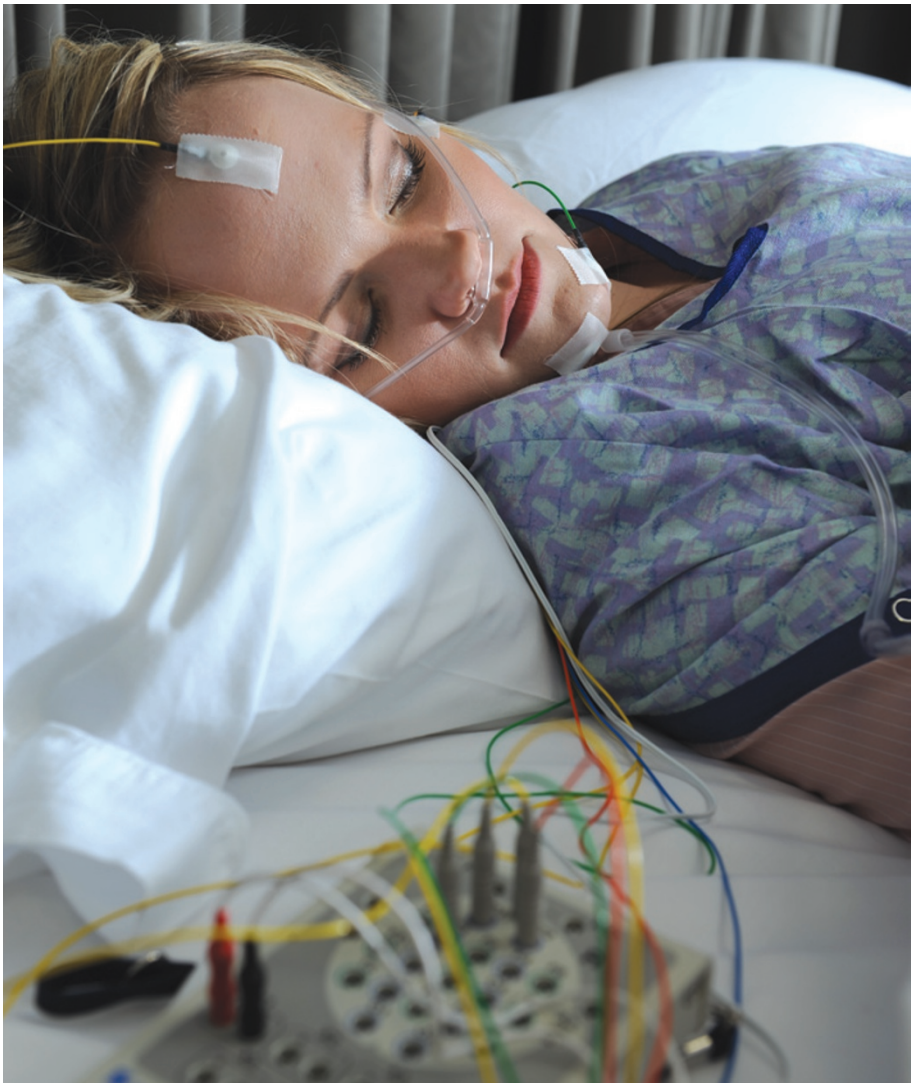

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Clinic-based studies allow researchers to control sleeping time and monitor any physiological changes.

DEPRIVATION

# A wake-up call

*Studies that restrict sleep show why a lack of shut-eye can lead to serious chronic disease.*

BY ELIE DOLGIN

What happens when people go to bed is usually a private matter. But on the eighth floor of the Beth Israel Deaconess Medical Center (BIDMC) in Boston, Massachusetts, sleep is a closely watched affair. Gold-cupped electrodes stuck to the faces and scalps of study participants monitor brain activity; wrist sensors detect movement; and finger cuffs track blood pressure. Even the flicker of an eye is registered, and bodily waste is treated as a commodity — all under the constant supervision of study coordinators.

On a Friday morning in February, researchers are busy cleaning up after the last participants and readying the ward for the next test subjects, who are due to arrive that afternoon. Two by two, trial participants come to the Harvard Catalyst Clinical Research Center here for a three-week 'sleep-over'. After a few nights of acclimation, each pair is randomly assigned either a full eight hours of sleep per night or recurring bouts of short sleep: three nights of four hours followed by a single night of eight hours, repeated for four cycles, with a recovery period of full sleep afterwards.

"We are trying to understand how physiological systems are altered if insufficient sleep goes on for a long time," says Janet Mullington, director of the BIDMC's Human Sleep and Inflammatory Systems Research Unit, who is leading the study. This 22-day trial is one of the longest of its kind to date.

Historically, most controlled sleep studies were short in duration but extreme in deprivation: volunteers were kept awake for periods ranging from 24 hours to five days in a row. Such acute sleep-deprivation trials have shown how sleep loss alters several mediators of inflammation, metabolism and other physiological pathways.

However, researchers worried that these all-night studies did not replicate one of the major sleep habits of modern life: getting some sleep each night, but not enough. According to the US Centers for Disease Control and Prevention, 30% of US workers get fewer than 6 hours of sleep per day[1] — far below the 7–9 hours that most experts recommend based on the existing evidence.

To find out what happens to someone getting fewer hours of sleep than recommended each night, scientists began to run longer trials, typically lasting a week or two, including repeated bouts of reduced or 'partial' sleep time. "What we will learn from these partial sleep-deprivation studies is in some ways more immediately transferable to real-world situations," says Mullington.

Prior epidemiological studies resulted in the first data linking people who tended to sleep less with increased rates of obesity, diabetes, cardiovascular disease, cancer and ultimately death. Now sleep researchers hope that controlled sleep-restriction studies can reveal the underlying mechanisms.

## ILL EFFECTS

The first study to investigate the ill effects of persistent partial sleep loss in a controlled setting was published in 1999 by Eve Van Cauter and her colleagues at the University of Chicago in Illinois. In that study, 11 young men were restricted to four hours of sleep a night for six consecutive nights. The researchers then measured the subjects' blood glucose levels and rates of insulin secretion in response to glucose. They found that both measures of sugar metabolism fell by about a third after the sleep deprivation[2].

More recently, Van Cauter's team has identified a molecular culprit for this metabolic impairment. They collected abdominal fat cells from study participants who slept just 4.5 hours per night for four nights in a row, and then again after four nights of full sleep, looking in particular at whether AKT, a key protein involved in insulin signalling, was in its active state in the fat cells. They found that AKT activity was much lower after the short sleep than after the full sleep — the reduced AKT levels were similar to those found in people with insulin resistance, obesity and type 2 diabetes (see

'Heavy sleepers', page S8). Restricting sleep is equivalent "to a change in weight of about 10 kilograms", says Van Cauter, who reported the findings[3] last year. "It's a big effect and it can happen quite quickly."

## DIVERSE PROBLEMS

Experimental sleep restriction is also uncovering health problems unconnected to metabolism. A 2003 study by Mullington and psychiatrist David Dinges, of the University of Pennsylvania's Perelman School of Medicine in Philadelphia, showed that sleeping for only 4 or 6 hours over 14 consecutive nights impairs people's alertness and performance in several cognitive tests[4]. Mullington and her BIDMC colleague Monika Haack later found that limiting participants' sleep to 4 hours per night for 12 nights can affect the immune system too[5]. Towards the end of the experiment, sleep-deprived individuals showed elevated blood levels of the immune signalling molecules interleukin-6 (IL-6) and C-reactive protein (CRP), both of which have been linked to inflammatory problems such as coronary artery disease.

"Even this modest sleep restriction creates a condition of low-grade inflammation," says Alexandros Vgontzas, a psychiatrist and sleep specialist at Pennsylvania State University College of Medicine in Hershey, who conducted a similar, as yet unpublished, trial. "Numerous studies have shown that these markers when elevated are associated with atherosclerosis, heart problems, diabetes and the like. So, we speculate that if people do not sleep enough on a long-term basis, this creates a condition that may lead to cardio-metabolic problems."

The immune deficits resulting from poor sleep can also undermine people's responses to vaccines. Last year, a team led by psychologist Aric Prather from the University of California, San Francisco, reported that 26.4% of middle-aged adults who slept fewer than 6 hours per night were not clinically protected against hepatitis B six months after receiving the standard three-dose vaccine series, compared with only 3.4% of those who slept more than 7 hours a night[6]. "This adds to our growing understanding of adding sleep to the cadre of important healthy behaviours," says Prather.

Too much sleep can also be a problem, though. In 2009, Sanjay Patel and Susan Redline, both now at the Brigham and Women's Hospital in Boston, Massachusetts, showed[7] that people who say they sleep more than eight hours per night have elevated blood levels of IL-6, CRP and tumour necrosis factor-α, another cytokine involved in systemic inflammation. Now Michael Irwin, a psychoneuroimmunologist in the David Geffen School of Medicine at the University of California, Los Angeles, is leading a study designed to test whether cutting back on excess sleep can reduce these inflammatory markers.

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For some of the latest results on sleep restriction:
go.nature.com/ugbr8z

The search for why sleep patterns can be unhealthy has recently moved deeper, to the activity of DNA. In a study published earlier this year by a team at the University of Surrey in Guildford, UK, 26 healthy participants slept for at least 8 hours per night for one week and just under 6 hours per night for another. After each week, they were kept awake for about 40 hours in a row while the researchers, led by Derk-Jan Dijk, measured gene expression levels in the subjects' blood cells.

A week of insufficient sleep altered the activity of 711 genes, the authors found[8]. As expected, the genes affected included those involved with stress responses, the immune system and cellular metabolism. However, the restricted sleep also affected several genes involved in overall gene regulation and chromatin remodelling, suggesting that chronic sleep loss could lead to many more negative changes than researchers previously recognized. What's more, the number of genes that responded to a subsequent night without any sleep jumped from 122 when the subjects were fully rested to 856 after a week of restricted sleep.

*"Even this modest sleep restriction creates a condition of low-grade inflammation."*

Such studies of the 'transcriptome' — exploring all the changes in gene activity in response to reduced sleep, for example — can yield much broader insights than simply considering one aspect of physiology, notes Mehdi Tafti, a neurogeneticist who studies sleep at the University of Lausanne in Switzerland. "It gives a much more global view of the changes going on because of sleep deprivation," he says.

Genetic differences have also been found to underlie variation between individuals in their response to partial sleep deprivation. For example, Dinges and Namni Goel at the University of Pennsylvania have linked a particular variant of a gene that encodes a cell surface marker involved in innate immune responses with sleepiness and fatigue levels — but not cognitive deficits — in healthy participants who were forced to sleep for only 4 hours per night for five nights in a row[9]. "Subjects who are positive for this allele are more vulnerable to the effects of sleep loss," says Goel, noting that the variant is found in 20–30% of the population.

## PRESSURE TO CHANGE

Attention is now shifting to how doctors can use the information garnered from controlled sleep studies to improve the wellbeing of patients. Haack and Mullington conducted a proof-of-concept study, published last year, in which 13 people with early signs of hypertension (high blood pressure) who habitually slept for fewer than 7 hours per night extended their sleep by one hour per night for six consecutive weeks, while another 9 people maintained their usual sleeping habits. At the end of the trial, those who had the extra sleep saw their average blood pressure readings drop from 142/82 to 128/74; in contrast, those who made no change experienced no significant reduction in blood pressure[10].

This study is already altering the behaviour of at least one individual, notes Haack. "One of our participants decided to continue with the extended bedtimes even after the study was over, and proudly reported that his cardiologist was able to lower his blood pressure medication," she says.

## SLEEP WELL

People whose lack of sleep could be damaging their health could benefit from drug treatments, although figuring out which drugs will help which people is a challenge. "If we were able to use a biomarker or a functional assay and identify those individuals who are not getting enough sleep and are at risk of adverse health outcomes, that could really help us give people feedback and perhaps target the mechanistic pathways," says Redline. "Maybe they would be more likely to benefit from an anti-inflammatory agent, or a lipid-control medication."

Drugs of this sort could help to mitigate the consequences of sleeplessness or poor sleep quality, but they are unlikely to be the perfect solution, researchers warn. "Because of the multiplicity of pathways, I cannot imagine a single pharmacological approach that will prevent the adverse effects of insufficient sleep," says Van Cauter. "You are not going to have a magic pill."

Ultimately, this research points to an obvious conclusion: we need to sleep well now to avoid health problems later. "It's almost like this is common sense," says Virend Somers, a cardiologist at the Mayo Clinic in Rochester, Minnesota, who studies the effects of sleep loss. "But sometimes when you show people hard and fast scientific data, show them the numbers and show them the experimental evidence, it becomes more forceful." ■

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