/ml ($P < 0.05$) in both sexes, whereas TNFα was increased only in men. Also, the peak cortisol secretion was lower after sleep restriction than at baseline, and this difference was stronger in men (55.18 ± 24.83 nmol/liter; $P < 0.05$) than in women (35.87 ± 24.83 nmol/liter; $P < 0.16$). We conclude that in young men and women, modest sleep loss is associated with significant sleepiness, impairment of psychomotor performance, and increased secretion of proinflammatory cytokines. Given the potential association of these behavioral and physical alterations with health, well-being, and public safety, the idea that sleep or parts of it are optional should be regarded with caution. (*J Clin Endocrinol Metab* 89: 2119–2126, 2004)

ALTHOUGH TOTAL OR severe partial sleep deprivation is not commonly practiced in the general population, a modest reduction of sleep time on a chronic basis appears to be a characteristic of modern civilization. It has been estimated that although in the first half of the 20th century the average person used to sleep 9 h/d, today an individual sleeps, on the average, 7.5 h/d(1). The increasing pressure from work, family, and social changes have resulted in many people sleeping a total of 6 h/d or even less (2). Although some researchers have expressed concern about the effects of chronic sleep curtailment or chronic sleep debt (3, 4), others have argued that an individual's body and mind can adapt to these changes without any detrimental effects (5). Thus, it was reported that acute deprivation of the last 3.5 h of sleep did not increase the delta (0–3 Hz) electroencephalograms (EEGs) in recovery sleep (6), suggesting that nondelta sleep might be unnecessary. These results supported the hypothetical division of sleep into core sleep, which consisted primarily of slow wave sleep (SWS), and optional stage 2 sleep, which might be "a time filler when the mammals have little else to do" (5).

However, significant daytime sleepiness has been reported after restricting sleep by 50% for 3 consecutive nights (6) or after reduction of habitual sleep by 33% for 1 wk (4) in young healthy adults. Furthermore, a recent study by Van Dongen *et al.* (7) showed that even a sleep restriction to 6 h in 13 healthy adults (10 men and three women) was associated with a deterioration of psychomotor performance. In our study we chose to restrict sleep from 8 to 6 h (25%) for 1 wk to mimic real-life situations and to test whether these 2 h of sleep are optional for healthy young men and women in terms of effects on daytime sleepiness, psychomotor performance, and physical health.

The potential impact of chronic sleep loss on human health, with the exception of the behavioral effects, has received little attention, and this only recently. In 1999, we published a study showing that in young men a night of total sleep loss was associated with sleepiness and fatigue, and a marked increase in the circulating concentrations of the proinflammatory cytokine IL-6 the next day (8). At about the same time, Van Cauter and her colleagues (9) reported that sleep restriction to 4 h/d for 6 d was associated with significant impairment of glucose metabolism. Thus, the aim of this study was to assess in young healthy men and women the impact of modest sleep loss not only on daytime sleepiness and performance, but also on plasma levels of the proinflammatory cytokines IL-6 and TNFα and the end product of the stress axis, cortisol.

Subjects and Methods

Subjects

Twenty-five normal sleepers (12 men and 13 women), 19–34 yr of age (mean ± SD, 25.6 ± 4.1 for men; 24.8 ± 3.4 for women), with a body mass index of 23.8 ± 2.3 (24.6 ± 1.5 for men; 23.1 ± 2.7 for women), were recruited from the community and from the medical and technical staff and students of Milton S. Hershey Medical Center. They were in good general health, physically active but not excessively so, had no sleep

Abbreviations: EEG, Electroencephalogram; MSLT, multiple sleep latency test; PVT, psychomotor vigilance task; REM, rapid eye movement; RT, reaction time; SWS, slow wave sleep.

JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.

complaints or circadian abnormalities, were not taking any medications, and were screened in the sleep laboratory for sleep disordered breathing, nocturnal myoclonus, or other primary sleep disorders. Also, a battery of clinical tests (including complete cell blood count, urinalysis, thyroid indexes, electrocardiogram, and urine screen for drug use) were negative for abnormal findings.

Protocol

Each subject participated in a sleep restriction experiment that lasted 12 d. Adequate sleep time and regular sleep schedules were verified with a sleep log and actigraphy for 2 wk before the study. During the first 4 consecutive nights in the sleep laboratory, the subjects were allowed to sleep for 8 h (2230–0630 h). During the subsequent 8 nights, the subjects were awakened 2 h earlier (0430 h). After staying in the laboratory for 2 h, they were dismissed to their daily activities. They were instructed not to nap, to stay on the same diet including caffeinated beverages, and not to deviate from their normal daily routines throughout the experiment. To assess the compliance of the subjects with the no nap instructions, the subjects were monitored with actigraphy attached to the wrist of the nondominant hand throughout the experiment. Blood sampling was performed for 24 h (0800–0730 h the next day) every 30 min on the fourth day (the last day before the sleep-restricted schedule) and the 12th day after the completion of 1 wk of sleep restriction (8, 10, 11). In women, both periods of blood sampling took place during the follicular phase, as evidenced by progesterone levels obtained on the 4th and 12th days of the experiment. Throughout sampling, the subjects were ambulatory and allowed to watch television, play computer and table games, go to the bathroom, *etc.* Also, they were instructed not to change their diet, and their three daily meals were at about 0700, 1200, and 1800 h. The subjects remained in a lying or sitting position for the rest of the experiment when awakened early with the room lights on. The brightness of the light in the room in which the blood drawing took place was, on the average, about 800 lux, ranging from a minimum of 200 to 1400 lux (Minolta III F digital light meter Konica, Minolta, Tokyo, Japan). The protocol was approved by the institutional review board, and each subject signed a written consent form.

Sleep recordings

Assessment of nighttime sleep. Each subject was monitored with EEG, electrooculograph, and electromyograph recordings continuously for 8-h (2230–0630 h) during the first 4 nights and for 6 h (2230–0430 h) of the remaining 8 nights. The sleep schedule in the sleep laboratory at baseline was similar to the subjects' normal sleep schedule. Polysomnographic recordings were obtained and scored in accordance with standard methods (12). Sleep parameters were assessed as previously described (8, 10, 11).

Assessment of daytime sleepiness and performance. Multiple sleep latency test (MSLT): During the 4th and the 12th days (days of blood sampling), the subjects' levels of sleepiness and alertness were evaluated using MSLT (13). In our study, we allowed six 20-min opportunities to sleep at 0900, 1200, 1500, 1700, 1900, and 2100 h to sample sleepiness throughout the day, including evening and presleep periods. The onset of sleep was established in two different ways: the first, which is the standard MSLT definition (13), requires the presence of any sleep stage for a duration of one epoch (30 sec) or longer, and the second requires that if the initial stage of sleep is stage 1, it must be followed, without any intervening wakefulness, by 60 sec of stage 2, 3, 4, or rapid eye movement (REM) sleep (10). Also, before each nap opportunity, subjective levels of sleepiness were assessed using a visual analog scale that ranged from 0 (not sleepy at all) to 10 (extremely sleepy) and a seven-point question: "how sleepy do you feel right now?"

Psychomotor vigilance task (PVT): The PVT is a test of behavioral alertness, and it involves a simple (as opposed to choice) reaction time (RT) test designed to evaluate the ability to sustain attention and respond in a timely manner to salient signals (7, 14). The primary variables assessed in our study are: 1) frequency of lapses, which refer to the number of times the subject fails to respond to the signal or fails to respond in a timely manner; 2) duration of lapse domain, which refers to shifts in lapse duration calculated from the 10% slowest RTs, a metric that reflects vigilance response slowing; 3) optimum response times, which are the average of the 10% fastest RTs per trial, and reflect the very best performance an operator is capable of producing; and 4) the median RT in the trial. In this study PVT was administered every hour during the 4th and 12th days. Also, the number of women who completed the PVT was lower than that of men because we obtained the PVT after the start of this experiment.

Hormone assays

Blood collected from the indwelling catheter was transferred to an EDTA-containing tube and refrigerated until centrifugation (within 3 h). The plasma was frozen at −70 C until assay. Cortisol levels were measured by specific immunoassay techniques, and plasma TNFα and IL-6 were measured by ELISA (R&D Systems, Minneapolis, MN) as previously described (10, 11).

Statistical analyses

To assess the effects of sleep deprivation on hormone variables as a function of time of day, differences in the 24-h TNFα, IL-6, and cortisol levels before and after intervention were analyzed using a mixed effects multivariate ANOVA, which takes into account the intra- and intersubject correlations. The intervention effect (*e.g.* sleep restriction) and group (*e.g.* gender) were treated as fixed effects. The subjects were treated as random effect, and the repeated measurements (*e.g.* 24-h blood samples) were nested within subjects (15). Time, gender, and their interaction effects were tested for significance. Similar approaches using multivariate ANOVA were used to analyze the effects of sleep deprivation on daytime sleepiness (MSLT) and performance (PVT). MSLT data are presented, with sleep onset defined as the presence of either any stage of sleep for 30 sec or at least 60 sec of stage 2 sleep. PVT data were analyzed as described previously (14). To compare the trends (quadratic *vs.* linear) of the MSLT data and the PVT data, random coefficient models were used. To assess the effects of sleep restriction on sleep, we compared averaged data from nights 10 and 11 to averaged data from nights 2 and 3 (baseline). Correlations of sleep variables with MSLT and hormone data were calculated using the Pearson product-moment correlation while adjusting for baseline MSLT or hormone values. Data are presented as the mean ± SE, except for demographic data (age and body mass index), for which we used SD to describe variance.

Results

Sleep at baseline and after 1 wk of partial sleep restriction

After 1 wk of partial sleep restriction, subjects demonstrated significantly shorter sleep latencies, increased percentage of total sleep time, and decreased percentage of wake time after sleep onset (Table 1). In terms of sleep stages, subjects spent more time in SWS (deep sleep) and less time in stage 1 sleep (light sleep). Also, REM latency was significantly decreased compared with baseline. Interestingly, the above-described responses of sleep la-

TABLE 1. Nighttime sleep pre- and postsleep restriction in 25 normal sleepers, young men and women

	Nights 2–3	Nights 10–11
SL (min)	13.3 ± 2.2	6.4 ± 0.6[a]
% WTASO	7.3 ± 0.9	3.7 ± 0.6[a]
% ST	90.2 ± 1.5	94.0 ± 0.8[a]
% Stage 1	3.3 ± 0.4	2.5 ± 0.3[a]
% Stage 2	60.2 ± 1.5	58.1 ± 1.5
% SWS	14.5 ± 1.4	16.9 ± 1.7[a]
% REM	21.9 ± 1.0	22.4 ± 1.0
REM latency (min)	83.4 ± 3.9	68.4 ± 3.8[a]

Data represent the mean ± SE. Sleep laboratory recording lasted 8 h during nights 2–3 and 6 h during nights 10–11. WTASO, Wake time after sleep onset; % ST, percentage sleep time; SWS, slow wave sleep.

[a] $P < 0.05$.

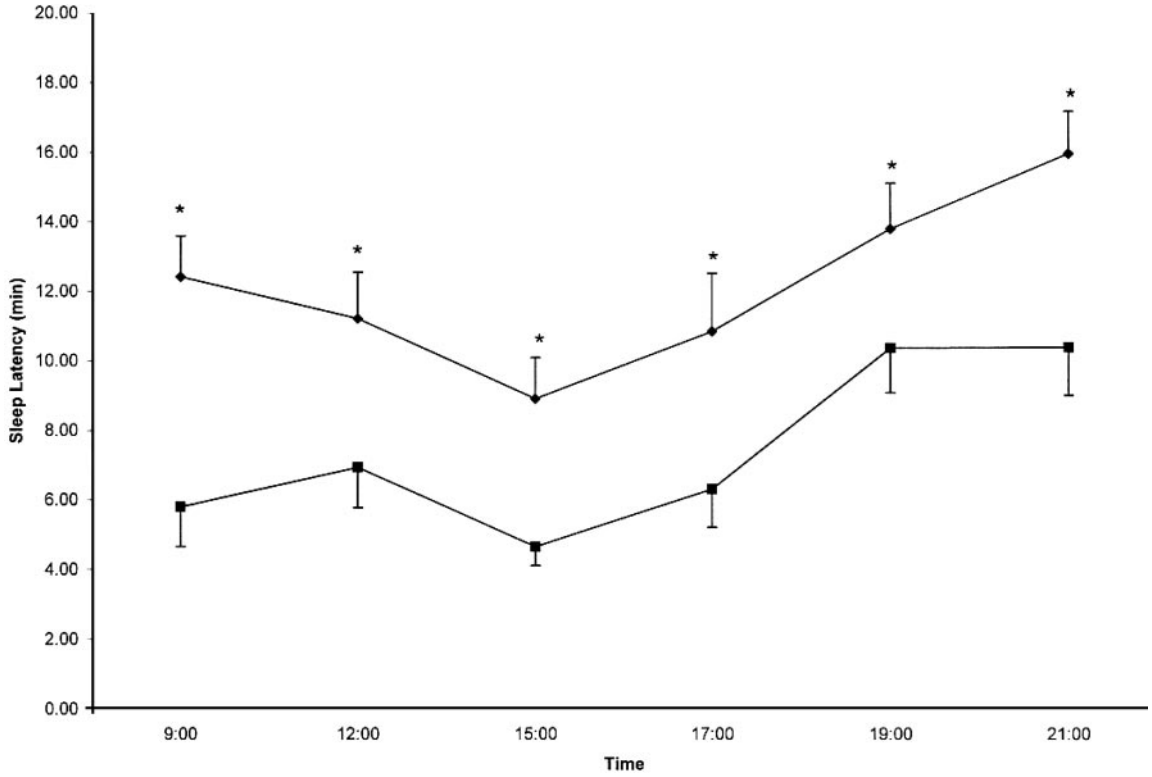

FIG. 1. Mean sleep latency during six daytime naps (MSLT) before (♦) and after (■) partial sleep restriction. Sleep onset was defined as the presence of any stage of sleep for 30 sec or more. *Bar* indicates SE. *, $P < 0.05$.

tency, percent sleep time (ST), and percent SWS to sleep restriction were significant in women, but not in men, who showed similar nonsignificant trends. Also, women at baseline had a higher amount of SWS than men (in terms of both percentages and absolute amounts; 17.7 ± 2.0% *vs.* 11.0 ± 1.7%, and 75.2 ± 7.9 *vs.* 47.9 ± 7.1 min, respectively; both $P < 0.05$).

Daytime sleepiness and performance

MSLT. After 1 wk of sleep restriction, both the average daily sleep latency as well as sleep latencies at each time point of the MSLT (0900, 1200, 1500, 1700, 1900, and 2100 h) were significantly shorter compared with baseline (Fig. 1). The differences were significant when we used the standard MSLT criterion of 30 sec of any stage of sleep (12.4 ± 1.2 *vs.* 5.8 ± 1.4, 11.2 ± 1.2 *vs.* 6.9 ± 1.2, 8.9 ± 0.9 *vs.* 4.7 ± 0.5, 10.9 ± 1.4 *vs.* 6.3 ± 0.9, 13.8 ± 1.3 *vs.* 10.4 ± 0.9, and 16.0 ± 1.2 *vs.*10.4 ± 1.0; all $P < 0.05$) or the criterion of 1 min of stage 2 sleep (15.0 ± 1.2 *vs.* 6.8 ± 1.3, 12.3 ± 1.4 *vs.* 7.3 ± 1.2, 10.7 ± 1.3 *vs.* 7.3 ± 1.1, 11.7 ± 1.4 *vs.* 7.1 ± 1.1, 15.9 ± 1.7 *vs.* 11.5 ± 1.3, and 17.6 ± 1.1 *vs.* 12.4 ± 1.5; all $P < 0.05$). The stronger responses were observed at 0900 and 2100 h, when sleep latency was decreased by 6.6 ± 1.3 and 5.6 ± 1.1 min, respectively (both $P < 0.01$). There were no gender differences. A concave quadratic curve was fitted both at baseline ($P < 0.01$) and after sleep restriction ($P = 0.03$). Subjective data also indicated that after 1 wk of sleep restriction, subjects were sleepier than at baseline ($P < 0.05$). Also, after adjusting for baseline MSLT values, the increase in percent ST and nocturnal SWS (minutes) after 1 wk of sleep restriction (nights 10 and 11 minus nights 2 and 3) was associated with decreased objective sleepiness ($r_{xy} = 0.43$; $P < 0.05$ and $r_{xy} = 0.38$; $P = 0.06$, respectively).

PVT. Analyses of performance data obtained from a subset of 18 individuals (13 men and five women) showed a significant deterioration of performance in all four variables evaluated (number of lapses, slowest 10% RTs per trial, fastest 10% RTs per trial, and median RT; Table 2). No time effects were detected. A line indicating deteriorating performance as the day progressed was linearly fit to the PVT data, both at baseline and after sleep restriction (both $P < 0.05$). There was no correlation between the change (pre- *vs.* postsleep restriction) in MSLT values and that in PVT values.

TABLE 2. Summary of performance variables pre- and postsleep restriction

	Pre-	Post-	Δ	*P*
PVT lapse total[a]	3.5 ± 0.4	6.0 ± 0.9	2.5 ± 0.5	0.01
PVT fastest 10% (msec)	176.3 ± 3.6	190.3 ± 5.7	14.0 ± 4.3	0.01
PVT slowest 10%[b]	2.3 ± 0.2	1.6 ± 0.2	0.6 ± 0.08	0.01
PVT median RT (msec)	228.7 ± 7.5	275.5 ± 21.3	47.0 ± 17.1	0.01

The results shown are based on data from 18 subjects.
[a] Conducted on transformed lapse frequency ($\sqrt{x} + \sqrt{x} + 1$]) (4).
[b] Conducted on transformed data 1/RT); data are presented in seconds (4).

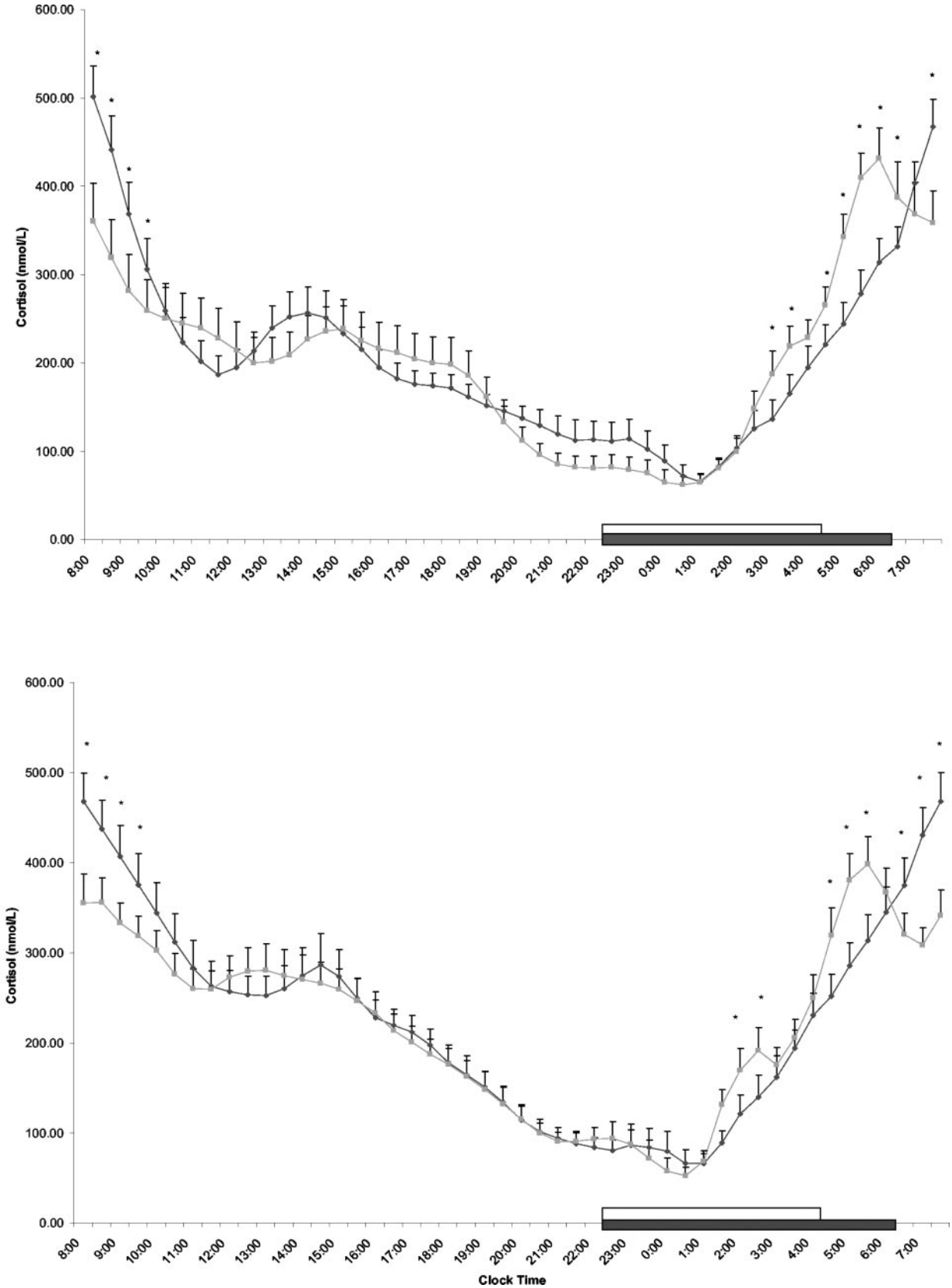

FIG. 2. Twenty-four-hour circadian secretory pattern of cortisol before (♦) and after (■) partial sleep restriction in women (*top*) and men (*bottom*). *Bar* indicates SE. The *thick black bar* on the *abscissa* represents the sleep recording period during baseline. The *open bar* on the *abscissa* represents the sleep recording period during partial sleep restriction. *, $P < 0.05$.

Effects of sleep restriction on cortisol, IL-6, and TNFα secretion

24-h cortisol secretion. Overall, sleep restriction did not significantly affect 24-h cortisol secretion in either men or women. However, there was a significant effect in terms of the circadian secretory pattern of the hormone, as indicated by the significant time effect and the time and gender interaction effect. Specifically, the peak cortisol secretion in the morning was lower after sleep restriction than at baseline (difference between pre- and postsleep restriction, 44.14 ± 16.55 nmol/liter; $P < 0.05$), and this difference was stronger in men (55.18 ± 24.83 nmol/liter; $P < 0.05$) than in women (35.87 ± 24.83 nmol/liter; $P = 0.16$; Fig. 2). Also, cortisol secretion during the morning hours after the early awakening (0430–1130) was significantly lower than baseline, and this difference was stronger in men (57.94 ± 11.04 nmol/liter; $P < 0.01$) than in women (22.07 ± 13.80 nmol/liter; $P = 0.08$). In both genders, the peak of cortisol secretion was shifted by 2 h earlier than baseline (0800 *vs.* 0600 h; $P < 0.05$).

Sleep restriction did not significantly affect the nadir value of cortisol secretion, or the afternoon or evening presleep levels. During the early part of sleep (2230–0130 h) after 1 wk of sleep restriction, there was a significant decrease in cortisol secretion compared with baseline in women, but not in men. In both genders, during the latter part of sleep on the same night (0130–0430 h), there was a significant increase in the rate of cortisol secretion compared with the corresponding time window at baseline (night 4; $P < 0.01$).

24-h IL-6 secretion. Sleep restriction was associated with a significant overall increase in 24-h secretion of IL-6 (post minus pre, 0.8 ± 0.3 pg/ml; $P < 0.05$; Fig. 3). No effects of gender, time, or their interaction were detected. Postsleep restriction IL-6 secretion peaked in the morning immediately after early awakening and in the evening before the sleep period. The strongest differences for both genders were detected between 0430–0630 h (1.4 ± 0.5 pg/ml; $P < 0.01$) and 1830–2230 h (1.3 ± 0.5 pg/ml; $P < 0.01$). The drop in IL-6 levels from the presleep period to early sleep was sharper in the postrestriction condition than at baseline.

24-h TNFα secretion. Because of significant gender effects, TNFα data were analyzed separately for the two genders. Sleep restriction was associated with a significant increase in the overall 24-h TNFα secretion in men (post- minus presleep restriction, 0.26 ± 0.1 pg/ml; $P < 0.01$; Fig. 4), but not in women (−0.06 ± 0.03; P = NS). Also, at baseline, women had a significantly lower 24-h TNFα secretion than men (2.0 ± 0.2 *vs.* 3.05 ± 0.4 pg/ml; $P < 0.05$).

Discussion

Our study shows that a modest daily restriction of sleep by 2 h/night for 1 wk in young healthy men and women is associated with significant increase in sleepiness, decrements in psychomotor performance, and increased secretion of the proinflammatory cytokines IL-6 and/or TNFα. This study also demonstrated that increased sleepiness and decreased performance occurred despite SWS preservation in terms of absolute amounts or increase as a percentage of total sleep. The behavioral and hormonal/cytokine effects of elimination of 2 h of sleep, which was primarily stage 2 sleep and REM sleep, argue against the distinction of core (*i.e.* SWS) *vs.* optional (*i.e.* stage 2) sleep and the suggestion that the latter is unnecessary for human homeostasis and well-being (5).

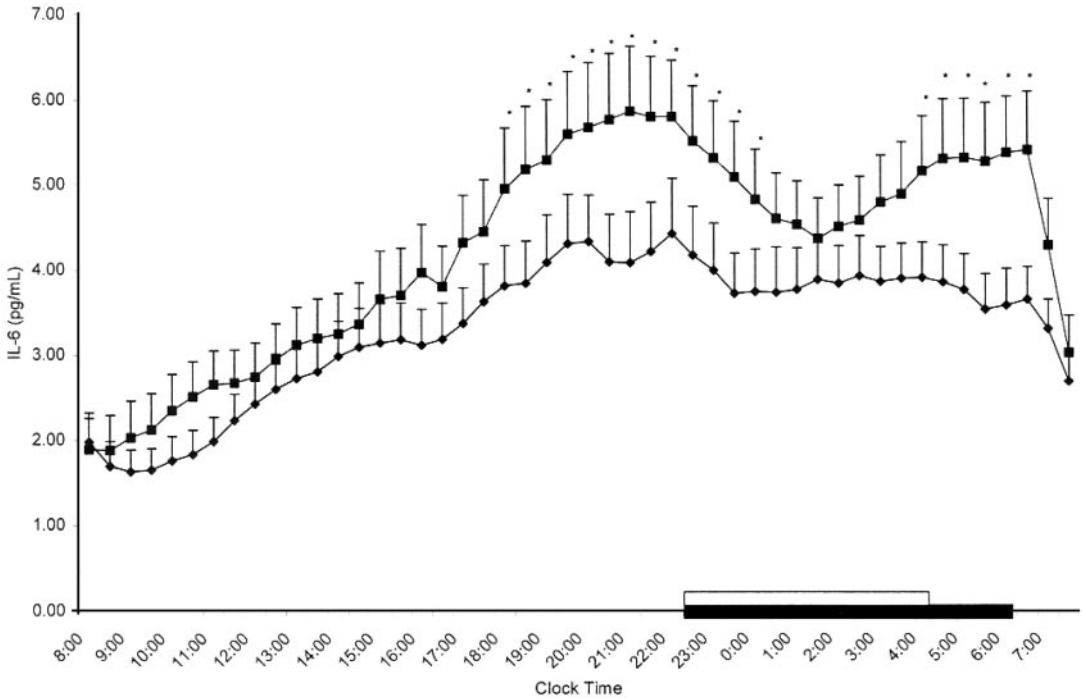

FIG. 3. Twenty-four-hour circadian secretory pattern of IL-6 before (◆) and after (■) partial sleep restriction. *Bar* indicates SE. The *thick black bar* on the *abscissa* represents the sleep recording period during baseline. The *open bar* on the *abscissa* represents the sleep recording period during partial sleep restriction. *, $P < 0.05$.

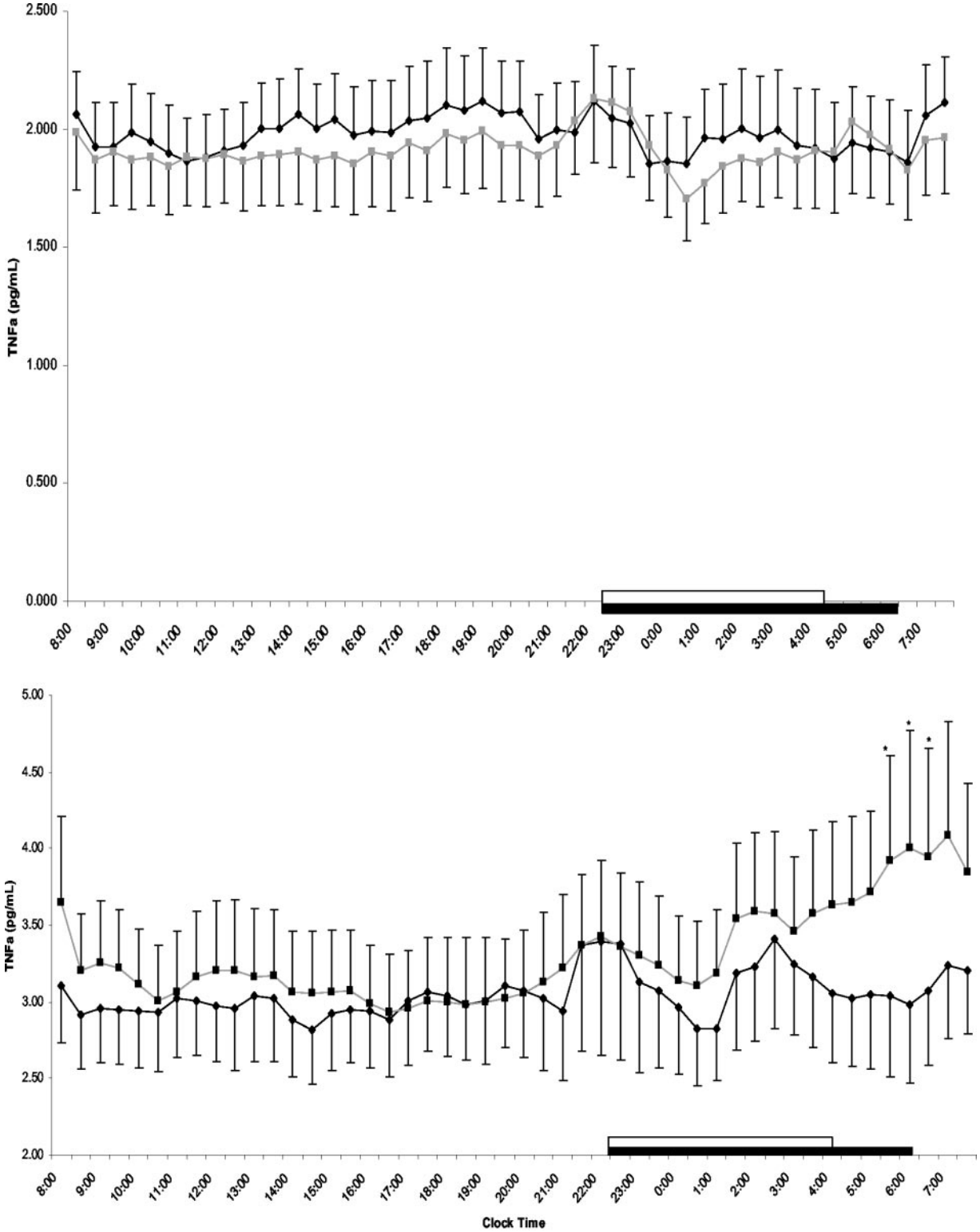

FIG. 4. Twenty-four-hour circadian secretory pattern of TNFα before (♦) and after (■) partial sleep restriction in women (*top*) and men (*bottom*). The *thick black bar* on the *abscissa* represents the sleep recording period during baseline. The *open bar* on the *abscissa* represents the sleep recording period during partial sleep restriction. *, $P < 0.05$.

Sleepiness and fatigue are not only troubling to the individual, but are also a major risk factor for public safety, including transportation accidents (16) and accidents in the workplace, especially under critical circumstances such as emergency room workers or physicians on call (17), workers in nuclear reactors, *etc.* Our study refutes views that sleep is

optional or a waste of time, views that have become increasingly popular among groups of the population, particularly those who are young and in their productive years.

Previous findings from our group (8) and other investigators (18) have shown that total sleep loss is associated with an increased secretion of IL-6 and TNFα the next day. Our study suggests that even modest sleep loss is associated with an increased secretion of these proinflammatory cytokines. It should be noted that the increase in daytime secretion of IL-6 for this study is similar to that observed after 1 night of total sleep loss (0.75 ± 0.3 *vs.* 0.95 ± 0.6 pg/ml; P = nonsignificant).

Both IL-6 and TNFα are markers of systemic inflammation that may lead to insulin resistance, cardiovascular disease, and osteoporosis (19, 20). This suggests that mild sleep loss, besides its immediate behavioral effects, *i.e.* sleepiness and decrements in performance, may also be associated with long-term risks of significant morbidity and mortality. Our study cannot address the issue of whether the effects on hormones/cytokines depend on the cumulative number of hours lost, which would have required an interim assessment. An important question arises: are the reported elevations of plasma cytokines of any clinical or biological relevance? Although there is no direct answer to this question from this study, it should be noted that the increases in plasma levels of IL-6 and TNFα that we observed in our study are similar to the increases associated with conditions such as obesity (21) or aging (10) that are associated with increased morbidity and mortality. Also, elevations of IL-6 and its surrogate marker C-reactive protein similar to those reported in our study have been associated with an increased risk for cardiovascular morbidity and mortality (22–24).

The response of cortisol to sleep restriction in this study is consistent with our previous study of total sleep loss (25), but it is different from other studies that reported increased cortisol secretion, particularly in the evening after total or partial sleep loss (9, 26). Methodological differences between these studies, such as delayed bedtime *vs.* advanced wake time, constant recumbent condition during sleep loss *vs.* ambulatory, calories given iv in the form of glucose *vs.* regular meals, may explain the variance in terms of cortisol response. Also, it has been shown that upright position (27) or the transition from dim light to bright light (28) in the morning induces an elevation of the cortisol level. In our study the subjects when awakened early remained in a lying or sitting position, whereas the light that they were exposed to was that of a regular sleep laboratory bedroom, which is much less bright compared with that in the study cited (28). Thus, it is unlikely that hormonal measures in our study were affected by posture or lighting.

Sleepiness affected to a lesser degree those subjects who demonstrated a stronger build-up of nocturnal SWS (deep sleep) during restriction, suggesting that individuals with the greatest build-up of slow wave activity during chronic sleep loss can tolerate sleep loss with the least increase in sleepiness (29).

An interesting finding of our study is that women appear to be more resilient to some extent than men to the effects of sleep loss. Potential gender differences in the response to sleep loss have not been assessed or reported previously. In our study after sleep restriction, the elevation in plasma TNFα and the drop in the maximum cortisol value were significant only in men. Furthermore, women at baseline had more SWS than age-matched men by about 30 min. Several studies have reported that men compared with age-matched women tend to lose SWS faster (30, 31) and that they have lower power density on sleep EEG in delta and theta frequency (32). Also, a recent analysis of men and women from large general population samples showed that women had a better quantity (total sleep time) and quality (SWS and REM sleep) of sleep (33, 34). In addition, women had a stronger homeostatic response to sleep loss and were more resistant to the sleep-disturbing effects of blood drawing (35). Collectively, these data suggest that healthy women appear not only to sleep better, but that they also can cope better with sleep loss/sleep disturbance in terms of inflammation markers, which, in part, may contribute to women's lower cardiovascular risks and greater longevity.

In summary, modest chronic sleep loss is associated with significant sleepiness, impairment of psychomotor performance, increased secretion of IL-6 and/or TNFα, and a significant drop of maximum values of cortisol. These changes occurred despite the fact that the quality of the restricted nocturnal sleep improved as a result of increased homeostatic pressure. The effects of sleep loss on TNFα and cortisol were stronger in men than in women. Given the potential association of these behavioral and physical alterations with health, well-being, and public safety, the idea that sleep or parts of it are optional should be regarded with caution.

Acknowledgements

Received September 5, 2003. Accepted February 1, 2004.

Address all correspondence and requests for reprints to: Alexandros N. Vgontzas, M.D., Department of Psychiatry, H073, Pennsylvania State University College of Medicine, 500 University Drive, Hershey, Pennsylvania 17033. E-mail: axv3@psu.edu.

This work was supported by National Institutes of Health Grant HL-64415.

References

1. **Webb WB, Agnew HW** 1975 Are we chronically sleep deprived? Psychon Bull Rev 6:47–48
2. **National Sleep Foundation** 2002 2002 sleep in America poll. Washington DC: National Sleep Foundation
3. **Bonnet MH, Arand DL** 1995 We are chronically sleep deprived. Sleep 18: 908–911
4. **Dinges DF, Pack F, Williams K, Gillen KA, Powell JW, Ott GE, Aptowicz C, Pack AI** 1997 Cumulative sleepiness, mood disturbance, and psychomotor vigilance performance decrements during a week of sleep restricted to 4–5 hours per night. Sleep 20:267–267
5. **Horne J** 1988 Why we sleep. New York: Oxford University Press
6. **Feinberg I, Gloyd TC, March JD** 1991 Acute deprivation of the terminal 3.5 hours of sleep does not increase delta (0–3 Hz) electroencephalograms in recovery sleep. Sleep 14:316–319
7. **Van Dongen HP, Maislin G, Mullington JM, Dinges DF** 2003 The cumulative cost of additional wakefulness: dose-response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. Sleep 2:117–126
8. **Vgontzas AN, Papanicolaou DA, Bixler EO, Lotsikas A, Zachman K, Kales A, Prolo P, Wong ML, Licinio J, Gold PW, Hermida RC, Mastorakos G, Chrousos GP** 1999 Circadian interleukin-6 secretion and quantity and depth of sleep. J Clin Endocrinol Metab 84:2603–2607
9. **Spiegel K, Leproult R, Van Cauter E** 1999 Impact of sleep debt on metabolic and endocrine function. Lancet 354:1435–1439
10. **Vgontzas AN, Zoumakis M, Bixler EO, Lin HM, Prolo P, Vela-Bueno A, Kales A, Chrousos GP** 2003 Impaired nighttime sleep in healthy old versus young adults is associated with elevated plasma interleukin-6 and cortisol

levels: physiologic and therapeutic implications. J Clin Endocrinol Metab 88: 2087–2095
11. **Vgontzas AN, Zoumakis M, Papanicolaou DA, Bixler EO, Prolo P, Lin HM, Vela-Bueno A, Kales A, Chrousos GP** 2002 Chronic insomnia is associated with a shift of interleukin-6 and tumor necrosis factor secretion from nighttime to daytime. Metabolism 7:887–892
12. **Rechtschaffen A, Kales A** 1968 Manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. Los Angeles: UCLA Brain Information Service
13. **Richardson GS, Carskadon MA, Flagg W, van den Hoed J, Dement WC, Mitler MM** 1978 Excessive daytime sleepiness in man: multiple sleep latency measurement in narcoleptic and control subjects. Electroencephalgr Clin Neurophysiol 45:621–627
14. **Kribbs NB, Dinges DF** 1994 Vigilance decrement and sleepiness. In: Harsh HR, Ogilvie RD, eds. Sleep onset mechanisms. Washington DC: American Psychological Association; 113–125
15. **Johnson RA, Wichern DW** 1988 Applied multivariate statistical analysis. Upper Saddle River: Prentice Hall Press
16. **National Transportation Safety Board** 1990 Safety study: fatigue, alcohol and other drugs, and medical factors in fatal-to-the-driver heavy truck crashes, Vol 2. Washington DC: US Government Printing Office (Publication NTSB/SS-90/02)
17. **Veasey S, Rosen R, Barzansky B, Rosen I, Owens J** 2002 Sleep loss and fatigue in residency training: a reappraisal. JAMA 288:1116–1124
18. **Shearer WT, Reuben JM, Mullington JM, Price NJ, Lee BN, Smith EO, Szuba MP, Van Dongen HP, Dinges DF** 2001 Soluble TNF-α receptor 1 and IL-6 plasma levels in humans subjected to the sleep deprivation model of spaceflight. J Allergy Clin Immunol 107:165–170
19. **Vgontzas AN, Bixler EO, Papanicolaou, DA, Chrousos, GP** 2000 Chronic systemic inflammation in overweight and obese adults. JAMA 283:2235–2236
20. **Chrousos GP** 2000 The role of stress and the hypothalamic-pituitary-adrenal axis in the pathogenesis of the metabolic syndrome: neuro-endocrine and target tissue-related causes [Review]. Int J Obes 24:S50–S55
21. **Vgontzas AN, Papanicolaou DA, Bixler EO, Hopper K, Lotsikas A, Lin HM, Kales A, Chrousos GP** 2000 Sleep apnea and daytime sleepiness and fatigue: relation to visceral obesity, insulin resistance, and hypercytokinemia. J Clin Endocrinol Metab 85:1151–1158
22. **Harris, TM, Ferrucci L, Tracy RP, Corti MC, Wacholder S, Ettinger Jr WH, Heimovitz H, Cohen HJ, Wallace R** 1999 Associations of elevated interleukin-6 and c-reactive protein levels with mortality in the elderly. Am J Med 106:506–512
23. **Ridker PM, Rifai N, Stampfer MJ, Hennekens CH** 2000 Plasma concentration of interleukin-6 and the risk of future myocardial infarction among apparently health men. Circulation 101:1767–1772
24. **Luc G, Bard JM, Juhan-Vague I, Ferrieres J, Evans A, Amouyel P, Arveiler D, Fruchart JC, Ducimetiere P** 2003 C-reactive protein, interleukin-6, and fibrinogen as predictors of coronary heart disease: the PRIME study. Arterioscler Thromb Vasc Biol 23:1255–1261
25. **Vgontzas AN, Mastorakos G, Bixler EO, Kales A, Gold PW, Chrousos GP** 1999 Sleep deprivation effects on the activity of the hypothalamic-pituitary-adrenal and growth axes: potential clinical implications. Clin Endocrinol (Oxf) 51:205–215
26. **Leproult R, Copinschi G, Buxton O, Van Cauter E** 1997 Sleep loss results in an elevation of cortisol levels the next evening. Sleep 20:865–870
27. **Hennig J, Friebe J, Ryl I, Kramer B, Bottcher J, Netter P** 2000 Upright posture influences salivary cortisol. Psychoneuroendocrinology 25:69–83
28. **Leproult R, Colecchia EF, L'Hermite-Baleriaux M, Van Cauter E** 2001 Transition from dim to bright light in the morning induces an immediate elevation of cortisol levels. J Clin Endocrinol Metab 86:151–157
29. **Borbély AA, Achermann P** 1999 Sleep homeostasis and models of sleep regulation. J Biol Rhythms 14:557–568
30. **Ehlers CL, Kupfer DJ** 1997 Slow-wave sleep: do young adult men and women age differently? J Sleep Res 6:211–215
31. **Hume KI, Van F, Watson A** 1998 A field study of age and gender differences in habitual adult sleep. J Sleep Res 7:85–94
32. **Carrier J, Land S, Buysse DJ, Kupfer DJ, Monk T** 2001 The effects of age and gender on sleep EEG power spectral density in the middle years of life (ages 20–60 years old). Psychophysiology 38:232–242
33. **Bixler EO, Vgontzas AN, Lin H-M, Vela-Bueno A, Kales A** 2003 Normal sleep and sleep stage patterns: effects of age, BMI and gender. Sleep 26(Suppl): A61–A62
34. **Redline S, Bonekat W, Gottlieb D, Iber C, Lind B, Quan SF, Rapoport DM, Sanders M, Smith PL** 1998 Sleep stage distributions in the sleep heart health study (SHHS) cohort. Sleep 21(Suppl):210
35. **Vgontzas AN, Zoumakis M, Bixler EO, Lin H-M, Follett H, Chrousos GP,** 2003 Healthy young women compared to men are more resilient to sleep loss and sleep disturbance than age-matched men: potential protective role of estrogen. Program of the 85th Annual Meeting of The Endocrine Society, Philadelphia, PA, 2003, pp 358–359

JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.