

The U-Shaped Association Between Sleep and Health: The 2 Peaks Do Not Mean the Same Thing

Comment on Patel SR; Malhotra A; Gottlieb DJ et al. Correlates of long sleep duration. *SLEEP* 2006;9(7):881-889.

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MUCH EVIDENCE HAS ACCUMULATED OVER THE PAST SEVERAL YEARS IMPLICATING SHORT SLEEP AS A RISK FACTOR FOR NUMEROUS MORBID CONDITIONS. In 1999, Spiegel and colleagues published a pivotal study that demonstrate in humans that sleep loss has negative consequences for the body beyond the brain.¹ In this laboratory experiment, 6 days of time in bed restricted to 4 hours in young men was associated with alterations in glucose metabolism that, over the long-term, could increase the risk of developing diabetes. A similar study using a shorter protocol with a crossover design also demonstrated that sleep loss was associated with alterations in the levels of hormones involved in appetite regulation, leptin, and ghrelin, which led to increased appetite^{2,3}—hormone changes that could ultimately increase the risk of weight gain. Similar associations between sleep duration and these hormones were observed in a larger sample from the Wisconsin Sleep Cohort Study,⁴ providing further evidence for the link between sleep and appetite regulation.

In addition to these laboratory findings, at least 35 epidemiologic studies have been published that observed an association between sleep duration and health outcomes: 18 articles examined body mass index or obesity in adults and children (see for example references 5, 6, and 7), 7 articles examined diabetes risk in adults (see for example references 8 and 9), 2 articles examined cardiovascular disease in adults,^{10,11} and 8 articles examined mortality risk in adults (see for example references 12 and 13). In most of these studies, short sleep durations were associated with increased morbidity or mortality risk. Surprisingly, however, long sleep durations (> 8 hours) have also been associated with an increased risk of morbidity or mortality, and the effect size of long sleep was sometimes greater than that of short sleep. For example, analysis of data from the Nurses' Health Study revealed a significant relative risk of mortality among women for those reporting sleeping 8 or more hours, whereas sleeping 6 hours or less was not associated with increased risk of mortality after adjustment for covariates.¹³ Of course, many of the covariates may actually be on the causal pathway between sleep loss and mortality (eg,

obesity, diabetes), which would explain why significance was lost. No studies published to date, however, have demonstrated a possible mechanism identifying long sleep as a cause of morbidity or mortality. The fact that adjusting for numerous diagnosed health conditions did not attenuate the association between long sleep and mortality suggests that long sleep does not cause any of these conditions, so long sleep would either have to directly cause death, with no intermediate steps such as disease, or we are missing something.

A paper in this issue of *Sleep* explores numerous factors in an attempt to identify those that predict long sleep (sleeping 9 hours or more) in a large epidemiologic cohort, the Nurses' Health Study II.¹⁴ The authors examined psychiatric, lifestyle, socioeconomic, medical, gynecologic, and sleep factors to predict the long sleepers. They also predicted the effect the significant associations between these factors and long sleep would have on mortality risk (the confounding rate ratio, CRR). The results suggest that depressive symptoms are a strong predictor of long sleep, and, due to their high prevalence, they are the most likely confounder of the association between long sleep and mortality risk. As the authors explain, if the reported associations between long sleep and mortality risk are not real, but are entirely due to omitted confounding variables, then the CRR for the omitted variable would have to be at least 1.3 to 1.5 to account for the reported risk of mortality due to long sleep. The CRR for depressive symptoms ranged from 1.03 to 1.18, depending on the risk of mortality due to depression, whereas the CRR for antidepressant use ranged from 1.05 to 1.43. Interestingly, low socioeconomic status (SES) was also significantly associated with long sleep. Other studies have shown a positive association between SES and sleep duration and quality,¹⁵ raising the possibility that a U-shaped association exists between SES and sleep duration as well. Furthermore, individuals of low SES are known to be at increased risk of morbidity and mortality and are more likely to have undiagnosed health conditions due to limited access to healthcare. These undiagnosed conditions could be confounding the association between sleep duration and mortality. According to the Patel study, unemployment status in particular may have a large impact on the association between long sleep and mortality. The CRR for unemployment status ranged from 1.03 to 1.29 depending on the risk of mortality due to unemployment. Although not all of the CRR values reported in this study are 1.3 or higher for any single variable, it is possible that in combination these variables could account for the observed association between long sleep and mortality risk.

Although other studies have often demonstrated a stronger association between long sleep and mortality or morbidity risk than

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that observed for short sleep, it is important to keep in mind that many more people are considered short sleepers than long sleepers. In the Nurses' Health Study II described in the Patel paper, only 5% of the sample qualified as long sleepers, whereas 30% of this sample reported sleeping 6 hours or less. In the 2002 National Sleep Foundation's Sleep in America Poll, 15% of adult Americans reported sleeping less than 6 hours and an additional 24% reported sleeping 6 to 6.9 hours, whereas only about 4% report sleeping 9 or more hours.¹⁶ Thus, although the potential association between long sleep and morbidity or mortality is very interesting, the effects of short sleep are more salient in terms of real-world effects.

Finally, it is important to note that no hypothetical mechanisms for long sleep causing disease or death have been investigated either in the current paper or in other laboratory or epidemiologic studies. Thus, it is not clear that sleeping 9 hours or more is inherently dangerous, particularly for a healthy individual. In fact, when Wehr and colleagues placed healthy men on a 10-hour light and 14-hour darkness light-dark cycle for 4 weeks, they found that the natural tendency was to sleep more than 8 hours when there was ample time in bed with no distractions.¹⁷ Currently, there is no evidence that if a healthy adult sleeps more than 8 hours he or she will do harm to himself or herself. Researchers must exercise caution when speaking to journalists about this issue because our brief sound bites could be turned into news stories such as, "Can Too Much Sleep Be Bad for You?"¹⁸ Forbes.com recently published online "10 ways to live longer," and the number 1 tip on their slideshow was "don't oversleep,"¹⁹ which could be misinterpreted to mean one should restrict sleep time. These are dangerous messages to send to the general public without any evidence supporting them. There is evidence, however, for mechanisms linking short sleep to morbidity, and short sleep is much more common in our society. Indeed, the Institute of Medicine recently published a report titled, "Sleep Disorders and Sleep Deprivation: an Unmet Public Health Problem," in which they stated, "The cumulative effects of sleep loss and sleep disorders represent an under-recognized public health problem and have been associated with a wide range of health consequences..."²⁰ Thus, we need to continue research on the effects of sleep loss on morbidity, which can lead to mortality, as well as perhaps use long sleep duration as a diagnostic tool because it may be secondary to some other mental or physiologic disorder.

REFERENCES

1. Spiegel K, Leproult R, Van Cauter E. Impact of sleep debt on metabolic and endocrine function. *Lancet* 1999;354:1435-9.
2. Spiegel K, Leproult R, L'Hermite-Baleriaux M, Copinschi G, Penev P, Van Cauter E. Leptin levels are dependent on sleep duration: relationships with sympathovagal balance, carbohydrate regulation, cortisol, and thyrotropin. *J Clin Endocrinol Metab* 2004;89:5762-71.
3. Spiegel K, Tasali E, Penev P, Van Cauter E. Sleep curtailment in healthy young men is associated with decreased leptin levels, elevated ghrelin levels and increased hunger and appetite. *Ann Intern Med* 2004;141:846-50.
4. Taheri S, Lin L, Austin D, Young T, Mignot E. Short sleep duration is associated with reduced leptin, elevated ghrelin, and increased body mass index. *PLoS Med* 2004;1:e62.
5. Hasler G, Buysse D, Klaghofer R, et al. The association between short sleep duration and obesity in young adults: a 13-year prospective study. *Sleep* 2004;27:661-6.
6. Gangwisch JE, Malaspina D, Boden-Albala B, Heymsfield SB. Inadequate sleep as a risk factor for obesity: analyses of the NHANES I. *Sleep* 2005;28:1289-96.
7. Chaput JP, Brunet M, Tremblay A. Relationship between short sleeping hours and childhood overweight/obesity: results from the 'Quebec en Forme' Project. *Int J Obes (Lond)* 2006 Mar 14; [Epub ahead of print].
8. Meisinger C, Heier M, Loewel H. Sleep disturbance as a predictor of type 2 diabetes mellitus in men and women from the general population. *Diabetologia* 2005;48:235-41.
9. Yaggi HK, Araujo AB, McKinlay JB. Sleep duration as a risk factor for the development of type 2 diabetes. *Diabetes Care* 2006;29:657-61.
10. Ayas NT, White DP, Manson JE, et al. A prospective study of sleep duration and coronary heart disease in women. *Arch Intern Med* 2003;163:205-9.
11. Gangwisch JE, Heymsfield SB, Boden-Albala B, et al. Short sleep duration as a risk factor for hypertension: analyses of the first National Health and Nutrition Examination Survey. *Hypertension* 2006;47:833-9.
12. Amagai Y, Ishikawa S, Gotoh T, et al. Sleep duration and mortality in Japan: the Jichi Medical School Cohort Study. *J Epidemiol* 2004;14:124-8.
13. Patel SR, Ayas NT, Malhotra MR, et al. A prospective study of sleep duration and mortality risk in women. *Sleep* 2004;27:440-4.
14. Patel SR, Malhotra A, Gottlieb DJ, White DP, Hu FB. Correlates of long sleep duration. *Sleep* 2006;29:881-9.
15. Moore P, Adler N, Williams D, Jackson J. Socioeconomic status and health: the role of sleep. *Psychosom Med* 2002;64:337-44.
16. 2002 Sleep in America Poll. Washington: National Sleep Foundation. Available at: http://www.sleepfoundation.org/_content/hottopics/2002SleepInAmericaPoll.pdf 2002. Accessed: May 22, 2006.
17. Wehr TA, Moul DE, Barbato G, et al. Conservation of photoperiod-responsive mechanisms in humans. *Am J Physiol* 1993;265:R846-57.
18. Stong C. Can too much sleep be bad for you? Available at: http://www.neurologyreviews.com/nov02/nr_nov02_toomuchslepp.html. Accessed: May 16, 2006.
19. Gisquet V. Ten Ways to Live Longer. Available at: http://www.forbes.com/health/2005/03/02/cx_vg_0302feat.html. Accessed: May 16, 2006.
20. Committee on Sleep Medicine and Research, Board on Health Sciences Policy. Colten H, Altevogt B, eds. *Sleep Disorders and Sleep Deprivation: An Unmet Public Health Problem*. Washington: National Academies Press; 2006.