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14. ABSTRACT

We have performed the spectral analysis of the sleep EEG in what is likely the largest group of subjects ever assembled and have demonstrated marked effects of age, sex and ethnicity. In these healthy non-obese volunteers who had demographics similar to the demographics of active duty Army personnel, BMI did not impact SWA. Between the ages of 21 and 30, there are large inter-individual variations in SWA that are only partly predicted by sex and ethnicity. Our hypothesis is that these individual differences may partly predict diabetes risk. We have demonstrated the feasibility of the clinical study and successfully obtained all planned assessments. The effort to increase our data base will be valuable to the entire project. While progressing through the analytical and experimental work, we have prepared two reviews on sleep loss and the risk of obesity and diabetes.

15. SUBJECT TERMS

Sleep, Diabetes, Slow-Wave activity, Weight Gain

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Table of Contents

Annual Report for Award Number W81XWH-07-2-0071

Table of Contents

Introduction

Chronic partial sleep loss, due to bedtime restriction, is a hallmark of modern society and highly prevalent in active duty army personnel. During the past few years, evidence from laboratory and epidemiological studies has indicated that decreased sleep duration has an adverse effect on glucose regulation and on the neuro-endocrine control of appetite (1-3). Taken together, the findings suggest that chronic partial sleep deprivation may be involved in the current epidemic of obesity and diabetes. Our group has strong evidence for the existence of large individual differences in metabolic as well as cognitive vulnerability to sleep loss. We have recently obtained preliminary data in a small group of young men that suggest that a specific heritable trait of the sleep electroencephalogram (EEG), known as slow-wave activity (SWA), accounts for the majority of individual variability in the adverse effects of sleep loss on diabetes risk.

The objectives are to identify SWA as a predictor of diabetes risk in a subject population with a gender, ethnic and age distribution similar to that of active duty army personnel and to test the hypothesis that individuals with low SWA are at much higher risk to develop diabetes following chronic partial sleep restriction than those with higher SWA. The studies will also explore the potential relationships between individual differences in diabetes risk following sleep loss and individual differences in risk of weight gain and in the magnitude of cognitive deficits.

Body of Report

Overview

The Statement of Work for the first 2 years of the award included:

Task 1: Testing role of EEG SWA as predictor of individual differences in baseline glucose disposition index (Months 1-6):

- Perform spectral analysis of sleep EEG for 56 subjects in whom EEG recordings and glucose and insulin levels during intravenous glucose tolerance testing are presently available
- Re-run minimal model analysis of ivGTT results for 56 subjects already tested
- Recruit and study 7 additional subjects using currently IRB-approved protocol in order to match gender, age and ethnic distribution of active army personnel

- Test the hypothesis that levels of SWA in the sleep EEG are a significant predictor of beta-cell responsiveness and insulin sensitivity after controlling for gender, age, BMI and ethnicity-based diabetes risk.
- Define lower and upper thirtiles of slow-wave activity associated, respectively, with putatively high and low diabetes risk during sleep curtailment

Task 2: preparation of clinical study of diabetes risk during sleep curtailment (Months 1-6):

- Submit protocol to and obtain approval from University of Chicago Institutional Review Board and Clinical Research Center
- Import Walter Reed Army Institute of Research battery of neurobehavioral testing and train personnel in its use
- Design database.

Task 3: Completion of clinical study of diabetes risk during sleep curtailment in 32 individuals (Mos. 7-42 – one study per month):

- Recruit and screen 60-70 individuals to enroll 16 individuals with SWA in lower third and 16 individuals with SWA in upper third of distribution with both groups matched for gender distribution
- Complete study in two groups of 16 individuals
- Generate individual data analysis and enter in database.

As noted in our 2008 annual report and in the USAMRMC review of this report, progress on tasks involving subject recruitment was significantly delayed due to the need to obtain Institutional Review Board (IRB) approval from the United States Army Medical Research and Material Command (USAMRMC) for the protocol for Task 1 which was already approved by the University of Chicago IRB by the time of the proposal submission. The need to obtain IRB approval from both the University of Chicago and the USAMRMC for the protocol in Tasks 2 and 3 was also a very lengthy process as multiple revisions had to be submitted in order to obtain approval from both IRBs. Further, once we obtained IRB approval, we had to submit the HRPO-approved protocols to the Internal Scientific Advisory Panel (ISAP) of the University of Chicago Institute for Translational Medicine (CTSA) to obtain approval for the use of the Clinical Resource Center (CRC).

Around the time of the submission of our 2008 annual report, we had responded to the ISAP comments for both protocols (August 10, 2008) and were expecting to submit revised versions to HRPO and the University of Chicago IRB. We are pleased to report that both protocols were finally approved by all three committees by October 23, 2008.

Research accomplishments associated with Task 1

Experimental work

During this past year, we recruited and studied 7 subjects (6 men, 1 woman) in the age range 17-20 years as proposed in the Statement of Work. Data from 2 of the 7 subjects could not be added to the data base as one subject was found to have mild sleep apnea and the polysomnography (PSG) recordings in the other subject had technical artifacts.

Analytical work

In our annual report for year 1, we indicated that we had performed the spectral analysis of the sleep EEG for 44 of the 56 subjects for whom the recordings were readily available at the time of the application.

We had also indicated that if the cut offs points for low and high SWA, respectively, were derived from a larger data base of recordings obtained in subjects with a sex, age, ethnic and BMI distribution similar to that of active duty Army personnel, these cut off points would have greater precision. Since the inception of this project, we have continually updated our data base of recordings accumulated in our laboratory. These data have been obtained as a result of baseline testing of volunteers entering IRB-approved NIH-funded studies where sleep duration or quality was subsequently manipulated. In each individual, baseline polysomnography was performed after at least 2 nights of normal bedtimes (8-9 hours) and a frequently sampled ivGTT was performed on the following day. In our 2008 report, we had assembled a data base of 171 subjects but the recordings had not been checked for completeness, accuracy and technical quality. We have since generated the EEG spectral analysis for 128 recordings, thus we analyze below a data set more than twice as large than that proposed in our original application (128 versus 63).

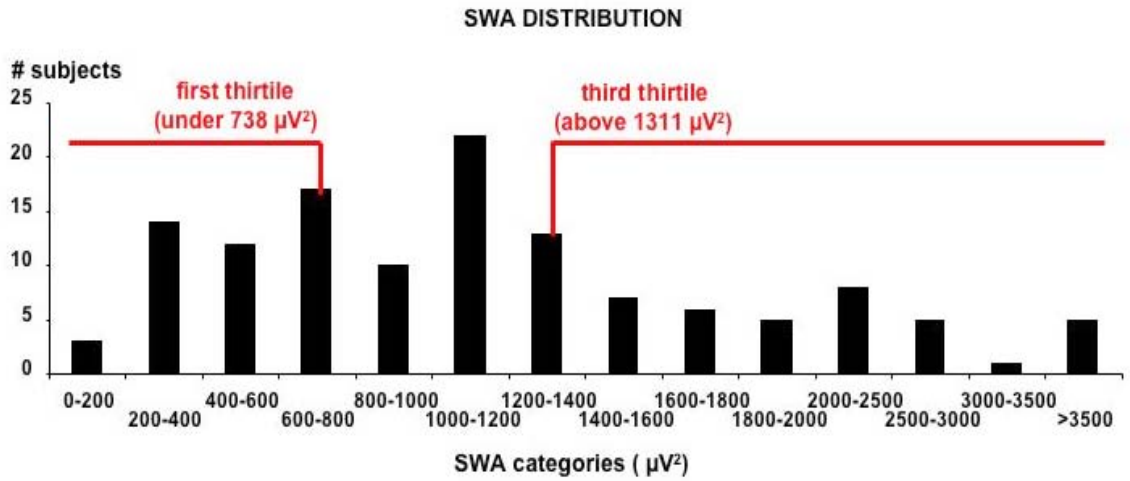
Tables 1 and 2 show the gender, age and ethnic distribution of subjects for whom we now have EEG spectral parameters. BMI was <27 kg/m^2 in women and <28 kg/m^2 in men, consistent with recommendations for active duty Army personnel. The data base has more than tripled in size (to 171 from 56) since our original submission. The gender and ethnic distributions are similar to that of active duty Army personnel. Very young individuals are still underrepresented in our sample, but as our analyses described below suggest, we feel that recruitment of additional young volunteers will not further contribute to the scientific output of the project.

TABLE 1	*The 2009 University of Chicago Database of EEG spectral analyses*		Active Duty Army Demographics (FY04)
MEN			
White	60	69.8 %	63.2 %
African American	19	22.1 %	19.9 %
Hispanic	3	3.5 %	10.2 %

Other	4	4.7 %	6.7 %
Total	86	100 %	100 %
WOMEN			
White	21	53.1 %	41.7 %
African American	14	28.6 %	38.8 %
Hispanic	5	10.2 %	11.1 %
Other	2	8.2 %	8.4 %
Total	42	100 %	100 %

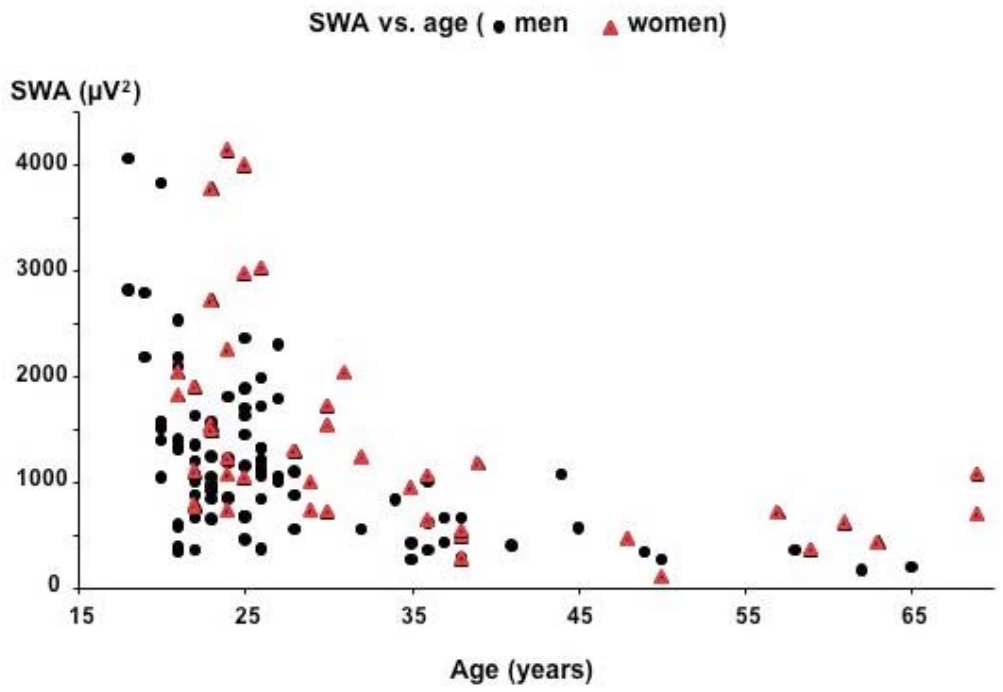
TABLE 2	*The 2009 University of Chicago Database of EEG spectral analyses*		Active Duty Army Demographics (FY04)
GENDER			
Men	86	67.2 %	85.3 %
Women	42	32.8 %	14.7 %
Total	128	100 %	100 %
AGE			
17- 20 years	15	7.0 %	14.2 %
21-24 years	65	35.2 %	26.7 %
25-29 years	42	26.6 %	21.1 %
30-39 years	31	18.8 %	27.7 %
≥ 40 years	18	12.5 %	10.4 %

Figure 1 illustrates the distribution of mean SWA in non-rapid eye movement sleep (NREM) in the first three hours of sleep (i.e. the time interval during which the bulk of SWA occurs) across the entire population of 128 subjects. The wide inter-individual variability is clearly apparent. The lower thirtile is under 738 μV^2 and the upper thirtile is above 1311 μV^2.



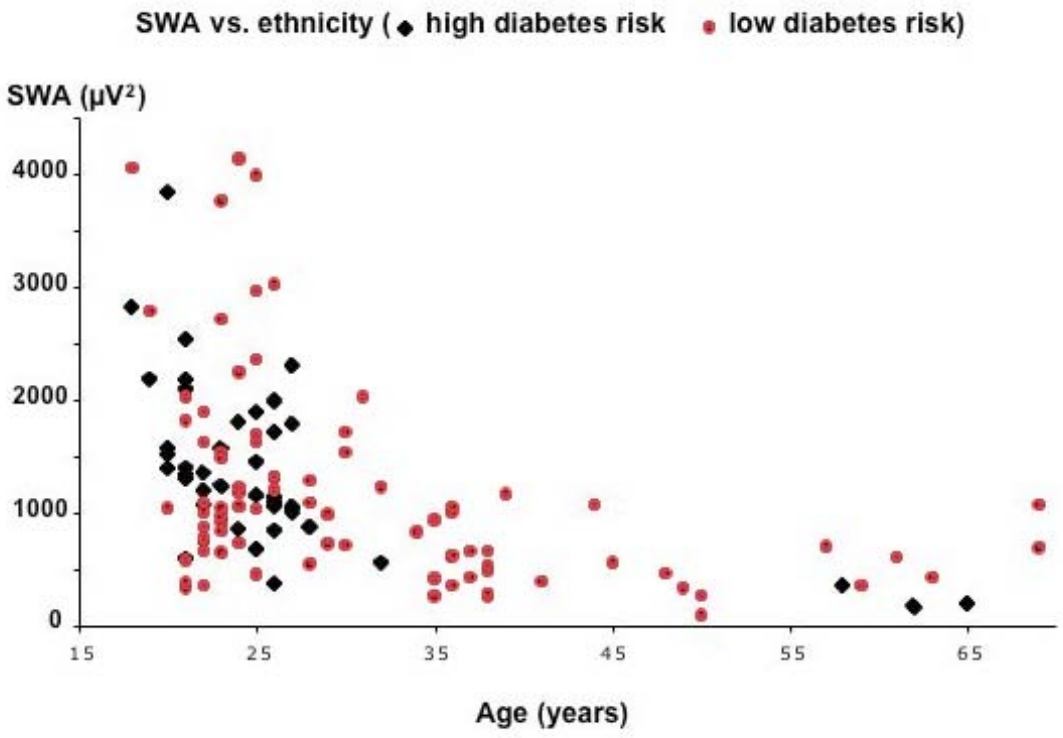
- Figure 1 -

Figure 2 shows the impact of age on SWA for both men and women. In an ANOVA with age, sex, ethnicity and BMI as factors, BMI was not a significant predictor of SWA but age (p=0.001), sex (p=0.0003) and ethnicity (p=0.002) were significant. Women have higher SWA than men. We plan, however, to normalize SWA in NREM sleep for SWA in REM sleep to determine whether this sex difference in SWA truly reflects a sex difference in homeostatic sleep regulation. In previous work in a small sample of older adults, we showed that the higher SWA levels in NREM sleep in older women partly reflected higher SWA in REM sleep and that when SWA in NREM sleep was normalized for SWA in REM sleep, the sex difference was essentially obliterated.



- Figure 2 -

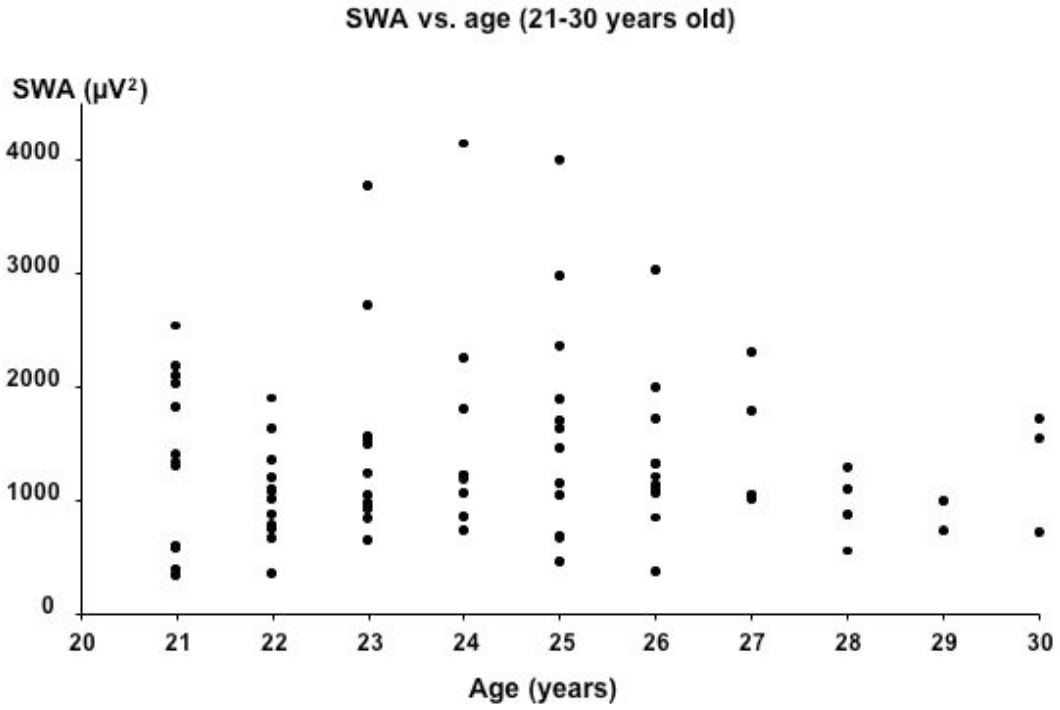
The impact of ethnicity across the age range is shown in Figure 3. African Americans and Hispanics have lower SWA than Whites and Asians, after adjusting for age and sex. Importantly for the focus of the present project, African Americans and Hispanics are known to be at a higher risk of type 2 diabetes than Whites and Asians. Further, the interaction between ethnicity and age was significant, indicating that the impact of age of SWA may be more pronounced in these populations who have an elevated risk of diabetes than in low risk populations.



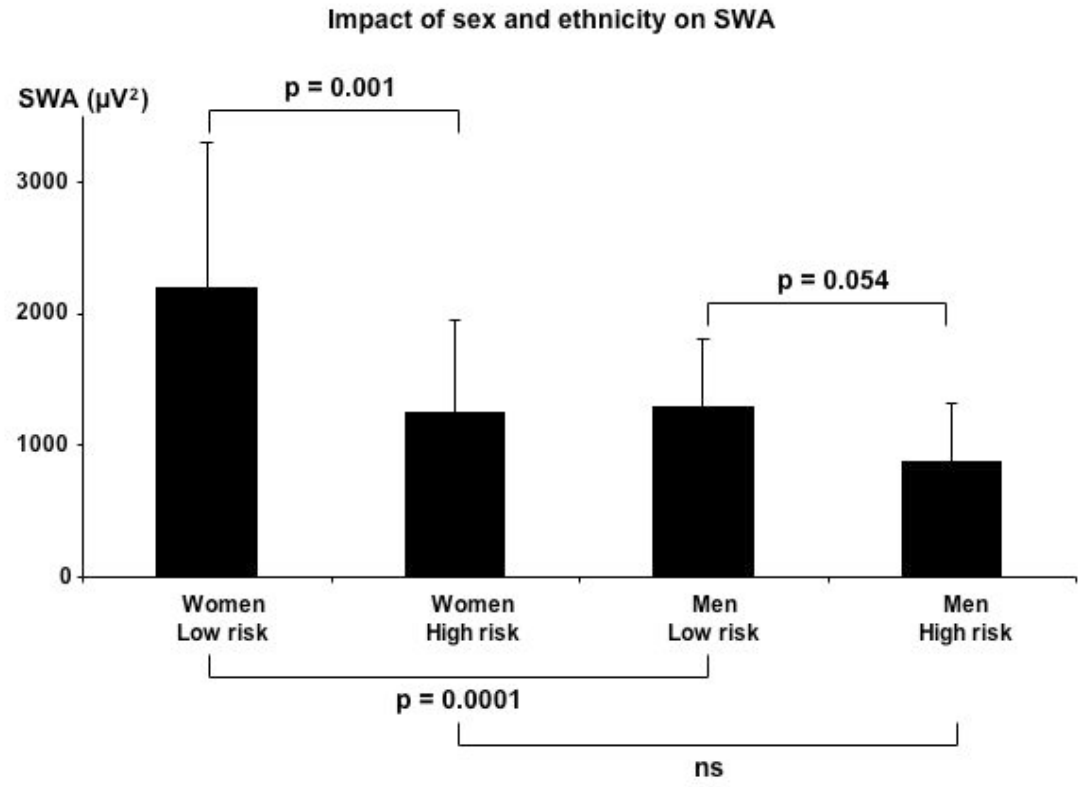
- Figure 3 -

The data shown in Figures 2 and 3 also indicate that SWA is highly variable and has its highest levels in the younger volunteers (the 17-20 age range). This is likely to represent the "tail" of the development and maturation as it is well known that SWA decreases during the transition from pubertal stages to adulthood. Individual variations in SWA in this age range may represent individual differences in maturational stage rather than stable individual differences in adulthood. Beyond 30 years of age, confirming and extending existing notions, our data base indicates that aging is associated with a rapid and drastic decline in SWA. It therefore appears that the critical age ranges to examine the impact of individual differences in SWA may be 21-30 years of age. This age range includes nearly 50% of active duty Army personnel and it is likely that this age group suffers from the most exposure to sleep deprivation and its putative long-term consequences. Figure 4 shows the variability of SWA in subjects between 21 and 30 years of age (n=81). Only sex and ethnicity are significant predictors.

Figure 5 compares SWA in the four sex and ethnicity groups, i.e. men and women with low (Whites and Asians) and high (African Americans and Hispanics) ethnicity-based diabetes risk.



- Figure 4 -



- Figure 5 -

Minimal model analysis of the results of intravenous glucose tolerance testing (ivGTT) for 92 of the 128 subjects for whom spectral analysis has been completed has been performed using standardized parameters. We are currently working on an important issue regarding modifications in the insulin assay used in the Endocrine Laboratories of the University of Chicago. A transition from an RIA assay to an Immulite assay occurred in the past few years. We have re-assayed samples from recent ivGTTs in both assays and are working out conversion formulas to correct the values of parameters extracted from the ivGTTs.

An abstract on the work accomplished under Task 2 has been submitted to the Military Health Forum 2009 and the communication will be presented by the Principal Investigator.

Research accomplishments associated with **Task 2**

Task 2 was to set up the clinical study of diabetes risk during sleep curtailment, including protocol approval (obtained October 23, 2008), import of the Walter Reed Army Institute of Research (WRAIR) battery of neurobehavioral testing and train personnel in its use and design of data base. These tasks have been completed. An "in service presentation" to the senior nursing and dietician staff of the CRC by the principal investigator took place on February 12, 2009. Dr. Tracy Rupp of WRAIR visited our laboratory on May 27, 2009 and gave a detailed presentation of the findings of the WRAIR group on the impact of sleep curtailment on performance on these tests. She spent a full day with Dr. Chapotot to review with him each and every task and left a complete volume of documentation.

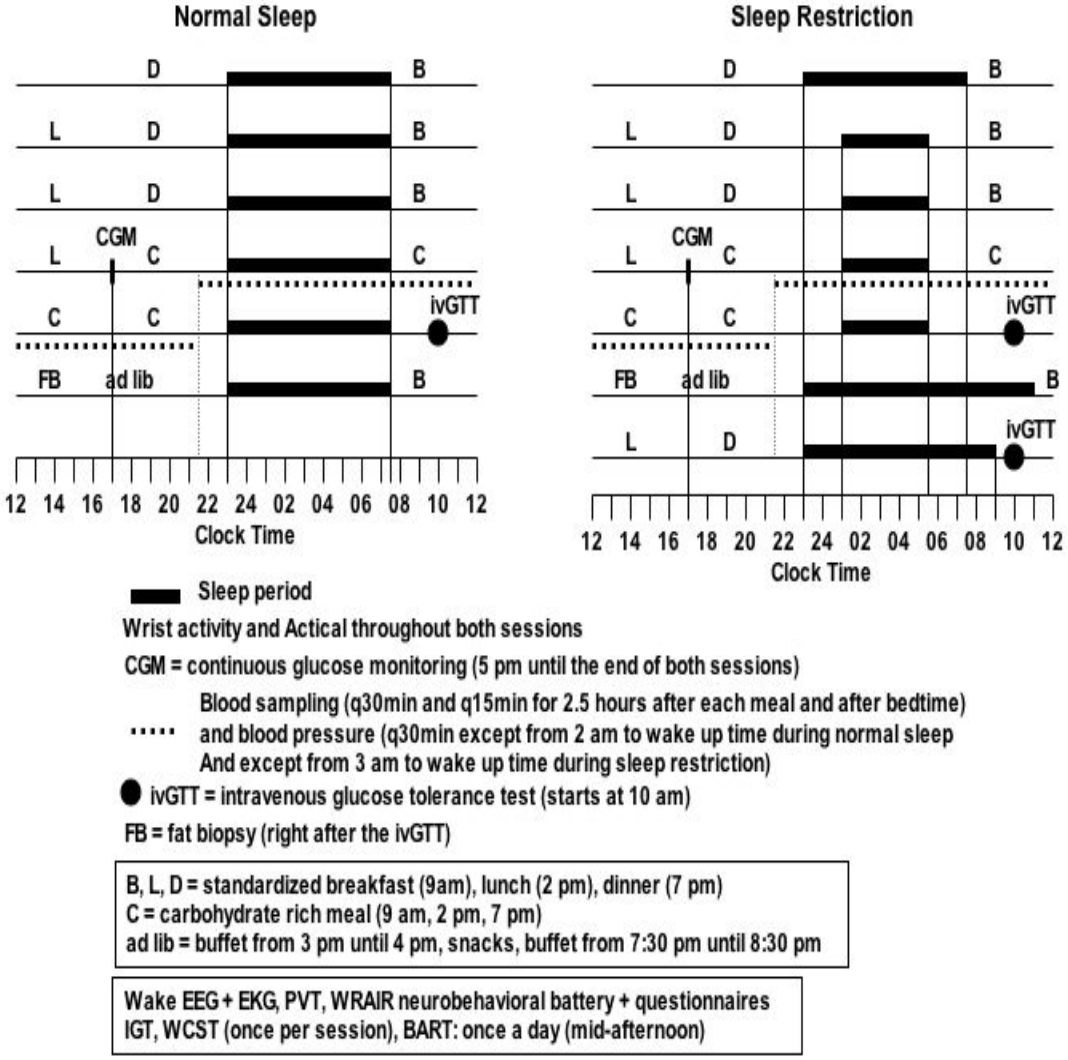
Research accomplishments associated with **Task 3**

Two subjects have completed the entire protocol. Two additional subjects have passed the screening tests and are waiting to be scheduled for the study. Recruitment efforts including posting flyers, putting adds in local free newspapers and using word of mouth are continuing.

The recent downsizing and understaffing of the University of Chicago Clinical Resource Center has limited our capacity to schedule a one-week study as this protocol involves. We have therefore initiated negotiations with the Medical Center Risk Management, Quality and Patient Safety in order to be able to use our own laboratory. We were required to develop a "Manual of Policy and Procedures" (23 pages) which has been reviewed by the University of Chicago Hospitals Office of Risk Management, Quality and Patient Safety and by the Biological Science Division Office of Clinical Research. Approval (received July 30, 2009) is conditional on upgrading our facility to obtain accreditation by the

Joint Commission. Meanwhile, we continue to request scheduling of studies in the CRC.

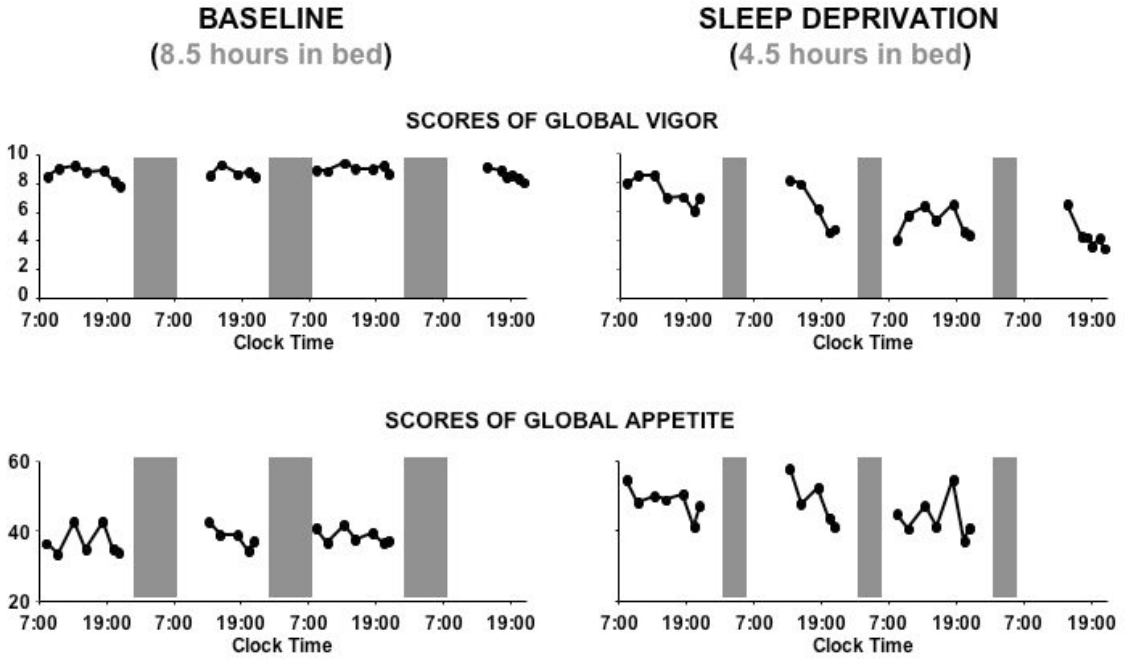
Figure 6 shows the currently approved experimental protocol. We introduced minimal modifications from the protocol proposed in the application. One is that the first night under both conditions is a 8.5 hour night. This adjustment was introduced when we realized (in similar projects) that it is not uncommon that volunteers initiate studies in a state of sleep debt. The second adjustment is that continuous glucose monitoring via a subcutaneous probe is conducted over a shorter period of time in order to avoid irritation and infection at the insertion site. Lastly, we are seeking additional funding to perform PET scans at the end of each study (as proposed in the original application). These scans would reveal the brain regions most affected by partial recurring sleep deprivation.



- Figure 6 -

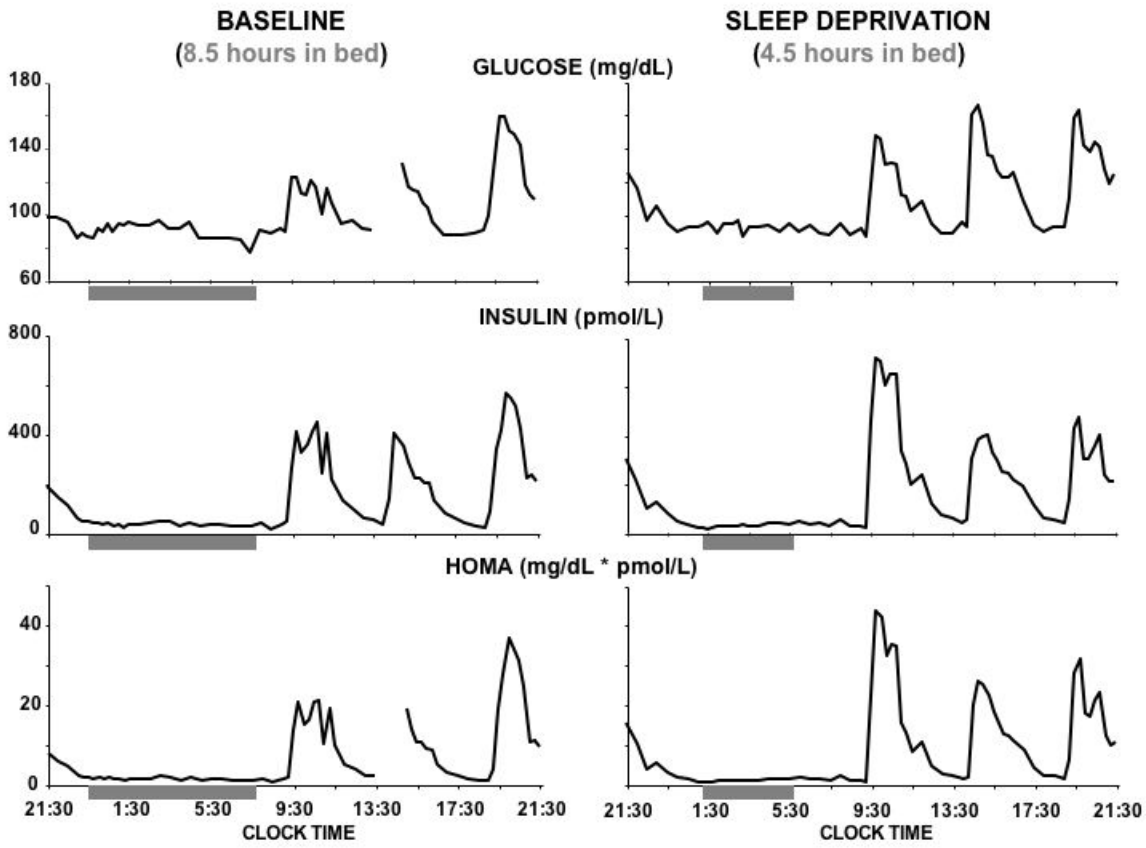
Figures 7 and 8 illustrate data from one of the subjects who completed the study and for whom most of the assays have been run. This subject has SWA in the upper thirtile.

Figure 7 shows the profiles of subjective vigor (top) and global appetite (lower) during the baseline study (4 nights of 8.5 hours in bed; left) and during the deprivation study (4 nights of 4.5 hours in bed; right). A clear and progressive decrease in global vigor and increase in appetite is apparent during recurrent sleep deprivation.



- Figure 7 -

Figure 8 shows the 24-h profiles of plasma glucose, plasma insulin and HOMA index (an index proportional to the product of glucose and insulin that is used as a marker of insulin resistance). These profiles were measured over the 4th night of each condition. An increase in glucose levels, despite a robust increase in insulin, is apparent. HOMA profiles are consistent with decreased insulin sensitivity as a result of sleep deprivation.



- Figure 8 -

Key Research Accomplishments

We have performed the spectral analysis of the sleep EEG in what is likely the largest group of subjects ever assembled and have demonstrated marked effects of age, sex and ethnicity. In these healthy non-obese volunteers who had demographics similar to the demographics of active duty Army personnel, BMI did not impact SWA. Between the ages of 21 and 30, there are large inter-individual variations in SWA that are only partly predicted by sex and ethnicity. Our hypothesis is that these individual differences may partly predict diabetes risk.

We have demonstrated the feasibility of the clinical study and successfully obtained all planned assessments.

The effort to increase our data base will be valuable to the entire project.

While progressing through the analytical and experimental work, we have prepared two reviews on sleep loss and the risk of obesity and diabetes (see appendices).

Reportable Outcomes

We have submitted an abstract to the Military Health Forum 2009. Two review articles (including one for a journal of the *Nature* group) have been

prepared and have been published or are currently in press. Both acknowledged support from this award. They are appended to this report.

Conclusions

The work has made substantial progress during the past year. We believe that the certification of our laboratory as a clinical research facility independent of the University of Chicago Clinical research center will accelerate the pace of studies. The preparation of review articles has indicated that the body of evidence supporting the hypotheses to be tested in the present project has clearly increased.

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Obesity AND METABOLISM

Sleep and diabesity

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ABSTRACT. *Over the past few decades, sleep curtailment has become a common behavior. Simultaneously, the aging of the population is associated with a higher prevalence of sleep disorders. We review the evidence indicating that chronic partial sleep loss and decreased sleep quality may increase the risk of obesity and diabetes. Experimental sleep restriction in healthy young subjects results in increased hunger, decreased levels of the satiety hormone leptin and increased levels of the hunger hormone ghrelin. The adverse impact of sleep loss on appetite regulation is probably driven by increased activity of orexinergic neurons. Consistent with the laboratory evidence, multiple epidemiologic studies have shown an association between short sleep and higher body mass index. Sleep curtailment is also associated with a rapid and marked decrease in insulin sensitivity without adequate compensation in beta cell function, resulting in an elevated risk of diabetes. Reduced sleep quality, without change in sleep duration, is also associated with an increased risk of diabetes. Epidemiologic findings are consistent with a causative role of sleep disturbances in the increased risk of diabetes. In summary, the current evidence supports a role for reduced sleep duration and quality in the current epidemic of diabesity.*

Obesity and Metabolism 2009; 5 (Suppl. to No. 1): ??-??.

Key words: Ghrelin, insulin resistance, leptin, orexin, sleep apnea, sleep loss.

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INTRODUCTION

A modulatory impact of sleep on metabolic and endocrine systems has been documented more than four decades ago. Remarkably, it is only in recent years that adverse effects of chronically reduced sleep duration or quality on hormonal and metabolic function have begun to be evaluated. Indeed, until less than 10 years ago, nearly all studies of sleep, hormones and metabolism focused on the effects of one or two nights of acute total sleep deprivation. The findings generally suggested that disturbances that developed during the sleepless night(s) were completely reversed following recovery sleep, and therefore persistent adverse effects seemed unlikely. Thus, the potential deleterious effects of chronic sleep loss and sleep disorders were long ignored.

Human sleep is comprised of rapid-eye-movement (REM) sleep and non-REM (NREM) sleep. Deep NREM sleep is characterized by the occurrence of "slow-waves" in the electroencephalogram. These slow-waves reflect a slow mode of synchronous firing of thalamo-cortical neurons. Slow-wave activity is a marker of sleep depth or intensity. During slow-wave sleep (SWS), brain glucose utilization is decreased, sympathetic nervous activity is decreased and vagal tone is higher. SWS is also associated with increased secretion of growth hormone (GH) while pituitary-adrenal activity is inhibited (1). Because of its impact on cerebral glucose metabolism, sympatho-vagal balance and counterregulatory hormone release, SWS plays an important role in total body glucose regulation and, more generally, in the restorative effect of sleep on peripheral function.

The discovery in 1998 of orexins A and B (also called hypocretins A and B), two distinct peptides that are synthesized by neurons in the lateral hypothalamus, demonstrated the existence of a molecular link between sleeping and feeding (2, 3). Orexin neurons play a central role in the maintenance of arousal but – as suggested by their name – also increase feeding, particularly at a time when normal food intake is low. Feeding requires the maintenance of wakefulness and the orexin system appears to play a central role in this vital interaction between feeding and arousal. Orexin neurons are active during the waking phase, activating all the components of the ascending arousal system and projecting diffusely to the entire cerebral cortex. Deficiencies in the orexin system are associated with sleep disorders involving chronic excessive daytime sleepiness. The orexin system also activates the appetite-promoting neuropeptide Y neurons in the arcuate nucleus of the hypothalamus. Furthermore, orexin neurons have dense projections to the dopaminergic ventro-tegmental area (VTA) and nucleus accumbens (NA), which are important in the hedonic control of food intake. Thus, overactivation of the orexin system is likely to increase both hedonic and homeostatic feeding. Orexinergic activity is in turn influenced by both central and peripheral signals, with glucose and leptin exerting inhibitory effects while ghrelin promotes further activation. When sleep deprivation is enforced behaviorally rather than the result of a pathological condition, the orexin system is overactivated, most likely to maintain wakefulness against the increased sleep pressure (4-6).

A profound and generalized impact of sleep loss and/or poor sleep quality on the endocrine system, and particularly on glucose and appetite regulation, should therefore be expected. Voluntary sleep curtailment has become an increasingly common behavior. The 2008 "Sleep in America" poll revealed that although working adults report a sleep need of an average of 7h18min to "function at best", 44% of them sleep less than 7 hours, and 16% sleep less than 6 hours on a typical week-night (7). The sleep times in the European countries follow a similar trend. The cumulative sleep loss per work week of a significant portion of the working adult population in industrialized countries may be close to one full night of sleep deprivation. Chronic sleep loss may also be the consequence of a sleep disorder, such as obstructive sleep apnea (OSA), a condition characterized by repetitive breathing disturbances and poor sleep quality, which is highly prevalent in obese individuals.

The following two sections of this article summarize the current laboratory and epidemiologic evidence for a link between short sleep and/or poor sleep and the risk for "diabesity". For the sake of brevity, we do not address the role of sleep disturbances in the cardio-metabolic consequences of obesity or in glucose control in type 2 diabetes. These clinically important topics have been the object of recent reviews (8, 9).

REDUCED SLEEP DURATION AND/OR QUALITY AS RISK FACTORS FOR OBESITY

To date, five published laboratory studies have examined the impact of recurrent partial sleep restriction (2 to 14 days) on the neuroendocrine regulation of appetite (10-14). In 2003, Guilleminault et al. assessed leptin levels at 6 time points of the 24-h cycle in volunteers studied after 7 days of sleep restriction to 4 hours per night, and reported a significant decrease in peak leptin levels (10). Two studies published in 2004 confirmed and extended these findings (11-12). One study compared the 24-h profiles of plasma leptin levels obtained after 6 days of sleep restriction to 4 hours in bed followed by 6 days of sleep extension to 12 hours in bed. The same volunteers participated in a separate study with normal 8-hour bedtimes. A remarkable "dose-response" relationship between sleep length and characteristics of the leptin profile was observed (11). Indeed, the overall mean leptin concentration, the level of the nocturnal maximum and the amplitude of the diurnal variation gradually decreased from the 12-h to the 4-h bedtime condition. Importantly, these differences in 24-h regulation of leptin levels between the three bedtime conditions occurred despite identical amounts of caloric intake, similar sedentary conditions and stable body mass indices (BMI). The reduction in mean peak leptin (26%) from the 12-h to the 4-h bedtime condition was equivalent to the impact of a caloric restriction by nearly 1000 calories per day. In a randomized cross-over design study of normal young adults, after 2 nights of 4 hours in bed vs 2 nights of

10 hours in bed, daytime leptin and ghrelin profiles were simultaneously assessed. The subjects also completed validated-scales for hunger and appetite for various food types at hourly intervals (12). Caloric intake was exclusively under the form of an intravenous glucose infusion at a constant rate calculated to match normal caloric requirements. The results are illustrated in Figure 1. In the 4-h sleep condition as compared to the 10-h sleep condition, leptin levels were decreased by an average of 18%, while ghrelin levels increased by 24%. The ghrelin-to-leptin ratio increased by more than 70%. Hunger increased by an average of 23% and appetite for high carbohydrate nutrients increased by more than 30%, suggesting that the participants would have consumed excessive amounts of calories if food had been available *ad lib*. A recent study of overweight middle-aged adults, studied in the laboratory during 2 weeks of sleep extension (+1.5 h per night) as compared to 2 weeks of sleep restriction (–1.5 h per night), under *ad lib* feeding conditions in a randomized cross-over design showed a higher food intake from snacks during sleep restriction as compared to extension (13). The volunteers consumed excessive amounts of calories form meals under both sleep conditions and gained similar amounts of weight. On the 14th day of the study, leptin and ghrelin profiles were similar for both sleep conditions. In another recent study comparing a single night of total sleep deprivation to a single night of 4.5 h or 7 h in bed, a dose-response relationship between amounts of sleep, hunger ratings and ghrelin levels was found, but leptin levels did not vary across sleep conditions (14).

As of September 2008, more than 50 epidemiological studies have examined the association between short and/or poor sleep and obesity. The majority of these studies were cross-sectional in design and used self-report to assess sleep variables. The vast majority of these published studies demonstrated a significant association between short/poor sleep and obesity. A recent meta-analysis including more than 600,000 adults and 30,000 children worldwide attempted to quantify the cross-sectional association between short sleep and obesity risk (15). The pooled odds ratio (OR) linking short sleep to obesity was 1.89 (95% CI 1.46-2.43; p<0.0001) in children and 1.55 (95% CI 1.43-1.68; p<0.0001) in adults (15). Another recent systematic review similarly concluded that short sleep duration, as assessed by self-report, appears independently associated with weight gain, particularly in younger age groups (16). While these analyses tended to suggest that the impact of sleep duration on adiposity may be less robust in older populations than in children and young adults, a recent

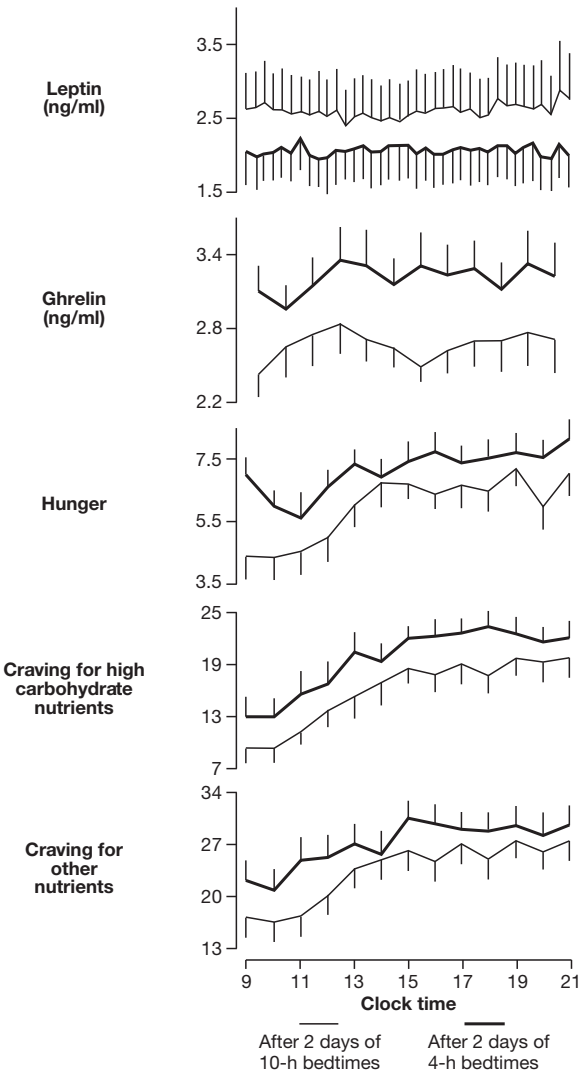

Fig. 1 - Mean (±SEM) daytime profiles of plasma leptin, plasma ghrelin, and ratings of hunger, appetite for high carbohydrate nutrients and appetite for other types of nutrient in subjects studied after 2 days with 4-h bedtimes or 2 days with 10-h bedtimes in a randomized cross-over design. Caloric intake was exclusively under the form of a glucose infusion at a constant rate. Data source (ref. 12).

cross-sectional analysis using wrist actigraphy to objectively assess sleep duration in more than 6000 older men and women, ages 67-99 years, provided strong evidence to the contrary (17). Compared to sleeping 7-8 hours per night, sleeping less than 5 hours was associated with a BMI that was, on average, greater than 2.5 kg/m^2 in men and 1.8 kg/m^2 in women, after adjusting for multiple potential confounders (17). These effect sizes are clearly clinically significant. Out of the 10 longitudinal studies that studied the impact of short sleep on the incidence of obesity in children and adults, eight reported that shorter sleep durations are associated with an increased risk for overweight and obesity over the follow-up period (18). This pattern is particularly consistent in pediatric populations (all 4 studies had positive findings). Two large cross-sectional epidemiologic studies further showed elevated leptin levels, after controlling for BMI or adiposity, in habitual short sleepers (19, 20).

A limitation of nearly all epidemiologic studies examining the relationship between sleep duration and BMI is that they did not simultaneously assess sleep quality. Thus, it remains to be determined whether short sleep in obese individuals is the result of bedtime curtailment or is due to the presence of a sleep disorder. A recent large scale study (21), where participants reported sleep duration as well as subjective sleep disturbances (insomnia, excessive daytime sleepiness, sleep difficulty) and a measure of chronic emotional stress, concluded that self-reported short sleep in obese adults may be a surrogate marker of subjective sleep disturbance and psychosocial stress. This hypothesis is consistent with the existence of a "vicious circle" where short sleep may initially promote weight gain and the resulting excess adiposity, and its associated continuous release of somnogenic cytokines would then induce a dysregulation of sleep mechanisms, with a net further decrease in total sleep time.

REDUCED SLEEP DURATION AND/OR QUALITY AS RISK FACTORS FOR TYPE 2 DIABETES

During the past 40 years, four independent studies reported a deleterious impact of total sleep deprivation on glucose homeostasis. This work received little attention, probably because total sleep deprivation cannot be sustained for long periods of time and deficits appearing during total sleep deprivation are promptly corrected after sleep recovery.

The first laboratory study designed to address the consequences of recurrent partial sleep restriction, examined metabolic profiles in young healthy men after 5-6 days of bedtime restriction to 4 hours and after full sleep recovery obtained by enforcing 12-h bedtimes for 5-6 consecutive days (22). The upper part of Table 1 summarizes the parameters of glucose tolerance derived from minimal model analysis of a frequently sampled intravenous glucose tolerance test (IVGTT). Glucose tolerance (Kg) was more than 50% lower on the 5th day of sleep restriction than on the 5th day of sleep extension and was consistent with a state of impaired glucose tolerance. This decrease in Kg was the combined consequence of a 20 to 30% decrease in glucose effectiveness (Sg), a measure of non-insulin dependent glucose utilization, and an approximate 30% reduction in the acute insulin response to glucose (AIRg). A trend for decreased insulin sensitivity (SI) failed to reach statistical significance because one of the subjects had paradoxically a much higher SI after sleep restriction than when fully rested (his relative change in SI was a significant outlying value; excluding this subject, the overall change in SI was a decrease of more than 20%). The product of SI and AIRg, i.e. the disposition index (DI), a validated marker of diabetes risk, was decreased by more than 40% after sleep restriction as compared to sleep extension. Oral glucose tolerance was assessed on the morning of the 6th day during a high carbohydrate breakfast; both peak glucose levels and the overall glucose response were increased, confirming a decrease in glucose tolerance following sleep restriction. When the integrated glucose and insulin responses were examined using the HOMA index, more than 50% increase of HOMA values was observed after sleep restriction as compared to the fully rested state, consistent with a decrease in insulin sensitivity.

Chronically decreased sleep quality, usually in association with decreased sleep duration, was associated with increased diabetes risk in various subject populations, including older adults and individuals suffering from OSA. Markedly decreased amounts of deep NREM sleep, i.e. SWS, are typical of these con-

Table 1 - Upper part: *parameters of glucose tolerance derived from minimal model analysis of a frequently sampled intravenous glucose tolerance test (IVGTT);* Lower part: *parameters derived from an IVGTT performed after 2 nights of undisturbed sleep and after 3 nights of experimental suppression of slow-wave sleep (SWS).*

	Well rested	After sleep intervention	p-level ≤	% change from well rested condition
5 nights of 4-h bedtimes (n=11)				
Glucose tolerance (%.min^{-1})	2.29±0.38	1.28±0.33	0.04	–57±20%
Acute insulin response to glucose (μU.ml^{-1}.min)	567±144	403±126	0.002	–31±10%
Glucose effectiveness	0.026±0.003	0.016±0.002	0.03	–26±17%
Insulin sensitivity (10^{4}min^{-1} (μU/ml)$^{-1}$)	7.10±1.04	5.19±0.51	0.15	–7±19% * (–24±9% **)
Disposition index	3123±537	1724±343	0.003	–47±7%
3 nights of slow-wave sleep suppression (n=9)				
Glucose tolerance (%.min^{-1})	2.00±0.13	1.54±0.20	0.03	–23±9%
Acute insulin response to glucose (μU.ml^{-1}.min)	314±41	323±36	0.73	+11±11%
Glucose effectiveness	0.024±0.003	0.019±0.002	0.19	–15±10%
Insulin sensitivity (10^{4}min^{-1} (μU/ml)$^{-1}$)	8.42±1.12	5.87±0.74	0.009	–25±8%
Disposition index	2347±299	1744±144	0.02	–20±7%

*Includes a statistically significant outlier; **Excludes the outlier.

ditions. Under normal circumstances, the initiation of SWS is temporally associated with decreased brain glucose utilization, stimulation of GH release, inhibition of cortisol secretion, decreased sympathetic nervous activity and increased vagal tone. All these correlates of SWS are likely to affect total body glucose homeostasis and, therefore, conditions of reduced or absent SWS, as occur in normal aging and in individuals suffering from OSA, may be associated with an increase in diabetes risk.

A recent study has directly tested this hypothesis by selectively suppressing SWS in healthy young adults and examining the impact on glucose tolerance (23). Suppression of SWS was achieved by delivering acoustic stimuli to the bedside. The acoustic stimuli were continuously calibrated to replace SWS by shallow NREM sleep without waking up the subjects. This intervention decreased the amount of SWS by nearly 90% - similar to what occurs over the course of four decades of aging - and induced a degree of sleep fragmentation typical of moderate-to-severe OSA. Importantly, it did not decrease total sleep duration or the amount of REM sleep. The lower part of Table 1 shows the parameters derived from an IVGTT performed after 2 nights of undisturbed sleep and after 3 nights of experimental suppression of SWS (23). After 3 nights of suppression of SWS, SI was decreased by ~25% reaching the level reported in older adults and in populations at high risk for diabetes. The decrease in SI following experimental reduction of SWS was not compensated for by an increase in insulin release, as AIRg remained virtually unchanged. Consequently, the DI was ~20% lower after SWS suppression. Consistent with an increased diabetes risk, glucose tolerance was reduced by ~23%, reaching the range typical of older adults with impaired glucose tolerance. Importantly, the changes in the two main determinants of glucose tolerance, i.e. SI and AIRg, were correlated with the changes in SWS after the intervention. These laboratory findings demonstrate unequivocally that disruptions in sleep quality, without change in sleep duration, may adversely affect glucose regulation. Under real life conditions, decreased sleep quality is often associated with shorter total sleep time such that the impact of sleep disturbances on glucose tolerance will combine both effects.

A number of cross-sectional as well as prospective epidemiologic studies have provided evidence for an association between short and/or poor sleep, and the prevalence or incidence of diabetes, after controlling for age, BMI and multiple other confounders. Longitudinal studies that have assessed sleep characteristics at baseline and incidence of diabetes over a follow-up period provide

some indication regarding the direction of causality. Six studies have examined the impact of self-reported sleep duration and an equal number has addressed the impact of sleep quality as determined by self-report of sleep problems such as difficulty initiating or maintaining sleep, use of sleeping pills, or presence of insomnia (8, 9). None of the studies has involved objective measures of sleep. Short sleep duration was found to predict a higher incidence of diabetes in 4 of the 6 studies while poor sleep quality was associated with an increased risk of diabetes in 5 of the 6 studies (8, 9).

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Effects of poor and short sleep on glucose metabolism and obesity risk

Karine Spiegel, Esra Tasali, Rachel Leproult and Eve Van Cauter

Abstract | The importance of sleep to hormones and glucose metabolism was first documented more than four decades ago. Since then, sleep curtailment has become an endemic behavior in modern society. In addition, the prevalence of sleep disorders, particularly obstructive sleep apnea (OSA), has increased. OSA is very common in endocrine and metabolic disorders, but often remains undiagnosed. This Review summarizes the laboratory and epidemiologic evidence that suggests how sleep loss, either behavioral or disease-related, and poor quality of sleep might promote the development of obesity and diabetes mellitus, and exacerbate existing endocrine conditions. Treatment of sleep disorders has the potential to improve glucose metabolism and energy balance. Screening for habitual sleep patterns and OSA might be critically important for patients with endocrine and metabolic disorders.

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Introduction

More than four decades ago, multiple studies demonstrated that sleep has a major role in the regulation of endocrine functions and glucose metabolism. In healthy adults, reproducible changes in the release of pituitary hormones and pituitary-dependent hormones follow the wake–sleep transition. The effect of sleep on hormone secretion is dependent on the occurrence of specific stages of sleep.[1,2]

Human sleep is composed of rapid-eye-movement (REM) sleep and non-REM sleep. Deep non-REM sleep is characterized by 'slow waves' in the electroencephalogram, which reflect a mode of synchronous firing of thalamocortical neurons. During slow-wave sleep, the brain uses less glucose, sympathetic nervous activity is decreased and vagal tone is increased, relative to both wakefulness and REM sleep. Slow-wave sleep is also associated with robust elevations in levels of growth hormone, while the activity of the pituitary–adrenal axis is inhibited.[2] Because of the effect of slow-wave sleep on cerebral glucose metabolism, sympathovagal balance and counter-regulatory hormones' release, this type of sleep is thought to have a major role in total-body glucose regulation and, more generally, in the restorative effect of sleep.

The 1998 discovery of orexin A and orexin B, two peptides synthesized by neurons which are concentrated in the lateral hypothalamus, demonstrated a molecular link between wake–sleep regulation and the neuroendocrine control of appetite. Orexin-containing neurons have a central role in the maintenance of arousal, but also increase food intake,[3,4] particularly at a time when normal food intake is low. Feeding requires the maintenance of wakefulness and the orexin system seems to have a key role in the interaction between feeding and arousal. Orexin-containing neurons are active during wakefulness and quiescent during sleep. Deficiencies in the orexin system are associated with sleep disorders that involve chronic, excessive daytime sleepiness, including narcolepsy and obstructive sleep apnea (OSA). By contrast, when sleep deprivation is behaviorally enforced, the orexin system is overactive—most likely to maintain wakefulness against the increased pressure to sleep. Increased orexin activity during periods of sleep deprivation has been shown in rats, dogs and squirrel monkeys.[5–7] A profound effect of sleep deprivation and/or poor-quality sleep on glucose metabolism and appetite regulation should, therefore, be expected.

Remarkably, the adverse effects of chronically reduced sleep duration and/or quality have only begun to be evaluated in the past few years. Voluntary sleep curtailment has, however, become a common behavior in modern society. Data from the 2008 'Sleep in America' poll indicate that, although working adults report that they need an average 7 h 18 min of sleep to function at their best, 44% of them sleep less than 7 h, and 16% sleep less than 6 h on a typical weeknight.[8] Sleep duration in European countries seems to follow a similar trend.[9] The cumulative sleep loss per working week of a substantial portion of the adult population may correspond to as much as one full night of sleep deprivation. Chronic sleep loss might also be the consequence of a pathological condition—particularly the most common sleep disorder, OSA, which is characterized by repetitive breathing disturbances during sleep and by poor-quality

Competing interests
E. Van Cauter has declared associations with the following companies: Actelyon and Sanofi-Aventis. See the article online for full details of the relationships. R. Leprout, K. Spiegel and E. Tasali declared no competing interests.

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Key points

- Sleep loss, be it behavioral or related to sleep disorders, is an increasingly common condition in modern society
- Experimental reduction of the duration or quality of sleep has a deleterious effect on glucose metabolism
- Experimental reduction of sleep duration downregulates the satiety hormone, leptin, upregulates the appetite-stimulating hormone, ghrelin, and increases hunger and appetite
- Numerous cross-sectional and prospective, epidemiologic studies have provided evidence of an association between short-duration and/or poor-quality sleep and the prevalence or incidence of diabetes mellitus or obesity
- Effective treatment of obstructive sleep apnea, a sleep disorder that is highly prevalent in metabolic and endocrine disorders, has the potential to improve glucose metabolism and energy balance
- Screening for habitual sleep patterns and obstructive sleep apnea might be critically important for patients with endocrine and metabolic disorders

sleep. The current epidemic of obesity in industrialized countries is paralleled by an epidemic of OSA.

The following two sections summarize the laboratory and epidemiologic evidence that links short-duration sleep and/or poor-quality sleep with an increased risk of diabetes mellitus and obesity. The evidence on adverse effects of poor-quality sleep is based on studies that involved an experimental reduction of sleep quality, and on population studies in which sleep quality was self-reported. Indeed, no systematic evaluations have been published to date on endocrine or metabolic disturbances in any sleep disorder, except in OSA. Reciprocally, associations between metabolic or hormonal conditions and the prevalence or severity of sleep disorders have only been examined for OSA. The last section of this review, therefore, focuses on the links between OSA and metabolic disorders, with a particular focus on diabetes mellitus, obesity and polycystic-ovary syndrome (PCOS).

Poor and short sleep and diabetes

Evidence from laboratory studies

Short-duration sleep and glucose regulation

The first study that assessed the consequences of recurrent, partial sleep loss on hormonal and metabolic variables involved restriction of participants' (healthy young men)[10] sleep time to 4 h per night for 6 consecutive nights, and then extending it to 12 h for 6 nights. Figure 1a shows the results from a frequently sampled, intravenous glucose-tolerance test performed on the fifth day of both study periods. Glucose tolerance, estimated as the rate of decrease of glucose levels, was 40% lower after sleep restriction than after sleep extension, and reached a range that is typical of aging people who have impaired glucose tolerance.[10] This decrease in glucose tolerance was the combined consequence of a 30–40% decrease in glucose effectiveness (which is a measure of noninsulin-dependent glucose utilization) and a near 30% reduction in the acute insulin response to glucose, despite a trend for decreased insulin sensitivity. The product of insulin sensitivity and acute insulin response to glucose (that is, the disposition index, a validated marker of diabetes risk),[11] was decreased by nearly 40% in the state of sleep debt.

The glucose and insulin responses to a high-carbohydrate breakfast were assessed on the sixth day of both sleep conditions. Both peak glucose level and the overall glucose response were increased following sleep restriction, which confirmed a decrease in glucose tolerance. When the integrated glucose and insulin responses were examined with the homeostasis model-assessment index (the normalized product of insulin and glucose levels), a greater than 50% increase of homeostasis model-assessment values was observed after sleep restriction, as compared to the fully rested state; these results are consistent with a reduction in insulin sensitivity. In a subsequent study, 12 healthy men were assessed after two 10 h nights versus two 4 h nights, in randomized order.[12] Similarly to the findings of the previous study, after only two nights of short-duration sleep, morning levels of glucose were higher than normal, whereas insulin levels tended to be lower than after two nights of long sleep. Preliminary data from an independent laboratory have confirmed and extended these findings: 1 week of sleep that is restricted to 5 h per night in healthy men resulted in a marked reduction in insulin sensitivity, as assessed by the hyperinsulinemic euglycemic clamp.[13]

Poor-quality sleep and glucose regulation

The initiation of slow-wave sleep is associated with a decrease in use of glucose by the brain, stimulation of growth-hormone release, inhibition of cortisol secretion, decreased sympathetic nervous system activity and increased vagal tone. All these correlates of slow-wave sleep affect total-body glucose homeostasis; therefore, low amounts of slow-wave sleep, which normally occur in aging individuals and in those who have sleep disorders, might be associated with decreased glucose tolerance.

A recent study directly tested this hypothesis by selectively suppressing slow-wave sleep in healthy young adults and examining the effect on glucose tolerance.[14] Suppression of slow-wave sleep was achieved by delivery of acoustic stimuli that were designed to replace slow-wave sleep with shallow sleep, but to avoid full awakenings. The amount of slow-wave sleep was reduced by nearly 90%—a similar reduction to that associated with four decades of aging. Such low levels of slow-wave sleep are also typical of moderate to severe OSA. Importantly, this intervention did not reduce total sleep duration. Figure 1b shows the results from an intravenous glucose-tolerance test performed after 2 nights of undisturbed sleep and after 3 nights of slow-wave sleep suppression. After suppression of slow-wave sleep, insulin sensitivity had decreased by around 25% and reached the level reported in aging individuals and in populations at high risk of diabetes mellitus.[15] This decrease in insulin sensitivity was not compensated for by an increase in

the acute insulin response to glucose; consequently, the disposition index decreased by around 20% after slow-wave sleep suppression. Consistent with an increased risk of diabetes mellitus, glucose tolerance was reduced by around 23%, which approaches the range typical of impaired glucose tolerance.[14] Importantly, the decrease in insulin sensitivity was strongly correlated to the decrease in slow-wave sleep. These laboratory findings demonstrate unequivocally that poor-quality sleep may adversely affect glucose regulation.

Evidence from epidemiologic studies

A number of cross-sectional, as well as prospective, epidemiologic studies,[16,17] have provided evidence of an association between self-reported short-duration and/or poor-quality sleep and the prevalence or incidence of diabetes mellitus, after age, BMI and various other confounding variables are taken into account. Studies that have assessed sleep at baseline and incidence of diabetes mellitus over a follow-up period provide some indication of the direction of causality. Six studies have examined the effect of sleep duration, and an equal number of studies have addressed the effect of sleep quality as determined by self-reported problems, such as difficulty initiating or maintaining sleep, use of sleeping pills, or presence of insomnia (reviewed elsewhere[18]). Short sleep duration was found to predict an increased incidence of diabetes in four of the six studies, whereas poor-quality sleep was associated with an increased risk of diabetes mellitus in five of the six studies.[18]

Poor or short sleep and obesity

Evidence from laboratory studies

In a randomized, crossover study that involved two nights of 4 h in bed versus two nights of 10 h in bed, the daytime profiles of the satiety hormone, leptin, and the appetite-stimulating hormone, ghrelin, were measured and the participants completed validated scales for hunger and appetite for various food categories (Figure 2a).[19] Overall leptin levels decreased by an average of 18%, while ghrelin levels increased by 28%; the ghrelin:leptin ratio increased by more than 70%. Hunger increased by 23%, and appetite for nutrients with a high carbohydrate content was increased by more than 30% when sleep was restricted. If this increase in hunger during sleep restriction were to translate into a commensurate increase in food intake, weight gain would be expected to occur over time. A randomized, crossover laboratory study of overweight, middle-aged adults who underwent 2 weeks of sleep extension (+1.5 h per night) and 2 weeks of restriction (–1.5 h per night) has shown an increase in food intake from snacks during the short-sleep condition.[20] However, the participants gained weight under both sleep conditions, and no differences were detected in leptin or ghrelin levels between the two study conditions.

In a separate study, a clear, dose-response relationship was observed between sleep duration and the 24 h serum leptin profile.[21] Figure 2b shows the 24 h leptin profiles that were obtained after 6 days of 4 h, 8 h, and 12 h periods of sleep in healthy, lean young men. All the characteristics

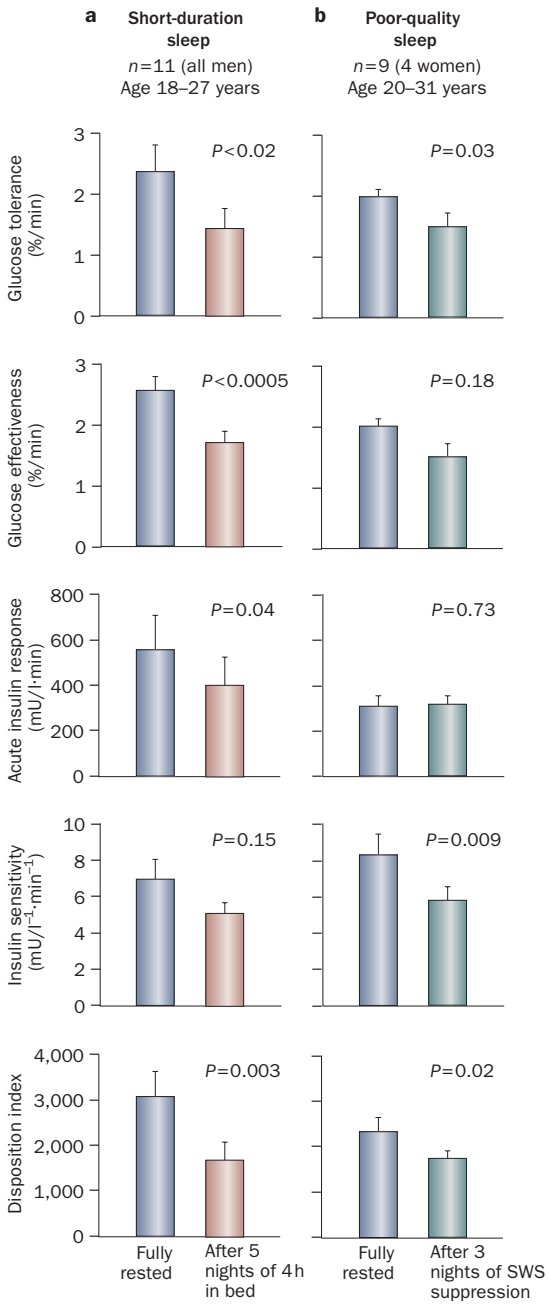

Figure 1 | Results from intravenous glucose-tolerance tests in healthy individuals when fully rested and after sleep manipulations. **a** | Results when fully rested and after 5 nights of 4 h in bed;[10] **b** | Results during baseline sleep and after 3 nights of suppression of slow-wave sleep.[14] Abbreviation: SWS, slow-wave sleep. Permission for part a was obtained from Elsevier Ltd © Spiegel, K. *et al.* Impact of sleep debt on metabolic and endocrine function. *Lancet* **354**, 1435–1439 (1999). Part b was adapted from Tasali, E. *et al. Proc. Natl Acad. Sci. USA* **105**, 1044–1049 (2008).

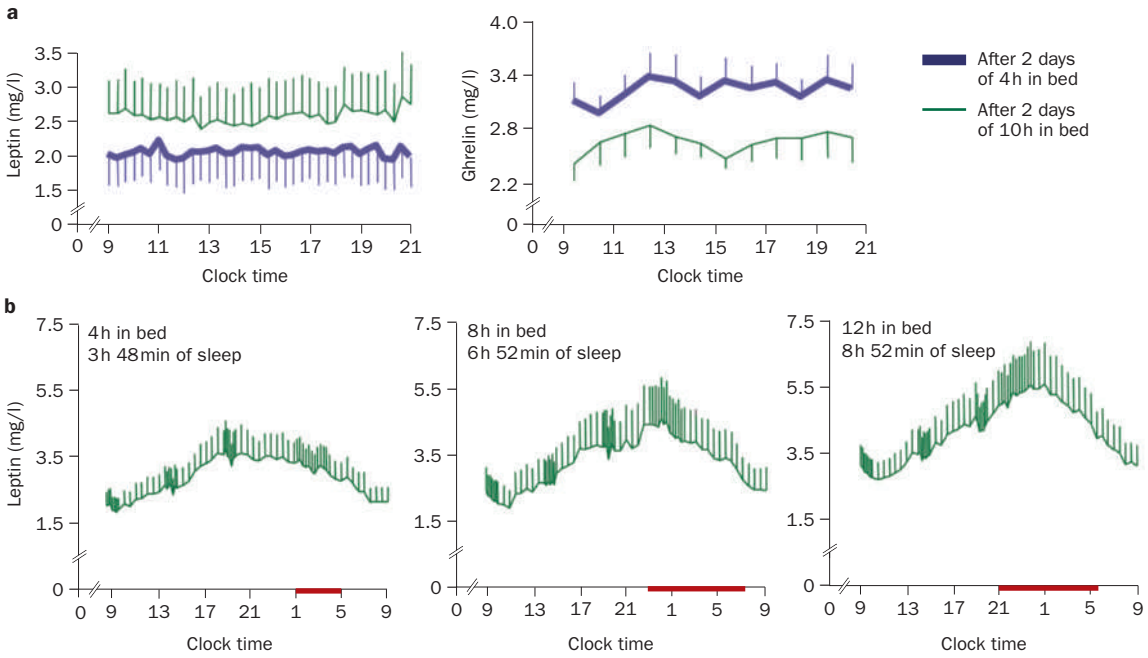

Figure 2 | Effect of sleep duration on leptin and ghrelin levels. **a** | Mean (±SEM) leptin and serum plasma ghrelin levels in healthy individuals after 2 days with 4 h or 10 h sleep periods. **b** | Mean (SEM) 24 h serum leptin profiles after 6 days of 4 h, 8 h and 12 h in bed in nine healthy, lean men, studied at bed rest who ate three identical carbohydrate-rich meals. At the end of these study periods, the participants slept an average of 3 h 48 min in the 4 h in bed group, 6 h 52 min in the 8 h in bed group, and 8 h 52 min in the 12 h in bed group. All characteristics of the 24 h leptin profile increased from the 4 h to the 12 h bedtime condition. The bars represent sleep periods. Permission for panel a was obtained from the American College of Physicians © Spiegel K *et al.* Brief communication: sleep curtailment in healthy young men is associated with decreased leptin levels, elevated ghrelin levels, and increased hunger and appetite. *Ann. Intern. Med.* **141**, 846–850 (2004). Permission for panel b was obtained from The Endocrine Society © Spiegel K *et al.* Leptin levels are dependent on sleep duration: relationships with sympathovagal balance, carbohydrate regulation, cortisol, and thyrotropin. *J Clin. Endocrinol. Metab.* **89**, 5762–5771 (2004).

of the 24 h leptin profile (overall mean level, nocturnal maximum, amplitude) gradually increased from the 4 h to the 12 h sleep-period condition. Importantly, these differences in 24 h regulation of leptin levels occurred despite identical amounts of caloric intake, similar sedentary conditions, and stable weight. Of note, the reduction in peak leptin levels (average of 26%) between the 4 h and the 12 h bedtime conditions was similar to that reported in healthy volunteers who were fed only 70% of their energy requirement during 3 consecutive days. These findings confirmed and extended the observations of an earlier study that assessed leptin levels 6 times during the 24 h cycle in volunteers studied after 7 days of sleep that was restricted to 4 h per night and reported a decrease in peak leptin levels.[22] Another study, which involved total sleep deprivation, or 4.5 h or 7 h of sleep for one night, also reported dose-response relationships between the duration of sleep, hunger ratings and ghrelin levels.[23] In this study, leptin levels were not affected.

The effect of sleep restriction on appetite regulation seems to be similar in the short term (2–6 days)[19,21] and in chronic conditions. Indeed, two epidemiologic studies have shown reduced leptin levels after controlling for BMI or adiposity in habitual short-duration sleepers.[24,25] High ghrelin levels were also associated with short-duration sleep.[24] A subsequent, small study, which involved only postmenopausal women, did not confirm the link between sleep duration, leptin and ghrelin levels;[26] however, very few participants in this study had short sleep durations.

Evidence from epidemiologic studies

An ever-growing number of cross-sectional, epidemiological studies (52 in September 2008) have provided evidence of an association between short-duration and/or poor-quality sleep and risk of obesity. Two meta-analyses, which included a total of more than 600,000 adults and 30,000 children from all over the world, attempted to quantify the link between short-duration sleep and obesity risk. In the first study, the pooled odds ratio (OR) that linked short-duration sleep to obesity was 1.89 (95% CI 1.46-2.43, $P<0.0001$) in children and 1.55 (95% CI 1.43–1.68, $P<0.0001$) in adults.[27] The second study reported an OR of 1.58 (95% CI 1.26–1.98) in children with short sleep duration, and an OR of 1.92 (95% CI 1.15–3.2) in children with the shortest sleep duration; these results suggest existence of a dose-response relationship between sleep duration and risk of obesity.[28] A third systematic review similarly concluded that short sleep duration seems to be independently associated with weight gain, particularly in young age groups.[29] Whereas these analyses suggest that

the effect of sleep duration on weight may be less robust in aging populations than in children and young adults, a cross-sectional analysis that used wrist actigraphy to objectively assess sleep duration objectively in more than 6,000 men and women aged 67–99 years, provided strong evidence to the contrary.[30] Compared with sleeping 7–8 h per night, sleeping less than 5 h was associated with a BMI that was, on average, more than 2.5 kg/m^2 in men and 1.8 kg/m^2 in women, after adjustments were made for multiple potentially confounding variables.

Of the 10 longitudinal studies on sleep duration and obesity risk in children and adults that have been performed, 9 reported that reduced sleep durations are associated with an increased risk of being overweight or obese a few years later.[17,31] This pattern is particularly consistent in children.[16]

This body of epidemiologic evidence supports the hypothesis that sleep curtailment may be a plausible 'nontraditional' lifestyle factor that contributes to the epidemic of obesity.[32] Increasing the duration of sleep for those who regularly curtail it has been suggested as a means to improve the health of the population as a whole.[33] Critics have argued that the effect of short-duration sleep in longitudinal studies is small (short-duration sleepers gain excess weight of 1–7 kg over 10 years) and that the number of short-duration sleepers (less than or equal to 5 h) in the general population is low.[34] Yet, the difference in weight gain between short-duration and normal-duration sleepers is well within the range of weight loss that can be achieved with pharmacological interventions, and in the two epidemiologic studies that assessed sleep duration objectively by monitoring wrist activity, more than 10% of the participants slept for fewer than 5 h per night.[30,35]

A limitation of nearly all of these epidemiologic studies is that they did not simultaneously assess sleep quality. Thus, whether short-duration sleep in obese individuals is the result of sleep-time curtailment, or the presence of a sleep disorder remains to be determined. A large study,[36] in which the participants reported sleep duration, subjective sleep disturbances (for example, insomnia, excessive daytime sleepiness, sleep difficulty) and a measure of chronic emotional stress, concluded that self-reported short-duration sleep in obese adults may be a surrogate marker of sleep disturbance and psychosocial stress. This hypothesis is consistent with the existence of a 'vicious circle', in which short-duration sleep may initially promote weight gain; the resultant excess adiposity would then induce sleep disturbances and psychological stress, with a net further decrease in total sleep time.

OSA and metabolic disorders

Prevalence of OSA

OSA is a highly prevalent sleep condition that is associated with increased morbidity and mortality. OSA is characterized by repetitive episodes of upper-airway obstruction that lead to intermittent hypoxemia and/or hypercapnia and sleep fragmentation. Diagnosis of OSA is based on the apnea–hypopnea index (AHI), which measures the total number of apnea plus hypopnea episodes per hour of sleep; individuals with an AHI of greater than 5 by polysomnography are considered to have OSA. Table 1 summarizes the prevalence of OSA in the general population and in populations with metabolic or endocrine disorders. Obesity is a major risk factor for OSA, and the prevalence of OSA in the morbidly obese population is strikingly high—(50% to 98%).[37]

Table 1 | Prevalence of OSA in various populations

Population of patients	Prevalence of OSA (%)
General population	
Patients with OSA (AHI>5) and excessive daytime sleepiness[81]	2–7
Patients with OSA (AHI>5)[82]	17
Patients with endocrine disorders	
Obese patients[82]	41–58
Morbidly obese patients[37]	50–98
Patients with diabetes mellitus[38–40]	17–97
Patients with polycystic-ovary syndrome[41,42]	44–70
Patients with acromegaly[43]	19–23
Patients with hypothyroidism[43]	50–100
Patients with Cushing syndrome[43]	18–32

Abbreviations: AHI, apnea–hypopnea index; OSA, obstructive sleep apnea.

The prevalence of OSA in metabolic and endocrine disorders is very high. In patients with diabetes mellitus, the prevalence of OSA is between 17%[38] and 48%.[39] In a preliminary report, which involved only obese patients with diabetes mellitus, undiagnosed OSA was found in 97% of the participants.[40] This evidence for an exceptionally high rate of OSA in individuals with diabetes mellitus might have important implications, including a need for systematic evaluation and treatment of OSA in this group. Polycystic-ovary syndrome (PCOS), the most common endocrine disorder of premenopausal women, involves obesity, insulin resistance and a substantially elevated risk of early-onset, impaired glucose tolerance and diabetes mellitus. Whereas the risk of OSA in healthy young women, even if they are overweight or obese, is less than 10%, in women with PCOS, recent reports have found a prevalence of OSA of 44–70%.[41,42] In acromegaly, hypothyroidism and Cushing syndrome, the prevalence of OSA is 19%–23%, 50%–100%, and 18%–32%, respectively.[43] The pathophysiology that underlies the high prevalence of OSA in endocrine disorders is likely to be multifactorial and include anatomic, functional and hormonal factors.

OSA involves respiratory disturbances, hypoxic stress, poor-quality sleep (owing to sleep fragmentation and low levels of slow-wave sleep) and reduced total sleep time. The alterations in glucose regulation and/or appetite regulation observed with experimentally reduced sleep duration and quality[10,19] suggest that poor-quality and short-duration sleep, in addition to hypoxia, could

Table 2 | Effect of CPAP treatment on glucose metabolism

Population of patients	Positive effect reported	No effect reported
Patients with T2DM[a]		
Total number of studies	5[49–53]	1[54]
Total number of patients	102	42
Nondiabetic patients[b]		
Total number of studies	4[55–58]	7[59–65]
Total number of patients	109	225

[a]Improvement of glucose metabolism in patients with T2DM was defined as decreased HbA_{1c} level and/or decreased postprandial glucose level by continuous glucose monitoring, and/or improved insulin sensitivity by hyperinsulinemic euglycemic clamp, and/or improved insulin sensitivity by fasting HOMA index. [b]Improvement of glucose metabolism in nondiabetic patients was defined as improved insulin sensitivity by hyperinsulinemic euglycemic clamp, and/or improved insulin sensitivity by fasting HOMA index, and/or decreased fasting glucose and insulin levels. Abbreviations: CPAP, continuous positive airway pressure; HOMA, homeostasis model assessment; T2DM, type 2 diabetes mellitus.

Table 3 | Effect of CPAP on leptin/ghrelin levels and weight

Outcome measure	Positive effect reported	No effect reported
Decrease in leptin level		
Total number of studies	6[59,60,63,68,70,71]	2[72,73]
Total number of patients	183	127
Decrease in ghrelin level		
Total number of studies	2[68,74]	NA
Total number of patients	51	NA
Decreased body weight or visceral adiposity		
Total number of studies	3[63,70,75]	3[65,76,77]
Total number of patients	83	230

Abbreviations: CPAP, continuous positive airway pressure; NA, no data available.

contribute to altered glucose homeostasis and weight gain in patients with OSA.

OSA and diabetes mellitus

Cross-sectional studies demonstrate an association between OSA and diabetes mellitus, independent of confounding factors.[44–47] By contrast, no evidence supports a causal role for OSA in the development of diabetes mellitus. Only one prospective study used polysomnography to assess OSA and its relationship to diabetes risk, but the results failed to show a significant association between incident diabetes mellitus and OSA at 4-year follow-up (OR 1.62, $P = 0.24$).[48]

A review of studies that assessed the effect of continuous positive airway pressure (CPAP) on glucose regulation suggests that the treatment gives more consistently positive results in patients with diabetes mellitus than in nondiabetic populations. Table 2 summarizes the findings from full reports in international journals that involved more than one night of CPAP treatment in adult populations. Of six studies that assessed glycemic control in a total number of 150 diabetic patients with OSA, five reported a positive effect (Tables 2 and 3).[49–53] Notably, the one study that did not find such a correlation reported an average nightly therapeutic CPAP use of only 3.6 h.[54] By contrast, in patients with OSA who do not have diabetes mellitus, a beneficial effect of CPAP on parameters of glucose regulation, including various measures of insulin sensitivity, has only been found in 4[55–58] of a total 11 studies,[55–65] which together involved more than 300 individuals.

These inconsistent results may be partly attributed to differences in sample sizes, study populations, durations of therapy, adherence to therapy, and changes in body composition during the study period. Importantly, most studies did not report objective data on CPAP usage, and in those that reported compliance, use of CPAP for greater than or equal to 4 h per night was considered 'compliant'.

OSA and regulation of food intake and weight

Patients with OSA seem to be more predisposed to weight gain than control individuals with similar levels of obesity who do not have OSA.[66,67] Consistent with the upregulation of ghrelin that is observed during short-duration sleep in healthy individuals,[19,23,24] patients with OSA have high ghrelin levels, which decrease after as little as 2 days of CPAP treatment.[68] By contrast, the decreased leptin levels that follow sleep restriction in normal individuals[19,21,22] are not consistent with the hyperleptinemia observed in OSA.[67] Whereas leptin levels are reduced in individuals with chronic short-duration sleep without OSA, independently of BMI and adiposity,[24,25] patients with OSA display higher leptin levels than BMI-matched controls.[67,69]

Tables 2 and 3 summarize the studies that have examined the effect of CPAP treatment on leptin levels.[59,60,63,68,70–73] Although the positive findings of these studies outnumber negative findings, the overall evidence is inconclusive. The hyperleptinemia in patients with OSA is thought to reflect leptin resistance. Thus, a putative reduction in leptin resistance after CPAP treatment would be expected to result in weight loss in these patients. Only two studies have measured post-CPAP ghrelin levels in patients with OSA, and both reported a decrease in ghrelin levels,[68,74] which should also lead to decreased hunger and a possible beneficial effect on weight (Table 3). However, findings on the effect of CPAP on body weight and/or visceral adiposity are mixed (Table 3). One study reported weight loss after 6 months of CPAP,[75] whereas another study found no weight loss after 1 year of treatment with CPAP.[76] Finally, 6 months of CPAP therapy added to a weight-reduction program have not resulted in increased weight loss.[77] From a metabolic point of view, loss of visceral fat is far more relevant than overall weight loss. Again, relevant studies are scarce and provide conflicting results; two[63,70] of only three studies[63,65,70] have reported a beneficial effect of CPAP on visceral adiposity.

OSA and polycystic-ovary syndrome

Polycystic-ovary syndrome (PCOS), the most common endocrine disorder of premenopausal women, is characterized by chronic hyperandrogenism, oligo-ovulation and anovulation, obesity, insulin resistance and a substantially

elevated risk of early-onset impaired glucose tolerance and diabetes mellitus. Insulin resistance is often referred to as a 'hallmark' of PCOS. OSA is highly prevalent in women with this syndrome. One study reported an AHI of greater than 5 in 56% of women with PCOS, compared with 19% of age-matched and weight-matched controls.[78] This study was the first to examine metabolic disturbances in women with PCOS after taking the presence and severity of OSA into account. The findings indicated that insulin resistance and reduced glucose tolerance in women with PCOS are largely the result of OSA.[78] Figure 3 shows the prevalence of impaired glucose tolerance and the degree of insulin resistance in control women without OSA, women with PCOS but without OSA, and women with PCOS and mild, moderate, or severe OSA. The prevalence of impaired glucose tolerance and the degree of insulin resistance increased in direct proportion to the severity of OSA. Furthermore, when women with PCOS who had preserved normal glucose tolerance were examined, they were no more insulin-resistant than control women who did not have PCOS.

Thus, PCOS seems to be composed of two subphenotypes: PCOS with OSA, and PCOS without OSA; the latter represents less than 50% of women with PCOS. PCOS with OSA is clearly associated with a higher risk of diabetes mellitus than PCOS without OSA. As insulin resistance is thought to contribute to both androgen overproduction and metabolic disturbances in PCOS, assessment of OSA in PCOS is highly recommended; the correction of OSA might greatly improve these women's prognosis. A quick and easy screen for OSA can be performed with the Berlin Questionnaire, a well-validated survey that identifies patients who have a high risk of OSA.[79] Unfortunately, most clinicians who treat women with PCOS today are not yet aware of the high risk of OSA in this group of patients.[80]

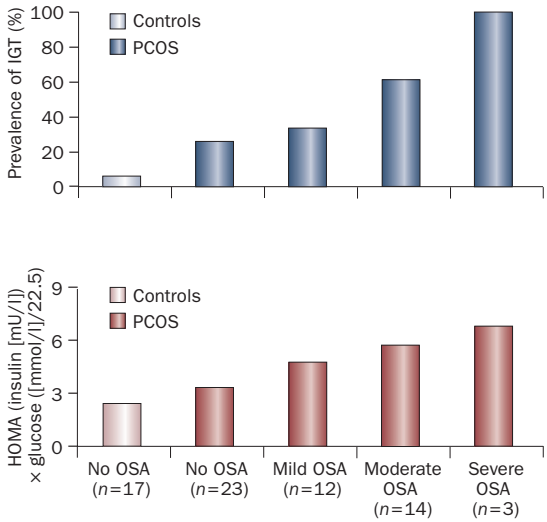

Figure 3 | Prevalence of impaired glucose tolerance and degree of insulin resistance, as assessed by the HOMA index, in control women without OSA, women with PCOS and without OSA, and women with PCOS and mild (5<AHI<15, moderate (15<AHI<30), and severe (AHI≥15) OSA. As expected, women who had PCOS with or without OSA displayed a higher prevalence of IGT and greater insulin resistance than controls. Among women with PCOS, the prevalence of IGT and degree of insulin resistance increased in direct proportion to the severity of OSA. Abbreviations: AHI, apnea–hypopnea index; HOMA, homeostasis model assessment; IGT, impaired glucose tolerance; OSA, obstructive sleep apnea. Permission obtained from The Endocrine Society © Tasali, E. *et al.* Impact of obstructive sleep apnea on insulin resistance and glucose tolerance in women with polycystic ovary syndrome. *J. Clin. Endocrinol. Metab.* **93**, 3878–3884 (2008).

Conclusions

Restorative sleep is essential for well-being, but sleep curtailment has become a common behavior in modern society. In addition, sleep disorders, particularly OSA, are very common in individuals with metabolic and endocrine disorders, but often remain undiagnosed. The accumulated evidence for a deleterious effect of short-duration or poor-quality sleep on metabolic and endocrine function supports the hypothesis that chronic, voluntary sleep curtailment and sleep disorders such as OSA may adversely affect the course of disease in patients with metabolic and endocrine disorders. Treatment of OSA by CPAP has the potential to improve glucose metabolism and appetite regulation. Screening for habitual sleep patterns and OSA—for which simple and inexpensive tools are available—such as sleep logs to characterize habitual sleep patterns and the Berlin Questionnaire, may be critically important in patients with endocrine and metabolic disorders.

Review criteria

A search for original and review articles that focus on sleep, hormones and metabolism was performed in PubMed. The search terms used were "sleep", "OSA", "sleep apnea", "CPAP", "obesity", "leptin", "ghrelin", "weight", "visceral", "diabetes", "glucose", "insulin", "metabolic", "endocrine", "acromegaly", "hypothyroidism", "polycystic ovary syndrome", and "PCOS". We also searched the reference lists of identified articles for further papers. Articles were restricted to human studies. In order to limit the number of references, we selected, whenever possible, a recent review complemented by original papers published after the review.

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