http://dx.doi.org/10.5665/sleep.1594

A Prospective Study of Sleep Duration and Pneumonia Risk in Women

Sanjay R. Patel, MD, MS[1]; Atul Malhotra, MD[1]; Xiang Gao, MD, PhD[2]; Frank B. Hu, MD, PhD[2]; Mark I. Neuman, MD, MPH[3]; Wafaie W. Fawzi, MD, DrPH[2,4]

[1]Division of Sleep Medicine, Brigham and Women's Hospital, Boston, MA; [2]Departments of Epidemiology and Nutrition, Harvard School of Public Health, Boston, MA; [3]Division of Emergency Medicine, Children's Hospital, Boston, MA; [4]Department of Global Health and Population, Harvard School of Public Health, Boston, MA

Study Objective: Experimental data suggest sleep deprivation may impair host immunity. We sought to assess the effect of poor sleep on pneumonia risk.

Design: Prospective, observational cohort study.

Participants: 56,953 female nurses (ages 37 to 57 years old) participating in the Nurses' Health Study II cohort free of cancer, cardiovascular disease, diabetes, and asthma with no prior history of pneumonia.

Measurements and Results: At baseline, participants reported their average sleep duration and whether this quantity was adequate for them. Questionnaires ascertaining a new pneumonia diagnosis were mailed every 2 years. Cases required physician diagnosis and chest radiograph confirmation. Cox proportional hazards models were used to assess the relative risk for incident pneumonia over 4 years. Over 217,500 person-years, 977 cases of pneumonia were identified. Relative to 8-h sleepers, both short and long sleep durations were associated with elevated pneumonia risk. The age-adjusted relative risk for pneumonia was 1.70 (95% CI 1.30-2.23) in those sleeping ≤ 5 h and 1.49 (95% CI 1.12-1.98) in those sleeping ≥ 9 h. After adjusting for potential confounders, the relative risks were 1.39 (95% CI: 1.06-1.82) in those sleeping ≤ 5 h and 1.38 (95% CI 1.04-1.84) in those sleeping ≥ 9 h. Perceived inadequate sleep was also associated with pneumonia with a relative risk of 1.50 (95% CI 1.29-1.74) in multivariate models.

Conclusions: Both reduced and prolonged habitual sleep durations are associated with increased risk of pneumonia. Further research is needed to understand how sleep habits can influence immunity.

Keywords: Sleep, sleep deprivation, pneumonia, infection

Citation: Patel SR; Malhotra A; Gao X; Hu FB; Neuman MI; Fawzi WW. A prospective study of sleep duration and pneumonia risk in women. *SLEEP* 2012;35(1):97-101.

INTRODUCTION

Chronic partial sleep deprivation is exceedingly common in today's society.[1,2] Evidence suggests that sleep durations have been progressively declining for the past several decades for a variety of technological and societal reasons.[3-5] This change in behavior has important ramifications given the fundamental role of sleep in maintaining health. Over a few days, restricting sleep to 4-5 hours per night has been found to have a multitude of adverse effects, including worsening of neurocognitive, mood, metabolic, and autonomic parameters.[6,7] Epidemiologic studies suggest chronically altered sleep habits are associated with elevated risks for diabetes, cardiovascular disease, cancer, and mortality.[8-11]

One area that has received relatively little attention has been the potential role of sleep in maintaining immune function and host defense. Animal studies suggest complete sleep deprivation can result in bacteremia and sepsis,[12] but differentiating the effects of lack of sleep from the stress used to maintain wakefulness in these models is difficult. Several studies have demonstrated that alterations in sleep can have effects on immune cell function and cytokine levels, but the physiologic relevance of these changes has been unclear.[13,14] Similarly, studies have demonstrated reduced antibody titers following vaccination in sleep deprived individuals, but this has not been correlated to differences in vaccine efficacy.[15,16] A recent report suggested that upper respiratory symptoms may be more likely in chronically sleep deprived individuals following viral inoculation.[17] Whether poor sleep increases risk of more severe infections is unclear.

In this work, we sought to better characterize the potential role of sleep in host defense by assessing the relationship between habitual sleep duration and incident cases of pneumonia, as a measure of a clinically relevant infectious outcome with substantial morbidity, in a large cohort of middle-aged women.

METHODS

Study Population

The Nurses' Health Study II (NHS2) cohort was established in 1989 when 116,686 U.S. female registered nurses, aged 25 to 45 years completed a mailed questionnaire on their medical history and lifestyle. Follow-up questionnaires to ascertain lifestyle factors and occurrence of diseases have been mailed biennially, and the follow-up rate exceeds 90% of potential person-years. Further details on the study design and data collection have been previously published.[18] In 2001, sleep questions were added to the biennial questionnaire for the first time, so this time point was used as the baseline for these analyses. In order to limit confounding by comorbid illnesses and reverse causation, individuals with cancer (except non-melanoma skin cancer), cardiovascular disease, diabetes, asthma or a prior history of pneumonia at baseline, were excluded from analyses.

A commentary on this article appears in this issue on page 15.

Submitted for publication March, 2011
Submitted in final revised form July, 2011
Accepted for publication July, 2011

Address correspondence to: Sanjay R. Patel, 221 Longwood Avenue, Room 225C, Boston, MA 02115; Tel: (857) 307-0347; Fax: (617) 278-6946; E-mail: spatel@partners.org

The protocol for this study was approved by the Institutional Review Board of the Harvard School of Public Health.

Ascertainment of Sleep Habits

Subjects were asked to report their average sleep duration over a 24-h period with the following choices for response: < 5 h, 5 h, 6 h, 7 h, 8 h, 9 h, or 10+ h. Because of the low frequency of extreme responses, women reporting ≤ 5 h were combined into one group, as were women reporting ≥ 9 h. An analogous question about habitual sleep duration has been previously validated against sleep diaries in a similar cohort.[11] In addition, participants were asked "Do you feel that your sleep duration is adequate?"

Identification of Cases of Pneumonia

Every 2 years, participants were asked to report cases of pneumonia. Medical records were obtained from all women who reported physician-diagnosed pneumonia confirmed by a chest radiograph, and records were reviewed by a physician to validate the findings. Only the first documented episode of pneumonia occurring between June 1, 2001 and May 31, 2005 was included. A validation study reviewing medical records of 76 women reporting pneumonia verified the radiographic presence of a pulmonary infiltrate in 82% of cases.[19] A second validation study reviewing medical records found only 1 of 99 cases might have represented nosocomial pneumonia rather than community-acquired pneumonia.[20]

Assessment of Covariates

A set of covariates was selected that had been found to predict incident pneumonia in the NHS2 cohort and/or that were associated with sleep duration. Body mass index (BMI) was calculated as the ratio of weight to the square of height using self-reported height from the start of the study and self-reported weight from the time of the sleep assessment. Cigarette smoking was assessed based on whether the woman smoked and the amount smoked. Alcohol and caffeine consumption were estimated from a semi-quantitative food frequency questionnaire. Snoring was based on self-report as a surrogate for sleep apnea. A history of shift work was defined as having spent ≥ 1 month working rotating shifts in the past 2 years. Hypertension was based on self-report of a physician diagnosis. Depressed mood was defined as a score ≤ 52 on the 36-Item Short Form Health Survey (SF-36) mental health index. Covariate information regarding age, BMI, smoking, and hypertension was updated based on questionnaire results every 2 years. Alcohol and caffeine consumption were obtained from the 1999 food frequency questionnaire at baseline and then updated with the 2003 questionnaire.

Statistical Analysis

The outcome considered in this study was incident pneumonia. Person-time of follow-up was calculated as the time from the return of the 2001 questionnaire until the first report of pneumonia, death, or the end of the study period (May 31, 2005). Cox proportional hazards models with updating of covariate data were used to estimate the rate ratio (RR) for incident pneumonia for each sleep duration category relative to the reference group of 8 hours. Similar models were developed to estimate the rate ratio for inadequate sleep. Additional analyses were conducted stratifying on age, body mass index (BMI), and smoking status to investigate the presence of effect modification by these factors. Interactions between sleep and each of these factors were tested for statistical significance using log likelihood tests. All statistical analyses were conducted using SAS version 9.1 (Cary, NC).

RESULTS

Of the 84,527 women who completed the sleep questions on the 2001 questionnaire and had follow-up data, 18,222 were excluded from this analysis due to the presence of baseline medical illness. This included 4,303 women with a history of cancer, 673 with heart disease, 591 with stroke, 2,155 with diabetes, and 10,500 with asthma. Another 9,352 women were excluded due to a history of pneumonia in the past. Thus, 56,953 women were included in this analysis. The distribution of habitual sleep duration was 5.2%, 23.3%, 42.7%, 23.7%, and 5.0% for ≤ 5, 6, 7, 8, and ≥ 9 h, respectively. The overall prevalence of perceived inadequate sleep was 48%, varying from < 20% in those sleeping ≥ 8 h up to 88% in those sleeping ≤ 5 h. Baseline characteristics of the cohort by habitual sleep duration are displayed in Table 1. Mean age and caffeine consumption decreased, while alcohol consumption increased with increasing sleep duration. Women reporting both long and short sleep durations tended to be heavier and more likely to have hypertension and depressed mood.

A total of 977 cases of pneumonia were identified over 217,500 person-years of follow up. Short sleep was associated with increased pneumonia risk (Table 2). The unadjusted incidence rates for pneumonia were 6.5, 4.8, 4.3, 3.8, and 5.7 cases per 1000 person-years for women sleeping ≤ 5, 6, 7, 8, and ≥ 9 h, respectively. In age-adjusted analyses, those sleeping ≤ 5 h/night were at 70% greater risk of pneumonia than 8-h sleepers (95% CI 30%-123%). After adjustment for alcohol, caffeine, and tobacco use, the RR remained elevated at 1.53 (95% CI 1.17-2.01). This association persisted after further adjustment for comorbidity, with a RR of 1.39 (95% CI 1.06-1.82). Interestingly, long sleep durations were also associated with elevated risk. Compared to 8-h sleepers, the RR associated with ≥ 9 h sleep was 1.49 (95% CI 1.12-1.98) in age-adjusted analyses. After covariate adjustment, this risk was only slightly attenuated (RR = 1.38, 95% CI 1.04-1.84).

Results from analyses stratified by age, BMI, and smoking status are presented in Table 3. The pattern of an increased pneumonia risk with extremes of sleep duration was found in each subgroup. Point estimates suggest an increased susceptibility to altered sleep in those younger than 45 years of age, the overweight, and active smokers. However, formal tests for interaction were not significant for any of these analyses.

Perceived inadequate sleep was also associated with increased pneumonia risk. In age-adjusted models, inadequate sleep was associated with a 1.55-fold increased risk of pneumonia (95% CI 1.37-1.76). Inadequate sleep remained an independent risk factor for pneumonia after adjusting for smoking, alcohol, caffeine, BMI, depressed mood, snoring, shift work history, and hypertension, with a RR of 1.44 (95% CI 1.26-1.64). After further adjustment for habitual sleep duration, those reporting inadequate sleep remained at elevated risk for pneumonia (RR = 1.50, 95% CI 1.29-1.74). The effect of sleep

Table 1—Baseline characteristics stratified by self-reported sleep duration in 2001

	Hours of Sleep per Day					Adequacy of Sleep	
	≤ 5	6	7	8	≥ 9	Inadequate	Adequate
Number of Subjects (%)	2957 (5.2)	13,290 (23.3)	24,326 (42.7)	13,517 (23.7)	2863 (5.0)	27,000 (47.7)	29,643 (52.3)
Mean (SD)							
Age (y)	47.1 (4.6)	46.7 (4.6)	46.5 (4.7)	46.2 (4.7)	46.1 (4.7)	46.3 (4.6)	46.7 (4.7)
BMI (kg/m^2)	27.3 (6.6)	26.6 (6.2)	25.9 (5.6)	25.7 (5.5)	26.4 (6.2)	26.5 (6.0)	25.8 (5.5)
Alcohol (g/day)	3.5 (7.4)	3.7 (6.7)	4.1 (7.0)	4.4 (7.7)	4.4 (8.3)	3.8 (6.8)	4.4 (7.5)
Caffeine (mg/day)	234 (221)	229 (206)	222 (194)	217 (193)	210 (192)	221 (200)	223 (196)
Sleep duration (h)	–	–	–	–	–	6.5 (0.9)	7.4 (0.8)
% of women							
Hypertension	19.6	16.5	13.5	13.9	14.5	15.8	13.6
Depressed mood	18.3	11.9	7.9	7.7	13.8	14.1	5.5
Current smoking	12.7	9.9	7.6	6.6	7.7	8.5	7.9
Regular snoring	7.3	6.2	5.2	5.6	7.2	6.4	5.1
Rotating shift work	17.2	12.7	8.9	8.0	8.7	12.1	8.1
Self-reported adequate sleep	12.1	21.6	53.5	83.1	81.6	–	–

All variables are significantly different across sleep duration categories ($P < 0.05$). All variables except caffeine intake are significantly different across sleep adequacy categories ($P < 0.05$). BMI, body mass index.

duration on pneumonia risk stratified by sleep adequacy is shown in Table 3. Interestingly, an adverse effect of short sleep was only seen in those reporting inadequate sleep, though it should be noted that a formal test of interaction did not meet standard criteria for statistical significance ($P = 0.09$). In contrast, a long sleep duration of ≥ 9 h was associated with an elevated pneumonia risk independent of sleep adequacy.

Table 2—Rate ratios (95% confidence intervals) of incident pneumonia by self-reported sleep duration

	Hours of Sleep Per Day				
	≤ 5	6	7	8	≥ 9
Number of Incident Pneumonia Cases	73	245	401	196	62
Age-Adjusted Relative Risk	1.70 (1.30-2.23)	1.29 (1.07-1.56)	1.15 (0.97-1.37)	1.00	1.49 (1.12-1.98)
Multivariate Model #1*	1.53 (1.17-2.01)	1.23 (1.02-1.49)	1.15 (0.97-1.36)	1.00	1.45 (1.09-1.93)
Multivariate Model #2§	1.39 (1.06-1.82)	1.17 (0.96-1.41)	1.14 (0.96-1.35)	1.00	1.38 (1.04-1.84)

*Adjusted for age, smoking status, alcohol consumption, and caffeine consumption. §Adjusted for above plus body mass index, depressed mood, hypertension, snoring, and shift work.

DISCUSSION

In this study, we have demonstrated that both reduced and prolonged habitual sleep durations are associated with an increased risk of incident pneumonia. Prior research has demonstrated that altered sleep can have important effects on immune function.[21] Sleep deprivation acutely reduces natural killer cell, T lymphocyte, and monocyte function.[13,22,23] In addition, alterations in sleep have been found to increase levels of cytokines and markers of inflammation.[13,14] These alterations appear to have physiologically relevant effects as sleep deprivation has been shown to impair antibody responses to vaccination.[15,16] Analysis of an occupational cohort comparing day shift, night shift, and rotating shift found those on a rotating shift had the worst quality sleep and also the highest rate of common colds, flu-like illnesses, and episodes of gastroenteritis based on self-report.[24] A prospective study found that those reporting lower habitual sleep times were more likely to develop clinical disease following controlled exposure to rhinovirus suggesting sleep deprivation may increase the susceptibility to upper respiratory infections.[17] In the present study, we demonstrate that reduced sleep also predisposes to pneumonia. Several studies have demonstrated that extremes of sleep duration are associated with increased risk of non-cardiovascular and non-cancer deaths.[11,25] Increased risk of severe infections such as pneumonia and sepsis may partially explain this association.

Several studies have suggested reduced sleep may increase the risk of heart disease,[9] diabetes,[8] and obesity,[26] all conditions that may increase the risk of pneumonia. Our study restricted analysis to women free of heart disease and diabetes and adjusted for BMI, suggesting the identified associations were independent of these potential pathways and instead more likely related to direct effects of sleep on the immune system.

Individual susceptibility to neurocognitive deficits from sleep deprivation varies substantially, suggesting individuals may have differing sleep needs.[27] Our findings support such variability in requirements for optimal immune function as well, in that perceived inadequate sleep predicted incident pneumonia independent of sleep duration. In addition, the adverse effect of short sleep on pneumonia risk was present only in those reporting inadequate sleep. While sleep adequacy is

Table 3—Age-adjusted rate ratios (95% confidence intervals) of incident pneumonia by self-reported sleep duration

	Hours of Sleep per Day					P-value for interaction
	≤ 5	6	7	8	≥ 9	
Age < 45 y	2.04 (1.32-3.16)	1.49 (1.11-2.02)	1.26 (0.96-1.66)	1.00	1.77 (1.16-2.73)	0.69
Age ≥ 45 y	1.52 (1.08-2.14)	1.17 (0.92-1.49)	1.08 (0.87-1.35)	1.00	1.30 (0.88-1.91)	
BMI < 25 kg/m^2	1.31 (0.83-2.06)	1.38 (1.05-1.80)	1.12 (0.88-1.43)	1.00	1.47 (0.96-2.23)	0.45
BMI ≥ 25 kg/m^2	1.88 (1.34-2.65)	1.18 (0.91-1.54)	1.18 (0.92-1.50)	1.00	1.47 (0.99-2.17)	
Not current smoker	1.63 (1.21-2.19)	1.25 (1.02-1.53)	1.11 (0.92-1.33)	1.00	1.33 (0.97-1.83)	0.38
Current smoker	1.95 (0.96-3.93)	1.57 (0.88-2.78)	1.60 (0.93-2.77)	1.00	3.19 (1.51-6.71)	
Inadequate sleep	1.52 (1.04-2.24)	1.10 (0.78-1.54)	1.14 (0.82-1.59)	1.00	1.37 (0.73-2.56)	0.09
Adequate sleep	0.20 (0.03-1.40)	0.98 (0.68-1.39)	0.97 (0.77-1.20)	1.00	1.55 (1.12-2.14)	

clearly correlated with sleep duration (as seen in Table 1), other factors beyond the quantity of sleep obtained and intrinsic sleep need may factor in to this construct. Inadequate sleep may also reflect poor quality sleep or altered sleep architecture. In addition, adequate sleep may require sufficient sleep duration at the appropriate circadian phase and as such, shiftwork may modulate the relationship between sleep duration and sleep adequacy. Further research into the determinants of sleep adequacy is clearly needed given the association of inadequate sleep with not only infectious outcomes but also metabolic and cardiovascular outcomes.[28,29]

An interesting finding of this study is that women sleeping 9 hours or more appeared to also be at elevated risk for pneumonia. The effects of prolonged sleep on leukocyte function or vaccine response are unknown, but an association with elevated levels of inflammation has been previously reported suggesting the potential for immune dysregulation.[14] Prior work suggests oropharyngeal aspiration is fairly common during sleep,[30] so that in those who sleep 9 or more hours, the potential immune restorative effects of sleep in protecting against pneumonia may be outweighed by increased microbial deposition in the lungs. Another possible explanation for the increased pneumonia risk in long sleepers may be that these individuals have poor quality sleep that results in both an elevated infection risk and a desire to sleep longer. Although we adjusted for two of the most common causes of poor quality sleep, depression and sleep apnea, residual confounding may be present, as we relied on questionnaire-based measures for these conditions. Arguing against this possibility is the fact that 9-hour sleepers were the least likely to report inadequate sleep and that the effect of sleeping 9 hours or more on pneumonia risk was similar in magnitude in those reporting adequate and inadequate sleep. These findings suggests that self-reported adequacy of sleep may not accurately reflect sleep requirements for optimal health.

The precise role of sleep remains a mystery but its conservation across species suggests a strong evolutionary benefit. A recent study suggests a primary role for sleep may be in support of host defenses. Habitual sleep duration across mammalian species is predictive of circulating levels of lymphocytes, neutrophils, and eosinophils.[31] In addition, the more a species sleeps, the lower the density of microbial pathogens.[31]

Several potential limitations of this study should be noted. First, our population was limited to women who were well-nourished and had a similar socioeconomic status. Although such homogeneity would reduce confounding by these factors, it may reduce the generalizability of our findings to other populations. For example, data from the Whitehall II cohort suggest women may be more susceptible to the pro-inflammatory effects of sleep deprivation than men.[32] In addition, we limited the study population to those without major comorbidities or prior history of pneumonia in order to limit the possibility of confounding or reverse causation. While this strengthens the argument that a causal relationship between sleep and pneumonia risk exists, such a restriction limits the generalizability of our findings to this healthy subgroup of the population. Second, our study was observational in design, and thus, we cannot conclude that modifying sleep duration will alter pneumonia risk. In addition, we cannot exclude the presence of unrecognized confounders not accounted for in our analyses as a cause of the reported associations. The effects of recognized confounders, such as shiftwork and sleep apnea, may also not have been adequately accounted for in this analysis because of the inability to measure them fully with the questionnaire instruments used.

The use of self-reported sleep duration to estimate exposure to sleep rather than a more objective assessment introduces the possibility of measurement error. However, we have previously validated our self-reported sleep question in a similar cohort, the Nurses' Health Study, where a Spearman correlation (ρ) of 0.79 was found between one question about usual sleep and the average sleep obtained from one week of sleep diaries.[11] In addition, objective measurement of sleep habits suggests individuals typically overestimate their actual sleep time,[33,34] and the less one sleeps, the greater the overestimate.[33] A similar pattern in overestimation with use of a single question about usual sleep was found in the Nurses' Health Study.[11] As a result of this reporting bias, the effect of reduced sleep on pneumonia risk would tend to be underestimated by relying on self-report. The stability of sleep duration in this cohort over the four years of this study is unclear, although prior work in the Nurses' Health Study suggests fairly good stability of self-reported response over two years.[11] To the extent that changes in sleep habits lead to misclassification, assuming this misclassification is non-differential between those with average and extremes of sleep duration, it would tend to lead to an underestimate of the effect of extremes of sleep duration on pneumonia risk. It should also be noted that we were unable to characterize sleep architecture

in order to identify which stages of sleep may be most strongly correlated with pneumonia risk. Lastly, we were unable to distinguish between viral and bacterial pneumonia, but even under the best of circumstances, the microbiological etiology of pneumonia is difficult to establish.[35,36]

Nevertheless, our findings suggest that both inadequate and excessive sleep are associated with an increased risk of severe infections. Further work is needed to identify the specific mechanisms by which altered sleep may impact normal immune function.

ACKNOWLEDGMENTS

This work was supported by National Institutes of Health grants CA50385, HL081385, HL093218, HL090897, HL085188, HL73146 and American Heart Association 0840159N.

DISCLOSURE STATEMENT

This was not an industry supported study. Dr. Patel has received research support from HealthRight Products and Philips Respironics. Dr. Malhotra has received consulting and/or research income from Philips, Apex, Apnicure, Pfizer, Merck, Sleep Group Solutions, Sleep HealthCenters, Ethicon, Medtronic, Cephalon, and Sepracor. The other authors have indicated no financial conflicts of interest.

REFERENCES

1. National Sleep Foundation. 2005 Sleep in America Poll. Washington: National Sleep Foundation; 2005.
2. McKnight-Eily LR, Liu Y, Perry GS, et al. Perceived insufficient rest or sleep among adults - United States, 2008. MMWR 2009;58:1175-79.
3. Basner M, Dinges DF. Dubious bargain: trading sleep for Leno and Letterman. Sleep 2009;32:747-52.
4. Williams GD, Dufour M, Bertolucci D. Drinking levels, knowledge, and associated characteristics, 1985 NHIS findings. Public Health Rep 1986;101:593-8.
5. Schoenborn CA, Adams PF. Health behaviors of adults: United States, 2005-2007. Vital Health Stat 2010;10.
6. Dinges DF, Pack F, Williams K, et al. Cumulative sleepiness, mood disturbance, and psychomotor vigilance performance decrements during a week of sleep restricted to 4-5 hours per night. Sleep 1997;20:267-77.
7. Spiegel K, Leproult R, Van Cauter E. Impact of sleep debt on metabolic and endocrine function. Lancet 1999;354:1435-9.
8. Ayas NT, White DP, Al-Delaimy WK, et al. A prospective study of self-reported sleep duration and incident diabetes in women. Diabetes Care 2003;26:380-4.
9. 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.
10. Schernhammer ES, Laden F, Speizer FE, et al. Rotating night shifts and risk of breast cancer in women participating in the nurses' health study. J Natl Cancer Inst 2001;93:1563-8.
11. Patel SR, Ayas NT, Malhotra MR, et al. A prospective study of sleep duration and mortality risk in women. Sleep 2004;27:440-4.
12. Everson CA. Sustained sleep deprivation impairs host defense. Am J Physiol 1993;265:R1148-54.
13. Irwin MR, Wang M, Campomayor CO, Collado-Hidalgo A, Cole S. Sleep deprivation and activation of morning levels of cellular and genomic markers of inflammation. Arch Intern Med 2006;166:1756-62.
14. Patel SR, Zhu X, Storfer-Isser A, et al. Sleep duration and biomarkers of inflammation. Sleep 2009;32:200-4.
15. Lange T, Perras B, Fehm HL, Born J. Sleep enhances the human antibody response to hepatitis A vaccination. Psychosom Med 2003;65:831-5.
16. Spiegel K, Sheridan JF, Van Cauter E. Effect of sleep deprivation on response to immunization. JAMA 2002;288:1471-2.
17. Cohen S, Doyle WJ, Alper CM, Janicki-Deverts D, Turner RB. Sleep habits and susceptibility to the common cold. Arch Intern Med 2009;169:62-7.
18. Curhan GC, Chertow GM, Willett WC, et al. Birth weight and adult hypertension and obesity in women. Circulation 1996;94:1310-5.
19. Baik I, Curhan GC, Rimm EB, Bendich A, Willett WC, Fawzi WW. A prospective study of age and lifestyle factors in relation to community-acquired pneumonia in US men and women. Arch Intern Med 2000;160:3082-8.
20. Neuman MI, Willett WC, Curhan GC. Vitamin and micronutrient intake and the risk of community-acquired pneumonia in US women. Am J Med 2007;120:330-6.
21. Dinges DF, Douglas SD, Zaugg L, et al. Leukocytosis and natural killer cell function parallel neurobehavioral fatigue induced by 64 hours of sleep deprivation. J Clin Invest 1994;93:1930-9.
22. Irwin M, McClintick J, Costlow C, Fortner M, White J, Gillin JC. Partial night sleep deprivation reduces natural killer and cellular immune responses in humans. FASEB J 1996;10:643-53.
23. Bollinger T, Bollinger A, Skrum L, Dimitrov S, Lange T, Solbach W. Sleep-dependent activity of T cells and regulatory T cells. Clin Exp Immunol 2009;155:231-8.
24. Mohren DC, Jansen NW, Kant IJ, Galama J, van den Brandt PA, Swaen GM. Prevalence of common infections among employees in different work schedules. J Occup Environ Med 2002;44:1003-11.
25. Ikehara S, Iso H, Date C, et al. Association of sleep duration with mortality from cardiovascular disease and other causes for Japanese men and women: The JACC study. Sleep 2009;32:295-301.
26. Patel SR, Malhotra A, White DP, Gottlieb DJ, Hu FB. Association between reduced sleep and weight gain in women. Am J Epidemiol 2006;164:947-54.
27. Van Dongen HP, Baynard MD, Maislin G, Dinges DF. Systematic interindividual differences in neurobehavioral impairment from sleep loss: evidence of trait-like differential vulnerability. Sleep 2004;27:423-33.
28. Wheaton AG, Perry GS, Chapman DP, McKnight-Eily LR, Presley-Cantrell LR, Croft JB. Relationship between body mass index and perceived insufficient sleep among U.S. adults: an analysis of 2008 BRFSS data. BMC Public Health 2011;11:295.
29. Shankar A, Syamala S, Kalidindi S. Insufficient rest or sleep and its relation to cardiovascular disease, diabetes and obesity in a national, multiethnic sample. PLoS One 2010;5:e14189.
30. Huxley EJ, Viroslav J, Gray WR, Pierce AK. Pharyngeal aspiration in normal adults and patients with depressed consciousness. Am J Med 1978;64:564-8.
31. Preston BT, Capellini I, McNamara P, Barton RA, Nunn CL. Parasite resistance and the adaptive significance of sleep. BMC Evol Biol 2009;9:7.
32. Miller MA, Kandala NB, Kivimaki M, et al. Gender differences in the cross-sectional relationships between sleep duration and markers of inflammation: Whitehall II study. Sleep 2009;32:857-64.
33. Lauderdale DS, Knutson KL, Yan LL, Liu K, Rathouz PJ. Self-reported and measured sleep duration: how similar are they? Epidemiology 2008;19:838-45.
34. Silva GE, Goodwin JL, Sherrill DL, et al. Relationship between reported and measured sleep times: the sleep heart health study (SHHS). J Clin Sleep Med 2007;3:622-30.
35. Korppi M. Non-specific host response markers in the differentiation between pneumococcal and viral pneumonia: what is the most accurate combination? Pediatr Int 2004;46:545-50.
36. van der Meer V, Neven AK, van den Broek PJ, Assendelft WJ. Diagnostic value of C reactive protein in infections of the lower respiratory tract: systematic review. BMJ 2005;331:26.