

MEDICAL AND GENETIC DIFFERENCES IN THE ADVERSE IMPACT OF SLEEP LOSS ON PERFORMANCE: ETHICAL CONSIDERATIONS FOR THE MEDICAL PROFESSION

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ABSTRACT

The Institute of Medicine recently concluded that on average medical residents make more serious medical errors and have more motor vehicle crashes when they are deprived of sleep. In the interest of public safety, society has required limitations on work hours in many other safety sensitive occupations, including transportation and nuclear power generation. Those who argue in favor of traditional extended duration resident work hours often suggest that there are inter-individual differences in response to acute sleep loss or chronic sleep deprivation, implying that physicians may be more resistant than the average person to the detrimental effects of sleep deprivation on performance, although there is no evidence that physicians are particularly resistant to such effects. Indeed, recent investigations have identified genetic polymorphisms that may convey a relative resistance to the effects of prolonged wakefulness on a subset of the healthy population,

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although there is no evidence that physicians are over-represented in this cohort. Conversely, there are also genetic polymorphisms, sleep disorders and other inter-individual differences that appear to convey an increased vulnerability to the performance-impairing effects of 24 hours of wakefulness. Given the magnitude of inter-individual differences in the effect of sleep loss on cognitive performance, and the sizeable proportion of the population affected by sleep disorders, hospitals face a number of ethical dilemmas. How should the work hours of physicians be limited to protect patient safety optimally? For example, some have argued that, in contrast to other professions, work schedules that repeatedly induce acute and chronic sleep loss are uniquely essential to the training of physicians. If evidence were to prove this premise to be correct, how should such training be ethically accomplished in the quartile of physicians and surgeons who are most vulnerable to the effects of sleep loss on performance without unacceptably compromising patient safety? Moreover, once it is possible to identify reliably those most vulnerable to the adverse effects of sleep loss on performance, will academic medical centers have an obligation to evaluate the proficiency of both residents and staff physicians under conditions of acute and chronic sleep deprivation? Should work-hour policy limits be modified to ensure that they are not hazardous for the patients of the most vulnerable quartile of physicians, or should the limits be personalized to enable the most resistant quartile to work longer hours? Given that the prevalence of sleep disorders has increased in our society overall, and increases markedly with age, how should fitness for extended duration work hours be monitored over a physician's career? In the spirit of the dictum to do no harm, advances in understanding the medical and genetic basis of inter-individual differences in the performance vulnerability to sleep loss should be incorporated into the development of work-hour policy limits for both physicians and surgeons.

After a comprehensive review of the medical and scientific literature as part of a year-long study initiated at the behest of the United States Congress and supported by the Agency for Healthcare Research and Quality, the Institute of Medicine (IOM) Committee on Optimizing Graduate Medical Trainee (Resident) Hours and Work Schedules to Improve Patient Safety concluded this past year that working for more than 16 consecutive hours without sleep is unsafe for both physicians in training (residents) and their patients⁽¹⁾. This latest IOM report builds on earlier work by the IOM Committee on Sleep Medicine and Research, which conducted an independent review of the adverse effects of sleep loss on neurobehavioral performance, learning, cognition, health and safety⁽²⁾. The IOM recommendations are consistent with the recommendations promulgated by the Association for American Medical Colleges (AAMC) in 2001 that resident physician work shifts be limited to no more than 12 consecutive hours in all high intensity clinical settings, such as intensive care units (ICUs) and emergency departments⁽³⁾.

Nearly forty years ago, it was recognized that—on average—interns made twice as many mistakes detecting cardiac arrhythmias when they were sleep deprived as compared to when they were more well rested (⁴). More recently, laparoscopic surgical simulator studies have revealed that, on average, error rates doubled in residents when they performed simulated surgery after a night on call as compared to when they were more well rested (⁵) (Figure 1). In a meta-analysis cited by the IOM, which was conducted by Accreditation Council on Graduate Medical Education (ACGME) Senior Vice President of Field Activities, Dr. Ingrid Philibert, she concluded that after 24–30 hours of sleep deprivation, individual cognitive performance of the average person drops from the 50th to the 15th percentile of their performance when rested (⁶), and that clinical performance of physicians drops from the 50th to the 7th percentile of their performance when rested (⁶). There is also growing evidence that sleep plays an essential role in learning and memory consolidation,

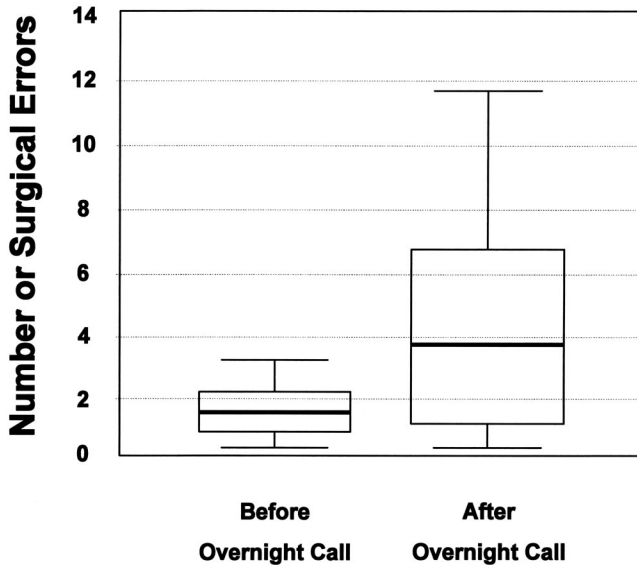


FIG. 1. Effect of Partial Sleep Loss during Hospital Call on Errors Committed by Surgeons during Simulated Surgery. Simulated laparoscopic surgery performance of surgical residents (median age 34) measured by a laparoscopic surgery simulator (task 6 of the MIST-VR, Mentice Medical Simulation, Gothenburg, Sweden) before and after a night on call (17.5 hours from 3:30 pm to 9 am; median reported sleep time 1.5 h; range 0–3 h). Horizontal bands indicate median number of errors on this task, boxes show 25th and 75th centiles, and whisker lines show the highest and lowest error values. Figure and legend reprinted with permission from: Grantcharov TP, Bardram L, Funch-Jensen P, Rosenberg J. *BMJ* 2001;323:1222–1223 (⁵).

and that chronic sleep deprivation has many deleterious health consequences, including an increased risk of obesity, diabetes, depression and cardiovascular disease (2, 7-15).

The conclusion that acute sleep loss impairs both cognitive and psychomotor performance and increases the risk of error among healthy young adults in both laboratory evaluations (16, 17) and in clinical settings (18) is consistent with previously published laboratory research on participant volunteers (2, 19, 20) and with the field data (21-26). As shown in Figure 2, sleep deprivation combined with misalignment of circadian phase creates a critical zone of vulnerability in the latter half of the night (17). Paradoxically, instead of slowing down to preserve accuracy as reaction time increases, sleep deprivation often leads people to make hasty decisions based on inad-

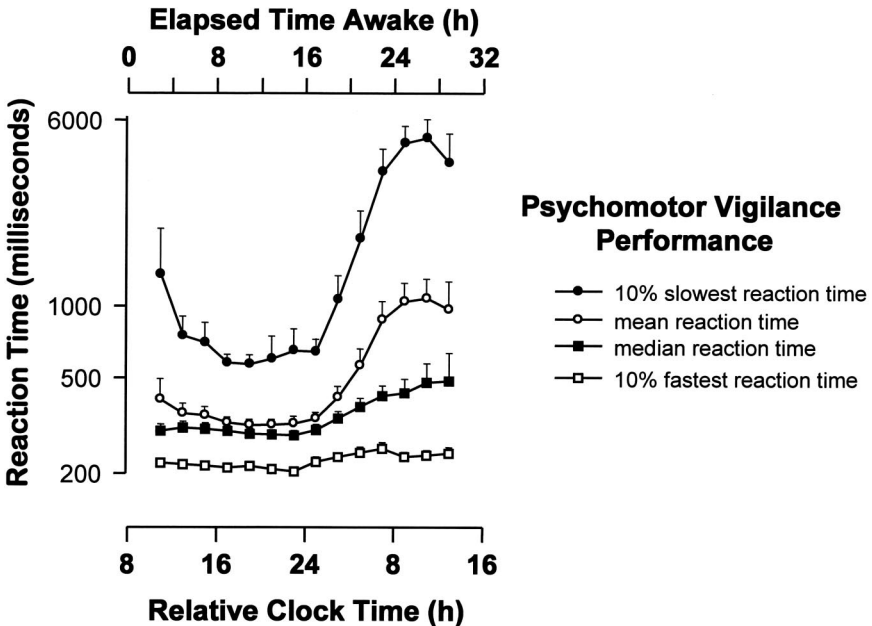


FIG. 2. Impact of Acute Total Sleep Deprivation on Reaction Time Performance. Time course of psychomotor vigilance task (PVT) performance [mean, median, 10% slowest and fastest reaction times in milliseconds (logarithmic scale)] during more than 28 hours of continuously monitored wakefulness under constant environmental and behavioral conditions are shown averaged across 10 subjects \pm standard error of the mean. All data are binned from 10-minute PVT tests administered at 2-hour intervals and expressed with respect to elapsed time since wake time (designated as a Relative Clock Hour of 8), which was scheduled at its habitual hour. Figure and legend reprinted with permission from: Cajochen C, Khalsa SBS, Wyatt JK, Czeisler CA, Dijk D-J. *Am J Physiol* 277: R640-R649, 1999 (17).

equate information (27). This results in increased rates of errors on selective attention tasks that require a search for targets in the visual field (27). Forty percent of interns working extended duration 'on call' shifts slept less than 2 hours in a 30-hour interval, and more than 15% obtained less than 1 hour of sleep during that interval (24) (Figure 3). Residents randomized to work extended duration (>24 hour) shifts experienced twice as many attentional failures (22) and—on average—made 36% more serious errors caring for patients in intensive care units, including 460% more serious diagnostic mistakes, as compared to the same physicians when they were scheduled to work no more than 16 consecutive hours in intensive care units (23). Nationwide, interns have a 168% increased risk of a motor vehicle crash driving home from extended duration (>24-hour) shifts (24) and were 73% more likely to suffer from a percutaneous injury when performing a procedure after

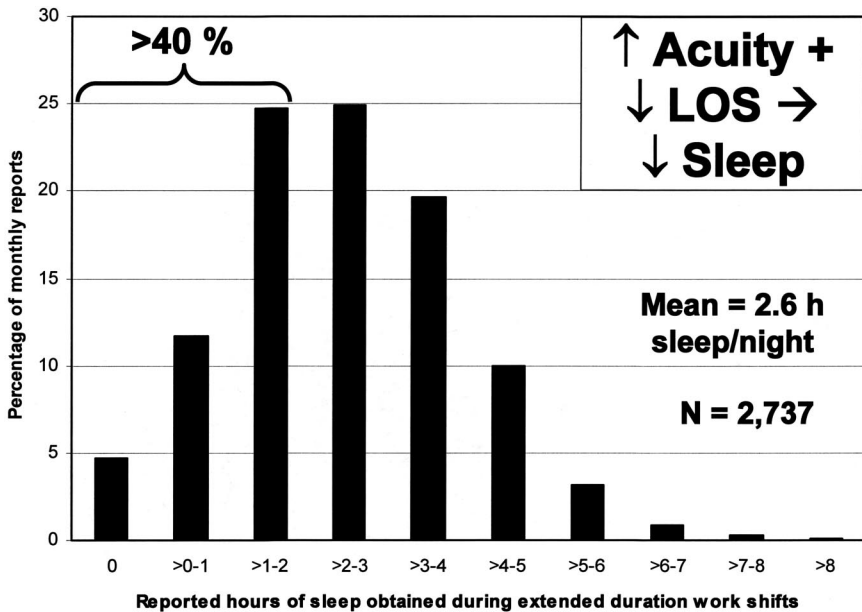


FIG. 3. Sleep Duration in the Hospital. Average hours that interns reportedly slept in the hospital during extended duration (greater than 24 hour) on-call shifts as a percentage of 17,003 monthly survey reports collected from 2,737 resident physicians. Average hours of sleep obtained during extended duration shifts reported by interns for each week were averaged over the four weeks of each month to derive the value for each monthly survey report. Figure and legend reprinted with permission from: Barger LK, Cade BE, Ayas N, Cronin JW, Rosner B, Speizer FE, Czeisler CA, N Engl J Med 2005;352:125-134 (24).

their 20th hour of work than during shifts that averaged less than 12 hours in duration (26).

On average, after being awake for 24 hours, impairment on a simple reaction time test in individuals who remain awake during testing is comparable with the impairment observed at a blood alcohol concentration of 0.10 g/dL (17, 28). In a survey of 2,737 resident physicians, our group found that one out of five first-year residents reported making a fatigue-related mistake that injured a patient, and one out of twenty first-year residents reported making a fatigue-related mistake that resulted in the death of a patient (25). In months when interns worked more than 5 extended duration (>24-hour) work shifts, the risks of such fatigue-related injuries and deaths increased by 700% and 300%, respectively.

Many within and outside the profession of medicine have hailed the IOM report as a long-overdue acknowledgement by the medical profession of the dangers of an obviously hazardous tradition (29). Yet, many conscientious physicians and surgeons argue vehemently that working for 24 consecutive hours is safe and that working such long hours is essential for the training of physicians and inherent in the practice of medicine (30, 31). What might be fueling such a passionate difference of opinion?

Wherever I have presented data on the average impact of sleep loss on performance, the most common question that I have been asked is about inter-individual differences. "Aren't some people more resistant to the effects of sleep loss than others?" The follow-up comments by such questioners usually reveals an underlying premise that individuals in certain professions (e.g., police officers, fire fighters, physicians, surgeons, aviators, special forces, astronauts) may be more resistant than the average person to the effects of acute sleep loss or chronic sleep restriction on performance. In fact, even among healthy young adults, there are profound inter-individual differences in the impact of sleep loss on performance (2, 32-38). In addition, healthy sleepers are likely to be much more resistant to the effects of sleep loss than the 50 to 70 million Americans who suffer from chronic disorders of sleep and wakefulness (2).

INTER-INDIVIDUAL DIFFERENCES IN TOLERANCE TO SLEEP LOSS IN HEALTHY YOUNG ADULTS

Differences in Vulnerability to Sleep Loss Due to Prior Sleep-wake History

The ability to sustain attention, maintain cognitive performance and prevent attentional failures deteriorates when sleep is chronically

restricted to 7 or fewer hours per night for a week or longer^(2, 39–41) (Fig. 4). Many habitually short sleepers may be harboring substantial sleep debt, as reflected by higher sleep tendency, suggesting that their habitually short sleep durations may not reflect a reduced underlying sleep need^(42, 43). Long work weeks together with commuting time often require those, who are not habitually short sleepers, to restrict the time available for sleep. This occurs to physicians during residency training, when weekly sleep durations are curtailed as weekly work hours increase^(22, 24, 44). Yet, our data also reveal up to a two-hour difference in average nightly sleep durations among interns working the same number of hours per week in an ICU⁽²²⁾.

There are many factors that may lead to the inter-individual differences in the average amount of sleep obtained by residents working the same number of hours in the hospital, including differences in their responsibilities outside the hospital. The very concept of residency has changed since it was first introduced in the U.S. at the Johns Hopkins University School of Medicine by Professor William Stewart Halsted in the 1890s. At the time, residents were required to live at the hospital and were discouraged from marrying⁽⁴⁵⁾. Today residents live outside the hospital, and many of these young physicians have families and become new parents during residency. The sleep of new mothers and fathers is often interrupted and curtailed by newborns, resulting in increased daytime fatigue^(46, 47). Multiple births exacerbate post-partum sleep deprivation and daytime fatigue, particularly for fathers⁽⁴⁸⁾. Children with sleep or health problems may also lead to sleep fragmentation, sleep deprivation and increased daytime fatigue in parents^(49, 50). Behaviorally induced insufficient sleep syndrome affects 7% of patients with excessive daytime sleepiness (EDS) in Japan and is associated with a high motor vehicle crash risk⁽⁵¹⁾. Both acute and chronic sleep loss, whether caused by work schedules, family responsibilities, social activities or health problems, will degrade tolerance and increase performance vulnerability to the sleep deprivation imposed by extended duration (>24-hour) work shifts.

Moreover, preliminary evidence suggests that even after 8 to 12 hours of recovery sleep, individuals with a history of recent exposure to chronic sleep loss may be more vulnerable to the effects of re-exposure to sleep restriction, exhibiting nearly double the deterioration in performance on a vigilance task upon acute sleep restriction to 4 hours of time in bed as compared with their response to the same challenge when their recovery sleep was not preceded by exposure to chronic sleep debt⁽⁵²⁾. Thus, resident work schedules that cause chronic sleep

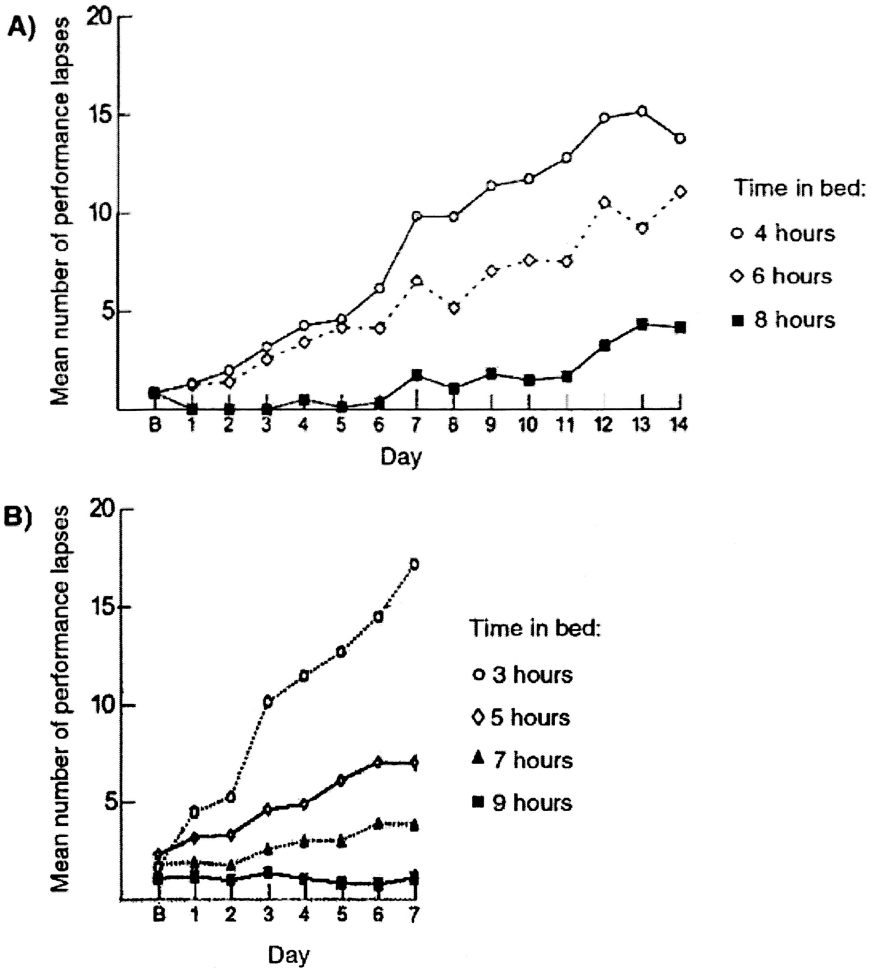


FIG. 4. Repeated Nights of Sleep Loss Result in Cumulative Cognitive Impairment. Higher number of attentional performance failures on the PVT indicates poorer performance and more unstable alertness. *Panel A* shows the average number of lapses of attention recorded during 10-minute PVT tests administered eight times daily (every two hours) during 14 consecutive days when the amount of time in bed was limited to 4 hours, 6 hours or 8 hours per night. Lower panel shows the average number of lapses of attention recorded during 10-minute PVT tests administered four times daily during 7 consecutive days when the amount of time in bed was limited to 3 hours, 5 hours, 7 hours or 9 hours per night. *Panel B* signifies data from the baseline day. Figure and legend reprinted with permission from the 2006 IOM Report entitled: Sleep Deprivation and Sleep Disorders: An Unmet Public Health Problem (2).

restriction and provide for only one night of recovery sleep per week may generate a deterioration of performance that becomes progressively greater with additional weeks of sleep curtailment. Despite intermittent opportunities for recovery sleep, individuals exposed to such schedules may become increasingly vulnerable to the adverse effects of sleep loss on performance. Four weeks of scheduled sleep extension (14 hours per night) can reduce fatigue and increase energy levels, but only after an average of more than 30 hours of accumulated sleep debt has been repaid⁽⁵³⁾. Irregularity in the timing of sleep and wakefulness can impede circadian adaptation to altered work-rest schedules⁽⁵⁴⁾; loss of circadian entrainment, in turn, impairs cognitive performance⁽⁵⁵⁾. Thus, available evidence indicates that prior sleep-wake history, including exposure to both acute and chronic sleep restriction, to sleep extension, and to irregular sleep-wake schedules, may greatly affect an individual's resiliency in the face of sleep loss⁽²⁾.

Age-related Differences in the Vulnerability to Sleep Loss

Thirty consecutive hours of sleep loss induces marked deterioration in neurobehavioral functions in healthy young participants⁽¹⁷⁾. So long as participants remain awake, average reaction time after 24 hours without sleep is three times longer than when the same individuals are rested⁽¹⁷⁾ (Figure 2). The risk of lapses of attention is much higher during the latter half of the night, with the slowest 10% of reaction times lengthening to nearly six seconds after 24 hours without sleep⁽¹⁷⁾. Remarkably, the impact of a single night of acute sleep deprivation on such measures is much less pronounced in older participants over the age of 55 years^(56–58) (Figure 5). This may be due to age-related loss of neurons in the ventro-lateral pre-optic (VLPO) area of the hypothalamus, which enables mammals to make the transition from wakefulness to sleep; age-related loss of VLPO neurons may also explain why the prevalence of insomnia rises with age. Because older people have greater difficulty obtaining recovery sleep at an adverse circadian phase⁽⁵⁹⁾, they are more vulnerable to the effects of a sequence of night shifts⁽⁶⁰⁾. Nonetheless, the data reveal that young adults are most severely affected by acute sleep deprivation; in fact, 55% of sleep-related motor vehicle crashes occur in drivers age 25 years or younger⁽⁶¹⁾ (Figure 6). Thus, it is both ironic and alarming that young resident physicians in this most vulnerable age group are subjected to acute sleep deprivation during 30-hour shifts twice per week while caring for patients and these young physicians then attempt to commute home from work.

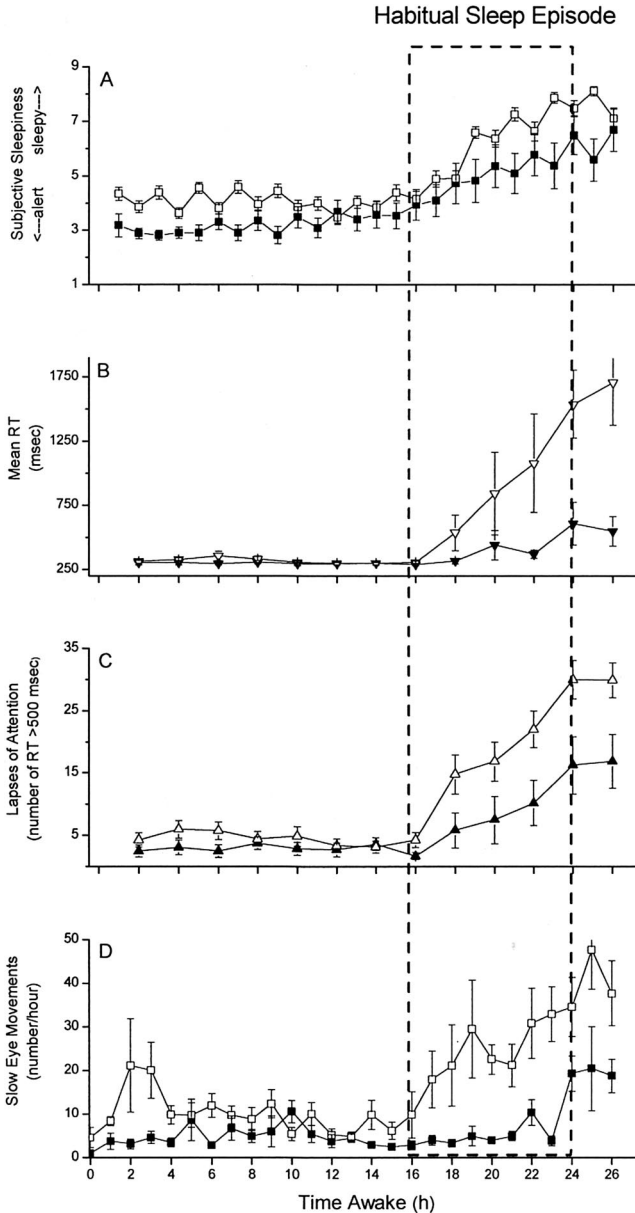


FIG. 5. Subjective Sleepiness, Reaction Time, Lapses of Attention, and Attentional Failures Across 26 Hours of Wakefulness in Young and Older Participants. Group average data (\pm standard error of the mean) are plotted with respect to time since scheduled awakening for 11 healthy older (mean age 68.1 ± 3.6 years; range 65 to 76 years; filled symbols) and 26 healthy young (mean age 21.9 ± 3.3 years; range 18 to 29

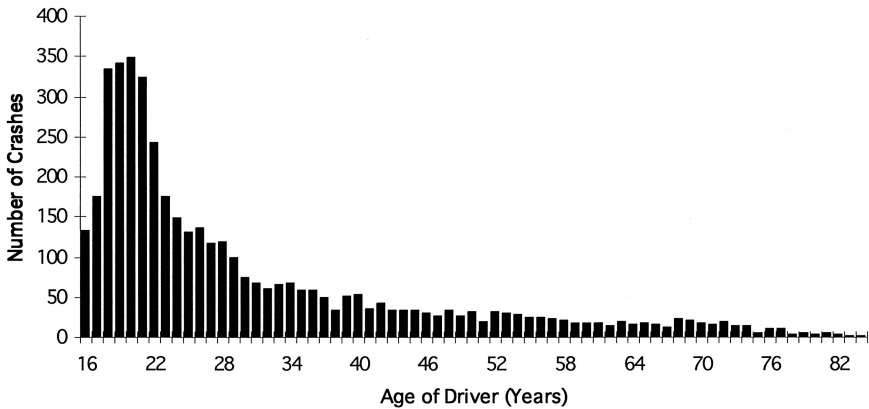


FIG. 6. Age Distribution of Crashes in Which Driver Was Not Intoxicated But Judged to Have Been Asleep. Data from 4,333 fall asleep crashes in North Carolina, where standard crash report forms, as mandated by state law, include 'fatigued' and 'asleep' in driver condition. Data for years 1990-1992, inclusive. In 55% of fall-asleep crashes, driver was age 25 or younger. Peak age of crashes was at age 20 years. Figure and legend reprinted with permission from: Pack AI, Pack AM, Rodgman E, Cucchiara A, Dinges DF, Schwab CW. *Accid Anal Prev* 27: 769, 1995 (61).

Trait Differences in Vulnerability to Sleep Loss

There are also inter-individual differences in the vulnerability of well-rested, healthy young adults to sleep loss. In my laboratory, among healthy participants who have maintained a schedule of 8 hours of sleep at the same time each night for three weeks, we have found that approximately one-quarter of the participants account for roughly two-thirds of the attentional failures recorded during ~30 hours of wakefulness. Interestingly, inter-individual differences in the vulnerability to sleep loss in healthy young adults appear to be task-dependent, such that reaction time in a sustained attention task is

years; open symbols) adults. Dashed box indicates time of usual sleep episode. Subjective sleepiness ratings from the Karolinska Sleepiness Scale (KSS; scale range from 1 = very alert to 9 = very sleepy) are presented in *Panel A*. Mean reaction time (RT, in milliseconds) from each 10-minute PVT is presented in *Panel B*. As indicated in the first 16 hours of data, the RT on the PVT in well-rested individuals averages ~250 milliseconds during the daytime, with minimal variability. The total number of lapses of attention (RT >500 milliseconds) from each 10-minute PVT are presented in *Panel C*. Well-rested individuals typically have very few (<5 per test administration) lapses of attention under these conditions. Attentional failures, defined as intrusions of slow eye movements (SEM) from continuous electro-oculographic recordings during EEG-verified wakefulness, were summed hourly and are presented in *Panel D*. Well-rested individuals typically have very few SEM under these conditions. Figure and legend reprinted with permission from: Duffy JD, Willson HJ, Wang W, Czeisler CA. *J Am Geriatr Soc* 2009; In Press. (56).

most affected by sleep loss in some individuals as compared to others, whereas sleep loss most adversely affects working memory in other individuals^(32, 34). Van Dongen and his colleagues⁽³²⁾ have found that when subjects are brought back to the laboratory for repeat visits, the same ones remain particularly vulnerable while others remain resistant to the adverse effects of sleep loss on cognitive performance. While all the subjects studied had more lapses of attention when performing the psychomotor vigilance task (PVT, a measure of simple reaction time) after a night without sleep, some individuals averaged only 10 lapses per 20-minute PVT test (about one lapse of attention every 2 minutes), whereas other individuals experienced nearly 100 lapses of attention per 20-minute PVT test (nearly five lapses of attention every minute)⁽³²⁾ (Figure 7). In a relatively homogeneous sample of healthy young adults, these investigators reported that stable individual trait differences accounted for 67% to 92% of the variance in the cognitive performance decrement induced by sleep loss. These inter-individual differences appear to be trait differences, since they persist even when participants are either comparably sleep satiated (12 hours in bed per night for a week) or comparably sleep restricted (6 hours in bed per night for a week) before they stay awake all night⁽³²⁾.

While the performance of most people deteriorates significantly when wakefulness extends beyond 16–18 hours, there are considerable inter-individual differences in the magnitude of this effect. There are likely also inter-individual differences in the effects of exposure to chronic partial sleep deprivation for several weeks.

Potential Genetic Vulnerability to Sleep Loss

Genetic polymorphisms may account for differences in the tolerability to acute sleep loss. A variable length tandem repeat polymorphism in the *PER3* gene (*PER3*^{5/5}) has been reported to confer a particular vulnerability to the performance-impairing effects of 24 hours of wakefulness in those with 5 rather than 4 copies of the sequence on both chromosomes^(62, 63). This polymorphism is present in about 10–15% of the population. When individuals with the *PER3*^{5/5} polymorphism are deprived of sleep at an adverse circadian phase, their cognitive performance at night is significantly worse than individuals with the *PER3*^{4/4} genotype⁽⁶³⁾ (Figure 8). Individuals with the *PER3*^{5/5} polymorphism reportedly experience significantly more attentional failures, as measured by slow rolling eye movements, than individuals with the *PER3*^{4/4} polymorphism. Executive functioning of the brain's pre-frontal cortex is said to be particularly compromised by

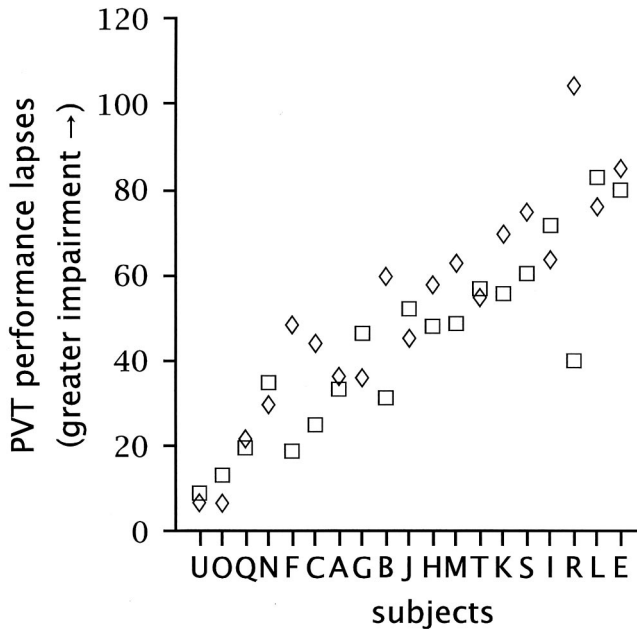


FIG. 7. Neurobehavioral responses to total sleep deprivation after two different prior sleep extension conditions. Each episode of sleep deprivation followed a week during which time the participants spent 12 hours in bed each night. The average number of lapses on 20-minute PVT tests administered every two hours over the last 24 hours of total sleep deprivation is shown. The abscissa shows the 19 individual participants, who were arbitrarily assigned the labels A through U. The participants are ordered by the magnitude of their impairment (averaged over the 2 sleep deprivations), with the most resistant participants on the left and the most vulnerable participants on the right. Responses in the first exposure to sleep deprivation following 7 days of prior sleep extension (mean \pm standard deviation of the average nightly sleep duration of 8.5 ± 1.0 hours) are marked by boxes; responses in the second exposure to sleep deprivation following 7 days of prior sleep extension (mean \pm standard deviation of the average nightly sleep duration of 8.8 ± 1.3 hours) are marked by diamonds. The panel reveals that subjects differed substantially in their responses to acute sleep deprivation, while the responses were relatively stable within subjects between the two exposures to acute sleep deprivation. Figure and legend reprinted with permission from: Van Dongen HPA, Baynard MD, Maislin G, Dinges DF. *Sleep* 2004; 27:423–433 (32).

the *PER3*^{5/5} polymorphism. On the other hand, a haplotype of the adenosine A2A receptor gene (*ADORA2A*), may be associated with resistance to the effects of sleep loss on performance (64). These preliminary data suggest that it may soon be possible to identify from a simple cheek swab a subset of individuals who will exhibit minimal performance degradation when deprived of sleep and another subset whose performance will deteriorate markedly when they are sleep deprived.

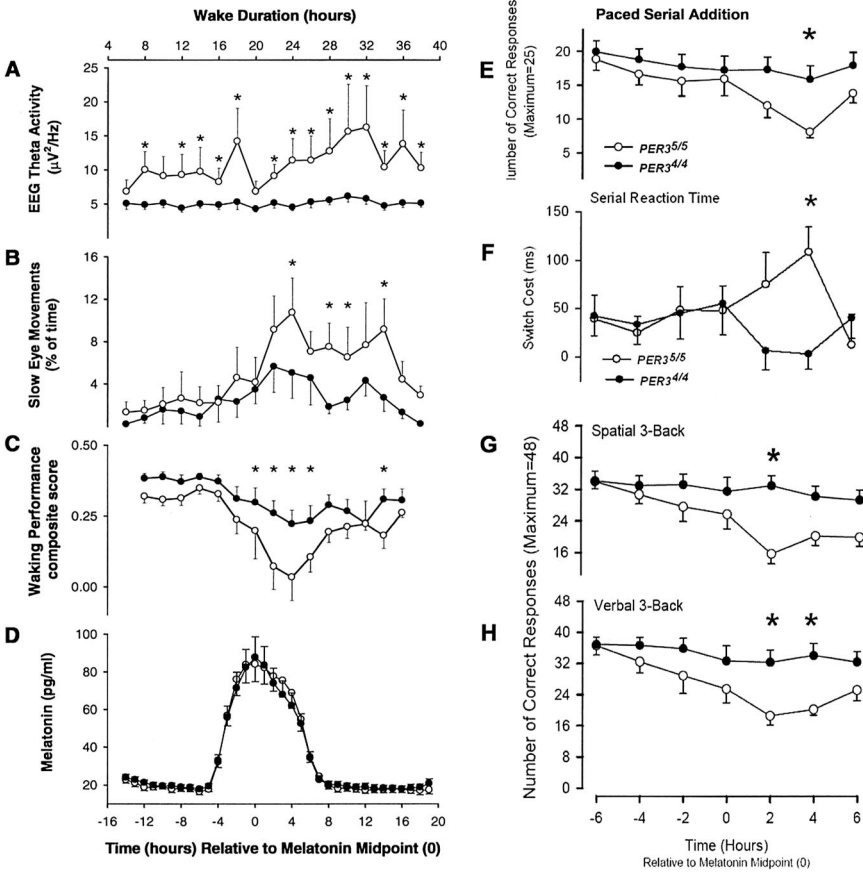


FIG. 8. Polymorphism in Period Gene and Vulnerability to Sleep Loss. Left Hand Side: Deterioration of waking performance and increase of theta EEG activity and slow eye movements during sleep deprivation is greater in $PER3^{5/5}$ than in $PER3^{4/4}$ participants. Time course of central EEG theta (5–8 Hz) activity during wakefulness (Panel A), incidence of slow eye movement (SEMs) (percentage of 30 s epochs containing at least one SEM) (Panel B), and waking performance (composite performance score) (Panel C) are plotted relative to the timing of the plasma melatonin rhythm (Panel D) in ten $PER3^{5/5}$ (open symbols) and 14 $PER3^{4/4}$ (filled symbols) homozygotes. EEG theta activity, SEMs, and waking performance data were averaged per 2-hour intervals, relative to the midpoint of the melatonin rhythm. (* indicates a significant difference between genotypes, $p < 0.05$; upper abscissa indicates approximate wake duration.) Right Hand Side: Overnight performance on the paced visual serial addition task in $PER3^{5/5}$ and $PER3^{4/4}$ participants. Mean numbers of correct responses are plotted relative to the midpoint of the melatonin rhythm (Panel E). Overnight performance on the serial reaction time task in $PER3^{5/5}$ and $PER3^{4/4}$ participants. Mean switch costs, i.e., increase in time to respond to random rather than learned sequences of stimuli, are plotted relative to the melatonin midpoint. Higher values indicate poorer performance (Panel F). Overnight performance on spatial N-Back performance in relation to memory load in

FOOD, DRUGS AND PHARMACEUTICAL AGENTS

Soporific Agents

Sleepiness is one of the most frequent side effects of prescription medications, including some anti-depressants, statins, anti-hypertensive agents, hypnotics, anti-anxiety medications, pain management medications, anti-epileptic agents, muscle relaxants and medications to block stomach-acid secretion. Many common over-the-counter drugs have effects on sleep propensity. For example, diphenhydramine is sold under various trade names, including Benadryl[®] for relief of allergies. Few who take diphenhydramine for allergies realize that, because of its action as an anti-histamine, the very same drug—diphenhydramine—is also the active ingredient in many of the most popular over-the-counter sleeping pills in the U.S. It is marketed as an over-the-counter sleep aid under the trade names Unisom,[®] Nytol,[®] Sominex,[®] Tylenol Simply Sleep[®] and, with acetaminophen, in Tylenol PM.[®] Thus, many people attempting to control their allergies during the daytime may be unwittingly taking a sleeping pill on their way to work, and thereby greatly reducing their tolerance to sleep loss. Diphenhydramine affects the areas of the brain that control the transition from wakefulness to sleep and thereby impairs performance. Even some newer ‘non-sedating’ anti-histamines cause drowsiness in a substantial fraction of patients. Some decongestants, in turn, disrupt nocturnal sleep, which can increase sleep pressure the following day.

Stimulants and Drugs of Abuse

Stimulants and drugs of abuse can have a profound effect on the ability to sustain alertness and performance in the face of sleep loss. Caffeine is the most widely used psycho-active agent in the world. In fact, it is the most widely used drug in the world, fueling our 24/7 society. Because caffeine antagonizes the actions of adenosine⁽⁶⁵⁾, a neuromodulator that mediates the sleep-inducing effects of prolonged wakefulness⁽⁶⁶⁾, at the adenosine A2A receptor, it can mask some of

PER^{3⁵/5} and *PER*^{3⁴/4} participants. Mean numbers of correct responses, are plotted separately for the 1-, 2-, and 3-back, relative to the melatonin midpoint (*Panel G*). Overnight performance on verbal N-Back performance in relation to memory load in *PER*^{3⁵/5} and *PER*^{3⁴/4} participants. Mean numbers of correct responses are plotted separately for the 1-, 2-, and 3-back, relative to the melatonin midpoint (*Panel H*). * $P < 0.05$, Bonferroni corrected. Error bars represent the standard error of the mean. Figures and legends reprinted with permission from: Viola et al., *Curr Biol*, 2007⁽⁶²⁾ (*left hand side*); and Groeger JA, Viola AU, Lo JC, von Schantz M, Archer SN, Dijk DJ. *Sleep* 2008;31:1159⁽⁶³⁾ (*right hand side*).

the effects of sleep deprivation on sleep propensity. Caffeine is marketed in coffee, colas and so-called energy drinks, and mixed with alcoholic beverages to increase the amount of alcohol that consumers can drink before becoming overcome with alcohol-induced fatigue. Caffeine is also available in tablet form, gum and in energy bars. Caffeine enhances performance during the daytime, although we have found that chronic caffeine administration in subjects on a demanding schedule may increase sleepiness, perhaps due to interference with recovery sleep ⁽⁶⁷⁾.

The National Transportation Safety Board (NTSB) found that plasma caffeine levels were highest in drivers involved in fatigue-related fatal crashes ⁽⁶⁸⁾. The NTSB concluded that the high levels of caffeine were insufficient to save those drivers from the effects of fatigue, which the NTSB found to be the leading cause of heavy truck crashes, equal to the fraction of crashes caused by both drugs and alcohol combined ⁽⁶⁸⁾. Moreover, while 80 to 90% of adults report regular consumption of caffeine-containing beverages and foods, some people who avoid or limit caffeine consumption report experiencing adverse effects of caffeine—such as anxiety, tachycardia, nervousness or tremors—even at low to moderate doses ⁽⁶⁹⁾. Twin studies have yielded heritability estimates of up to 77% for caffeine use and for tolerance to the side effects of caffeine, leading to the recent discovery that a genetic polymorphism in the adenosine A2 receptor gene is associated with both reduced caffeine consumption ⁽⁶⁹⁾ and with greater subjectively and objectively measured sensitivity to the adverse effects of caffeine on sleep ⁽⁷⁰⁾. Thus, while most physicians use caffeine extensively to cope with sleep deprivation induced by extended duration work shifts and long work weeks, hundreds of thousands of physicians may be less able to avail themselves of the wake-promoting effects of caffeine due to a genetic variation in the adenosine 2A receptor that increases their sensitivity to the side effects of caffeine.

With 7.74% of children ages 4–17 diagnosed with attention-deficit hyperactivity disorder (ADHD) and 4.33% (6.2% of boys and 2.4% of girls) receiving ADHD medications, amphetamines and other stimulants used to treat ADHD are now readily available ⁽⁷¹⁾. An unintended consequence of this popularity is that one-third of college students illegally use the mixed amphetamine salts in Adderall to “stay awake to study” when academic workload is high ⁽⁷²⁾. It is unknown whether the illegal use of such stimulant medications, which can induce insomnia, will persist when this cohort of students enters medical school and then residency training. If so, this trend would harken back to the man who established and directed the first surgical residency program at

Johns Hopkins in the 1890s, as it was cocaine use⁽⁷³⁾ that enabled Professor William Stewart Halsted, who laid the foundation for present-day graduate medical education work-hour policies, to maintain his reputation as an indefatigable surgeon⁽⁷⁴⁾. Sedation, sleep deprivation and insomnia are common side effects of opiates, to which Dr. Halsted was also addicted^(75–77). In healthy subjects, morphine and methadone decrease deep slow wave sleep⁽⁷⁸⁾. It is also likely that opiates increase the risk of attentional failures and degrade performance under conditions of sleep deprivation.

Alcohol, another major drug of abuse, is a central nervous system depressant that increases sleep propensity during wakefulness but disrupts sleep consolidation after sleep onset. One third of U.S. medical students regularly drink alcohol excessively⁽⁷⁹⁾. An estimated 4.9% of emergency medicine residents meet diagnostic criteria for alcoholism⁽⁸⁰⁾. An estimated 10–12% of practicing physicians in the United States develop a substance use disorder⁽⁸¹⁾, with 50% of physicians in rehab centers treated for abuse of alcohol, 36% for opiates and 8% for stimulants⁽⁸¹⁾.

These various agents, used commonly by a substantial fraction of practicing physicians and residents, have a profound effect on sleep-wake homeostasis and vulnerability to the effects of acute and chronic sleep loss on alertness and performance. Even low doses of alcohol synergistically interact with sleep loss to greatly increase sleep propensity, degrade driving performance and increase crash risk in a driving simulator^(82–84). Healthy professional drivers who were awake for 18 to 21 hours *and* were exposed to legal low-dose alcohol (blood alcohol concentration of 0.03 g/dL) had significantly more attentional failures and greater variation in both lane position and speed in a driving simulator than they did when their blood alcohol concentration exceeded 0.05 g/dL—a level associated with significantly increased risk of a motor vehicle crash⁽⁸⁵⁾. Few programs have adopted the random drug testing procedures recently introduced for anesthesia residents, but not for practicing physicians, at the Massachusetts General Hospital in Boston⁽⁸⁶⁾. Therefore, physicians whose performance has been compromised by the use of such agents—even on non-work days—are not being identified and are being scheduled to work lengthy shifts of the same duration (e.g., 30 consecutive hours) and at the same frequency (e.g., twice per week) as those who have not used such agents. The practice of scheduling physicians to work for 30 consecutive hours without sleep does not take into account the widespread use among physicians of psychoactive agents that affect tolerance to sleep loss.

IMPACT OF MEDICAL CONDITION ON VULNERABILITY TO SLEEP LOSS

A number of medical conditions and/or the medications used to treat those conditions are associated with increased sleep tendency, increased risk of attentional failures and increased risk of sleep-related errors and accidents⁽⁸⁷⁾. These common conditions make it more difficult to sustain wakefulness during the day and increase performance vulnerability to sleep loss. For example, pregnancy is a non-pathologic condition that often interferes with sleep, particularly in the last trimester, induces fatigue and can greatly affect stamina and the ability to cope with sleep loss. Yet many residents are scheduled to work 30-hour shifts throughout pregnancy. Many infectious diseases also increase sleep tendency, including the common cold, mononucleosis and hepatitis. Other conditions, such as chronic pain and nocturnal asthma, cause chronic sleep loss that reduces tolerance to further sleep deprivation. Primary sleep disorders, such as narcolepsy and sleep apnea, as well as disturbances of sleep or wakefulness secondary to a medical condition or its treatment can affect tolerance to sleep loss. While there are 90 recognized sleep disorders⁽²⁾, I have selected five to illustrate the issues raised by these common conditions, which collectively affect at least one out of five residents and practicing physicians in the U.S.

Sleep-related Breathing Disorders

Obstructive sleep apnea/hypopnea (OSAHS) syndrome results in sleep fragmentation and consequent daytime sleepiness. EDS is reported in about 80% of patients with OSAHS, 80 to 90% of whom remain undiagnosed and untreated; it often takes several years from the time a patient presents to a physician with symptoms until the correct diagnosis is made⁽²⁾. Performance related to executive functions such as verbal fluency, planning and sequential thinking—the purview of the frontal cortex, an area of the brain that imaging studies has revealed to be exquisitely sensitive to sleep loss—is very adversely affected by OSAHS⁽⁸⁸⁾. Vigilance and the ability to sustain attention are also degraded in patients with OSAHS. Reaction times on a sustained attention task in patients with mild to moderate OSAHS have been reported to be comparable to or worse than those of a young adult with a blood alcohol concentration of 0.080 g/dL⁽⁸⁹⁾. Untreated patients with OSAHS perform much more poorly in a driving simulator (in terms of lane deviations, tracking errors, off-road events and collisions with obstacles) and are 6 to 10 times (i.e., about 500% to 1,000%)

more likely to have an actual motor vehicle crash than people without OSAHS (90–103).

It is not known how many physicians in training or practicing physicians suffer from OSAHS. Snoring and the occurrence of attentional failures when driving a motor vehicle are cardinal symptoms of OSAHS (2). Obesity is the most prominent risk factor for OSAHS (2), though OSAHS can occur without obesity. Obesity confers such a high risk of OSAHS that Medical Advisory Board of the Federal Motor Carriers Safety Administration (FMCSA) has recommended mandatory objective OSAHS screening of all commercial motor vehicle drivers with a body mass index (BMI) greater than 30 kg/m², as measured at the bi-annual commercial driver license (CDL) physical exam. Data from available cohorts suggest that at least 50,000 practicing physicians and up to 10,000 residents would be affected if similar criteria were applied to those seeking to obtain or renew a license to practice medicine, as an estimated 6% to 18% of practicing physicians (104–107) and 10% of residents (108) are obese (BMI > 30 kg/m²). Since long work hours leave little time for exercise, and sleep restriction increases ghrelin levels, decreases leptin levels and increases carbohydrate craving, appetite and weight (2), physicians in training gain weight during residency (109, 110), exacerbating the condition.

Thus, it is likely that a significant fraction of both residents and practicing physicians are at risk for OSAHS. Nearly two decades ago, the prevalence of OSAHS in the U.S. was estimated to be 4% of adult men and 2% of adult women (111). With the increased prevalence of obesity in the U.S. (112), the prevalence of OSAHS among both residents and practicing physicians is now at least 3 to 4 times higher. We have recently found that over one-third of a younger cohort of 4,471 North American employed law enforcement officers (mean age: 38.5 ± 8.3 years; mean BMI: 28.7 ± 4.6 kg/m²) screened with a sensitive and specific survey instrument were at high risk for OSAHS (113).

Fortunately, for the 10 to 20% of OSAHS patients who are correctly diagnosed and treated, there are a number of therapies available that can improve the subjective sleepiness associated with this condition. Splinting the airway open with continuous positive airway pressure (CPAP) treatment has been the standard treatment for this condition for more than two decades. While the symptoms of OSAHS, including the increased risk of motor vehicle crashes, are usually significantly improved with CPAP treatment (101, 114–116), less than half of patients diagnosed with OSAHS actually use CPAP for at least 4 hours on 70% of observed nights (117). Moreover, while the impact of CPAP treatment on the most widely used objective measure of daytime sleepiness, the

Multiple Sleep Latency Test (MSLT), is statistically significant, it is rather modest in size, with the improvement in sleep latency averaging less than one minute ⁽¹¹⁸⁾.

Thus, a substantial fraction of patients who are compliant with CPAP therapy remain pathologically sleepy. Daily use of modafinil (200 mg.) has been demonstrated to be effective as an adjunct therapy in the treatment of residual subjective sleepiness in this population of OSAHS patients treated with CPAP ⁽¹¹⁹⁾. However, subjective sleepiness was only normalized (Epworth Sleepiness Scale < 10) in half of the modafinil-treated patients and objective sleep tendency, as measured by the MSLT, was not significantly improved by modafinil treatment ⁽¹¹⁹⁾. In summary, OSAHS is likely to have a substantial prevalence among physicians, and most physicians with this condition will remain impaired by EDS for the following reasons: lack of diagnosis and treatment in 80–90% of those affected, failure to comply with nasal CPAP treatment in half of those diagnosed, and residual impairment notwithstanding compliance with CPAP treatment and adjunctive pharmacotherapy in others ⁽²⁾. Increased sleepiness and neurobehavioral deficits due to chronic sleep loss and sleep fragmentation will likely render physicians afflicted with OSAHS much more susceptible to the adverse effects of acute and chronic sleep deprivation induced by extended duration work schedules typically required of both residents and practicing physicians.

Shift Work Disorder

Excessive sleepiness and/or insomnia that occur in association with work that is scheduled during hours usually reserved for sleep are symptomatic of a condition known as Circadian Rhythm Sleep Disorder (CRSD), Shift Work Type (Shift Work Disorder, SWD) ⁽¹²⁰⁾. About 5 to 10% of such workers suffer chronically from moderate to severe SWD ⁽¹²¹⁾. Most employees nod off or fall asleep regularly while working at night or while commuting to or from night work ⁽¹²²⁾. One-third of nurses who work at night report that they fall asleep in the hospital every week of night work ⁽¹²³⁾, with half admitting that they fall asleep at the wheel while driving to or from the hospital; twice as many night-working nurses reported making medication errors or having motor vehicle crashes as compared to those who worked the day and evening shifts, but did not work at night ⁽¹²³⁾.

Extended duration work shifts that routinely exceed 24 consecutive hours combined with very long work weeks that do not allow sufficient time for sleep can elicit attentional failures during work in most if not all employees ⁽²²⁾, effectively inducing SWD in all workers in the same

way that depriving people of food will eventually induce malnutrition in all people who are starved. Exposure to less extreme work schedules reveals considerable variability in the ability of individuals to cope with the demands of work schedules that require employees to work during times that they would otherwise be asleep. Continuous polysomnographic monitoring of 80 licensed commercial drivers without OSAHS during 7,500 hours of long-haul trucking operations revealed that more than half of the long-haul truck drivers experienced episodes of drowsy driving, mostly during night driving (¹²⁴). Predictably, these episodes of drowsy driving were not distributed evenly across the 80 drivers. In fact, more than half of the drowsy driving episodes occurred in just 8 (10%) of the 80 drivers (¹²⁴), revealing the differential vulnerability of this subset of drivers to the sleep deprivation and circadian misalignment associated with night driving. This is consistent with the differential vulnerability to nocturnal sleep loss observed in laboratory studies (^{32, 35–37, 125, 126}). A number of countermeasures and treatments can be effective in treating the symptoms of SWD, including improvements in work scheduling, use of properly timed exposure to light, administration of nutritional supplements such as caffeine and melatonin, and use of pharmacologic agents such as the wake-promoting therapeutic modafinil (^{22–24, 67, 122, 127–130}), although none eliminate them.

Insomnia

Insomnia is the most common sleep disorder, with symptoms of disturbed sleep affecting most adults at some time in their lives (²). The clinical definition of insomnia is a chronic (> 6 months) complaint of latency to sleep onset or awakenings from sleep of at least a half hour occurring at least three times per week. The prevalence of insomnia associated with a daytime complaint of increased sleepiness or fatigue is 8% to 18% (¹³¹). Broadly, insomnia may be psychophysiologic or secondary to the sleep environment, an irregular sleep schedule, a sleep-related movement disorder, a psychiatric condition, a medical condition, a medication or substance, or a circadian rhythm sleep disorder (CRSD) such as SWD (²). Insomnia in non-depressed adults is a risk factor for depression (¹³²). Insomnia syndrome, which includes increased daytime sleepiness, it is associated with an increased rate of work absenteeism, reduced productivity and increased risk of accidents (^{2, 133}).

Narcolepsy

Narcolepsy is a neurological sleep disorder characterized by “EDS that typically is associated with cataplexy and other REM sleep phe-

nomena such as sleep paralysis and hypnagogic hallucinations ⁽¹²⁰⁾." Cataplexy, a sudden muscular weakness often brought on by strong emotion, together with disturbed nocturnal sleep, are hallmarks of this condition, which affects about 5 out of every 10,000 adults in the U.S. Thus, an estimated 50 resident physicians and 400 practicing physicians in the United States have narcolepsy, assuming that the affected individuals have not self-selected out of the profession. Since narcolepsy often presents late in the second decade or in the third decade of life, affected individuals may already be in medical school or in a residency program before clinical symptoms are manifested. Despite the severity of sleep-wake impairment associated with this primary sleep disorder, it often takes more than five years from the time of symptom presentation to a physician until the correct diagnosis is made. Patients with narcolepsy often have difficulty sustaining attention during the day, and must rely on wake-promoting therapeutics to reduce EDS and minimize the occurrence of sleep attacks. This may be due to a deficiency of the hypothalamic neurotransmitter orexin (hypocretin), which is often associated with narcolepsy. Patients with narcolepsy perform poorer on a driving simulator and have a significantly higher rate of motor vehicle crashes than do control subjects ⁽⁹⁹⁾.

Psychiatric Disorders

Sleep disturbance is often secondary to a number of psychiatric disorders and other conditions that may render affected individuals more susceptible to the effects of sleep deprivation. These include several medical and psychiatric disorders such as depression, which is common among practicing physicians and residents. A recent large-scale multi-site study revealed that 12% of medical students and residents had probable major depression, and 9.2% had probable mild/moderate depression ⁽¹³⁴⁾. Burnout has been reported by half of medical students in two studies ^(135, 136); 11.2% of the medical students reported suicidal ideation; 20% of pediatric residents meet screening criteria for depression, and 74% meet the criteria for burnout ⁽¹³⁷⁾.

Sleep disturbance is one of the most common symptoms of burnout, anxiety disorders and mood disorders, including depressive disorders and bipolar disorder. Burnout is also associated with persistent insomnia ⁽¹³⁸⁾, with increased arousals and sleep fragmentation ⁽¹³⁹⁾. Abrupt awakenings often occur in anxiety disorders, such as post-traumatic stress disorder, in which sleep is frequently disturbed by nightmares. Burnout, which is precipitated by occupational stress, induces EDS and mental fatigue throughout the day, which may be a consequence of the sleep disturbance ⁽¹³⁹⁾. While insomnia is one of the most common

features of mood disorders, hypersomnia can occur as well, especially during depressive episodes. Changes in sleep architecture, including reductions in deep slow wave sleep and earlier onset of REM sleep, occur in depression. Acute sleep deprivation can have an immediate anti-depressant effect, although its therapeutic effect is reversed as soon as recovery sleep is obtained. Sleep disturbance is one of the most common residual symptoms after effective treatment of depression, estimated to continue in up to 44% of patients in remission⁽¹³¹⁾. For these reasons, the cognitive performance of physicians with mood disorders is likely to be more vulnerable to the effects of sleep loss and misalignment of circadian phase. Many of the medications used to treat these patients have side effects that affect sleep tendency. The adverse effects of depression and its treatment on sleep and consequent daytime functioning probably contribute the increased risk of medical errors in depressed pediatric residents, who make 6.2 times as many medication errors per resident month as residents who are not depressed⁽¹³⁷⁾.

ETHICAL CONSIDERATIONS

The evidence upon which the ACGME and the IOM have relied in developing resident work- hour policy limits has been largely derived from laboratory studies of healthy subjects who have passed physical examinations and volunteered to participate in relatively brief sleep restriction or sleep deprivation studies. In continuing to sanction every other work shift to be 30-consecutive hours in duration (Fig. 9) throughout years of residency training, the ACGME has implicitly assumed that the population of residents is entirely healthy, highly resistant to the effects of sleep deprivation, and free of concurrent family responsibilities, premises that are not accurate. Working such long hours that the risk of unnecessary patient injury rises sharply violates the ethical principle of *nonmaleficence*⁽¹⁴⁰⁾. The principle of *beneficence* requires implementation of safer work schedules that reduce risk by not scheduling physicians to care for patients after 16 hours without sleep. Exhausted physicians who have worked >16 consecutive hours without sleep should not endanger themselves and others by driving automobiles^(141, 142). Since 24-hours of wakefulness degrades performance comparably to alcohol intoxication^(28, 143–147), the principle of *autonomy* requires that physicians respect the right of the patient to be informed of the impairment and to withhold consent to the risk of receiving care from sleep-deprived providers⁽¹⁴⁰⁾. The principle of *justice* requires that those most vulnerable to sleep loss not

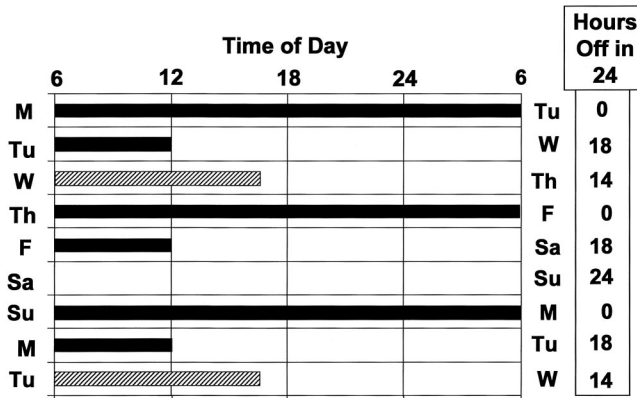


FIG. 9. Illustration of Eight Consecutive Days of a Typical Resident Physician Work Schedule Sanctioned by Current 2009 ACGME Guidelines. Every other shift is 30 hours in duration on this schedule. Because each 30-hour shift includes two calendar days, this schedule results in the resident physician spending every third night in the hospital. Black bar indicates scheduled 30-hour shifts. Hatched bar indicates an 8- to 10-hour swing shift, when resident physicians are not scheduled to work overnight. Box on right indicates how many hours residents are not scheduled to work for each 24-hour interval, beginning at 6 am each day.

shoulder a disproportionately large burden [i.e., a higher rate of fatigue-related errors, accidents and adverse health effects ⁽²⁾] than those who are resistant to sleep loss ⁽¹⁴⁰⁾, particularly for the convenience or financial benefit of teaching faculty or academic medical centers.

Systematic falsification of resident work-hour records (Fig. 10) ^(1, 148–150), which the IOM found to be widespread ⁽¹⁾ and the ACGME recently admitted after years of official denial ⁽¹⁵¹⁾, violates the principle of *truthfulness and honesty* ⁽¹⁴⁰⁾. It sets a regrettable precedent for trainees, especially when it occurs out of fear of reprisal from ⁽¹⁵²⁾ or with the tacit approval, awareness or expectation of residency program directors or institutional leaders ⁽¹⁵¹⁾. Falsification of work-hour records by those who have caused harm have led to felony convictions, hefty fines and imprisonment, not only for those who falsified reports but for chief executives and supervisors complicit in the falsifications of work-hour records ^(153–163). At its core, resident work hour reform is an issue of *human dignity* for patient and physician ⁽¹⁴⁰⁾. Burdening a physician with a workload that s/he cannot carry creates an ethical dilemma in which—on the one hand—the more hours that the physician works, the greater is the risk to both the patient and to the physician, whereas—on the other hand—the physician cannot ethi-

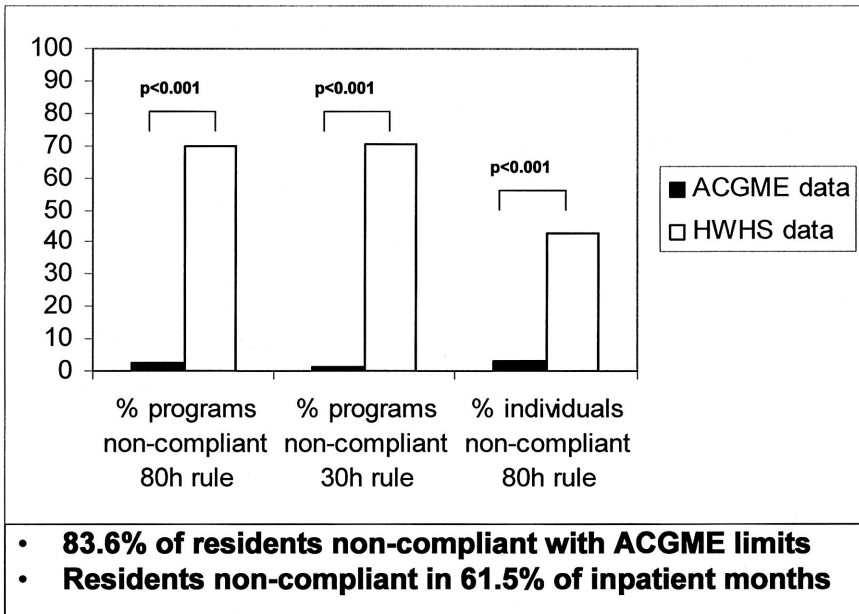


FIG. 10. Reported Non-Compliance with ACGME Work-Hour Limits as Reported by Residents Non-Confidentially to the ACGME vs. Confidentially to the Harvard Work-Hours Health and Safety (HWHS) Group. After the ACGME implemented the 2003 limits on resident physicians work hours, 83.6% of interns reported to the HWHS Group work hours that were in violation of the ACGME standards during 1 or more months. Working shifts greater than 30 consecutive hours was reported by 67.4% of interns (open bar, middle pair). Averaged over 4 weeks, 43.0% of interns reported working more than 80 hours weekly (open bar, right pair), and 43.7% reported not having 1 day in 7 off work duties (data not shown). Violations were reported during 61.5% of months during which interns worked exclusively in inpatient settings. Violations were reported to the HWHS Group from 85.4% of the 707 represented residency programs (open bar, left pair). During the same reporting period, the ACGME reported near-universal compliance with the ACGME standards (filled bars), claiming that only 5.0% of residency training programs were not compliant with the standards and that only 3.3% of surveyed residents reported violations of the 80-hour rule. Differences between the ACGME and HWHS Group data were statistically significant on each of these measures ($p < 0.001$). Data and legend from: Landrigan CP, Barger LK, Cade BE, Ayas NT, Czeisler CA. JAMA 2006;296:1063⁽¹⁴⁸⁾ Figure courtesy of Christopher P. Landrigan, M.D., M.P.H.

cally stop working and abandon a patient in need of medical care. Sleep deprivation should not be presented as a proxy for dedication.

Education about the impact of sleep deprivation and sleep disorders on performance, health and safety should be provided so that physicians and trainees understand that working when sleep deprived constitutes working in an impaired state, comparable to being under the

influence of alcohol (1, 2, 17, 28, 82–84, 143–147). 30-hour work shifts are not necessary for training physicians, since GME programs in many other countries (1) (Table) and in the U.S. have eliminated them years ago, including the surgical residency training program at the Brigham and

TABLE
Summary of work-hour regulations for various occupations in selected countries

Current Work-Hour Regulations	
Occupation	Limits
U.S. Airplane Pilots (1–2 pilot airplanes): 1950s	<8 daily flight hours <16 daily work hours >8–12 hours rest required (since 1985) <34 hours flight time per week
U.S. Nuclear Power Plant Operators: 1982; 2009	<16 consecutive work hours <72 work hours per week >34 consecutive hours off every 9 days
U.S. Railroad Operators: 1907, modified 1969 & 1976	<12 work hours per day >8–10 hours rest required per day
U.S. Interstate Truck and Bus Drivers	<11 driving hours within a 14-hour interval <14 consecutive hours from start to end of work >10 consecutive rest hours <60 work hours per 7 days; <70 work hours per 8 days >34 consecutive hours off between work weeks
E.U. All Occupations (including resident physicians and practicing physicians): 2004; 2009	<13 consecutive work hours <56 work hours per week until 2009; 48 hours thereafter >11 hours rest time per day
New Zealand Resident Physicians: 1985	<16 consecutive work hours (labor agreement) <72 work hours per week
U.S. Resident Physicians	UNLIMITED: no federal laws of regulations Self regulation by profession (ACGME): 2003 <30 consecutive work hours (two allowed per week) <80 work hours per week (averaged over 4 weeks) Monitoring by self-report (84% non- compliance)
El Salvador Resident Physicians	UNLIMITED Extended duration work shifts (36 hours) and long (>120 hours) work weeks common during internship

Women's Hospital in Boston. As in other safety-sensitive industries in the U.S. and in residency training in other countries (^{1, 164}), work-hour limits for residents should be based on work hours that are safer for most people, not a select few (Table). Prior to the threat of federal legislation (¹⁵¹), many medical and surgical training programs in the U.S. required residents to work 120 to 140 hours per week (^{21, 24}), as they currently do in El Salvador (¹⁶⁵) (Table). 25 years ago, the tragic death of Libby Zion thrust the issue of resident work hours onto the national stage (¹⁶⁶). As the IOM has recently concluded, now is the time for meaningful resident physician work-hour limits (¹), which the federal government has the authority to implement (¹⁶⁷) and for which the boards of directors of the Sleep Research Society and the National Sleep Foundation have endorsed enforcement by law or regulation (^{21, 168, 169})

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DISCUSSION

August, New York: The prevalence, you were saying, is about 25% of this polymorphism?

Czeisler, Boston: Polymorphism is about 10 to 15%. This is the first polymorphism that has been identified. There are a whole series of new genes that are being looked for, and there may be several other genetic markers that can identify the rest of that though.

August, New York: Are there any gender differences? You might expect that there would be in terms of traditionally women being awake during the night with feeding babies and things like that.

Czeisler, Boston: That is a good question. We have not looked into gender differences. That 25% most vulnerable cohort does not separate out based on gender or intelligence or any other of the usual suspects, race and so on, but it does seem to be related to this genetic marker.

Chapman, Jackson: There is a variation of alertness and our ability to do certain skills between generally 2 and 4 in the afternoon and 2 and 4 in the morning for those that work night shifts. When would that take into account some of the variability that you see?

Czeisler, Boston: The genetic vulnerability that I discussed is particularly when people are trying to function both sleep-deprived and at an adverse circadian phase. They don't seem to perform differently during the daytime when they are not at that most vulnerable phase.

Chapman, Jackson: So the circadian rhythm is not disrupted.

Czeisler, Boston: Right, so it's a combination of circadian misalignment and sleep deprivation that brings out this particular vulnerability, and there is a continuum as you saw from that other slide; but if you were trying to pick people who were resistant to sleep deprivation, you would be down to about 10 to 15% of the population, but that may be enough to fill the medical schools.

Boyer, New Haven: What about jet lag? Is there any relationship between the disruptions of circadian rhythm in jet lag and genotype?

Czeisler, Boston: That's a great question. We just finished an unpublished study

that we are in the process of submitting for publication in which we show that the same people who are most vulnerable to staying awake all night are actually less vulnerable to the dislocation associated with eastward travel across time zones. They tend to be morning types—well we are all morning types as we get older—but they tend to be morning types in their 20s, and they may be morning types because they are building up homeostatic sleep drive at a faster clip so that they go to bed earlier so that when they go to England, for example, they have much less difficulty sleep on British time than do people with the more common genotype.

Tweardy, Houston: Excellent talk Charles, and, in fact, this could open up a field of personalized genomic career advising as opposed to personalized genomic medicine. My question is, as our previous speaker, Steven, I am interested in pathophysiologic pathways, and I am curious to know how polymorphism links to the pathophysiology of sleep and its effects on sleep cycles.

Czeisler, Boston: Well no one knows the answer to that question. We are beginning to look to different populations, in Papua, New Guinea for example. This particular polymorphism is somewhere between 50 to 80% of the population, and we are looking to begin investigations in different regions of the world to try to understand how it might be related to the occurrence of sleep disorders. Certainly it may be directly related to the pathophysiology of shift work disorder, which is again a subset of the population that is about the same size that are particularly vulnerable not just to the performance impairments but also to adverse medical outcomes—cardiovascular disease and other issues associated with shift work.

Berl, Denver: If you are going to use this as a screening test for those vulnerable to this problem, do you have a sense of the sensitivity and specificity of this?

Czeisler, Boston: It's too early to say right now, and I am not actually advocating that it be used for a screening test. Just to clarify, my position is that the work hours should be designed in such a way as to accommodate the full range of the population, because I have not seen any evidence that these 30 hour shifts are critical for training; but I know that many people in this room would disagree with me.