Sleep Habits and Susceptibility to the Common Cold

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Background: Sleep quality is thought to be an important predictor of immunity and, in turn, susceptibility to the common cold. This article examines whether sleep duration and efficiency in the weeks preceding viral exposure are associated with cold susceptibility.

Methods: A total of 153 healthy men and women (age range, 21-55 years) volunteered to participate in the study. For 14 consecutive days, they reported their sleep duration and sleep efficiency (percentage of time in bed actually asleep) for the previous night and whether they felt rested. Average scores for each sleep variable were calculated over the 14-day baseline. Subsequently, participants were quarantined, administered nasal drops containing a rhinovirus, and monitored for the development of a clinical cold (infection in the presence of objective signs of illness) on the day before and for 5 days after exposure.

Results: There was a graded association with average sleep duration: participants with less than 7 hours of sleep were 2.94 times (95% confidence interval [CI], 1.18-7.30) more likely to develop a cold than those with 8 hours or more of sleep. The association with sleep efficiency was also graded: participants with less than 92% efficiency were 5.50 times (95% CI, 2.08-14.48) more likely to develop a cold than those with 98% or more efficiency. These relationships could not be explained by differences in prechallenge virus-specific antibody titers, demographics, season of the year, body mass, socioeconomic status, psychological variables, or health practices. The percentage of days feeling rested was not associated with colds.

Conclusion: Poorer sleep efficiency and shorter sleep duration in the weeks preceding exposure to a rhinovirus were associated with lower resistance to illness.

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IT IS COMMONLY THOUGHT THAT poor sleep increases our susceptibility to the common cold. However, there is little direct evidence for this assertion. Experimental studies have demonstrated that sleep deprivation results in poorer immune function, such as reduced natural killer cell activity, suppressed interleukin-2 production, and increased levels of circulating proinflammatory cytokines.[1-3] Sleep deprivation has also been found to attenuate antibody response to both hepatitis A[4] and influenza immunizations.[5] The only direct evidence that sleep habits are associated with cold susceptibility derives from a secondary analysis of data from a rhinovirus (RV)-challenge study in which a single retrospective questionnaire assessing sleep habits during the previous month was used to assess sleep efficiency (the percentage of time a person actually sleeps between lying down to sleep and waking up the next morning).[6] Efficiencies below 80% predicted a greater risk for the development of verifiable illness.

In this study, we examined whether sleep habits are associated with resistance to a common cold. Instead of retrospective reports, we obtained estimates of sleep habits by averaging respondent reports of sleep duration, efficiency, and "feeling rested" across 14 consecutive days. After sleep assessments were completed, the participants were exposed to an RV and were monitored to see whether they developed clinical illness. Infection and signs and symptoms of illness were assessed the day before and for 5 days after the viral challenge. This design extends previous work by providing reliable (averaged over 14 days) online (collected daily) measures of baseline sleep; by allowing the comparison of the relative importance of sleep duration, efficiency, and feeling rested for cold susceptibility; and by providing the opportunity to test for graded relationships between sleep measures and disease susceptibility.

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DESIGN

During the prechallenge baseline period, we assessed virus-specific neutralizing antibody titers, demographics, and height and weight in healthy volunteers. We also interviewed the volunteers about their sleep quality during the previous night on 14 consecutive days. Other interview and questionnaire data collected during the prechallenge baseline included health practices and psychological factors. The participants were then quarantined in separate rooms, exposed to RV-39, and monitored for 5 days to assess infection and signs and symptoms of illness.

PARTICIPANTS

The data were collected between 2000 and 2004. The study included 78 men and 75 women (age range, 21-55 years; mean [SD] age, 37.06 [8.95] years) who responded to advertisements, were judged to be in good health, and had no missing data (2 participants were excluded because of missing data) on relevant variables. They were studied in 6 groups and received $800 for their participation. The study received institutional review board approval, and informed consent was obtained from each participant.

EXPERIMENTAL PLAN

The temporal sequence of events for a study trial is presented below.

Baseline period
Eligibility screening (5-10 weeks before viral exposure)
- Physical examination
- Check blood sample for preexisting antibody to virus
- Demographics
- Height and weight
- Perceived social status

14 Daily interviews (beginning 20-23 days before viral exposure)
- Sleep
- Positive emotions
- Health practices

Quarantine baseline day 0 (before viral exposure)
- Psychological questionnaires
- Nasal lavage for baseline virus culture
- Baseline signs and symptoms of respiratory illness

Viral exposure
Quarantine baseline day 0 (end of day)
- Viral inoculation

Postexposure follow-up
Quarantine days 1-5
- Nasal lavage for virus culture
- Signs and symptoms of respiratory illness
28 Days after viral exposure
- Check blood sample for antibody to virus

The volunteers underwent medical screenings and were excluded if they had a history of nasal surgery or any chronic disorder (eg, asthma, cardiovascular disorders, or sleep apnea); had abnormal findings on urinalysis, complete blood cell count, or determination of blood enzyme levels; were pregnant or currently lactating; were positive for human immunodeficiency virus; or were taking medication regularly (including sleep medication). They were also excluded if they had been hospitalized for psychiatric problems during the last 5 years or were currently taking medications for psychiatric problems. To maximize the infection rate, we also assessed specific levels of serum antibody to the challenge virus and excluded the participants with titers higher than 4. Demographics, weight, height, and perceived social status were also measured at screening, while sleep, health practices, and other psychological measures were assessed within the 23-day period just before the viral challenge.

During the first 24 hours of quarantine (prechallenge), the volunteers underwent a nasal examination and nasal lavage. Baseline symptoms, nasal mucociliary clearance, and nasal mucus production were also measured. None of the volunteers reported cold signs or symptoms, and no viral pathogen was isolated from any of the obtained nasal lavage samples. The participants were then given nasal drops containing 125 times the dose of RV-39 needed to infect 50% of tissue cultures exposed to the virus. On each day of quarantine, they recorded their respiratory symptoms and were assessed for nasal mucociliary clearance and nasal mucus production, and nasal lavage samples were collected for virus culture. Approximately 28 days after the challenge, blood samples were collected for serologic testing. The investigators were blinded to all measures.

SLEEP MEASURES

The participants were interviewed by phone on 14 consecutive evenings, with the first interview occurring 20 to 23 days before viral exposure. They were asked the following questions based on key items from the Pittsburgh Sleep Quality Index and the Pittsburgh Sleep Diary[7,8]: What time did you lie down to go to sleep last night? What time did you get out of bed this morning? How many minutes of sleep did you lose between the time you lay down to go to sleep (interviewer stated actual time) and the time you got out of bed (interviewer stated actual time) because you had difficulty falling asleep or you woke up and could not get back to sleep? Did you spend any time in bed between lying down to go to sleep (interviewer stated actual time) and getting out of bed (interviewer stated actual time) intentionally awake (eg, reading or watching television)? If yes, for how many minutes? Did you feel rested from your sleep when you awoke this morning (yes or no)?

The sleep scores were calculated for each of the 14 interview days. Sleep duration was scored as the number of hours slept (from the time the participant lay down to go to sleep until the time he or she got out of bed minus the minutes of sleep lost minus the minutes he or she was intentionally awake), and sleep efficiency was scored as sleep duration divided by time in bed (from the time the participant lay down until the time he or she got out of bed).[7] We then averaged across the 14 days (at least 8 days of complete data were required; mean [SD] number of days, 13.44 [1.31]) to create the average sleep duration, the average sleep efficiency, and the percentage of days that the participant felt rested.

CONTROL VARIABLES

We controlled for viral immunity as assessed by the prechallenge antibody titer; age; body mass index[2]; race; income; education; sex; season of exposure (ie, spring, summer, autumn, or winter); psychological variables previously found to be associated with risk for colds, including perceived social status, perceived stress, positive emotional style, extraversion, and agreeableness[9-11]; smoking rate; alcohol consumption; and exercise. The participants described their primary racial or ethnic group by choosing from the following 6 categories: (1) white, Caucasian; (2) black, African American; (3) Native American, Eskimo, Aleut; (4) Asian or Pacific Islander; (5) Hispanic, Latino; or (6) other. For analysis, the racial or ethnic groups were

dummy coded, with all but whites (n=81) and blacks (n=59) collapsed into a single "other" category (n=13). Income was assessed by the question, "Which category best describes your yearly household income before taxes?" There were 13 categories ranging from "less than $5,000" to "$150,000 or more." Income was defined as the median income of the identified category. Income scores were log (base-10) transformed to normalize the distribution.

Education was assessed by the question, "What is the highest grade or year of school you have completed?" There were 18 categories ranging from "no formal education" to "doctoral degree." The participants were assigned a number of years of education based on their response (eg, high school, 12 years; associate's degree, 14 years; and PhD, 20 years).

At each of the 14 daily baseline interviews, we assessed health practices during the last 24 hours. For exercise, participants were asked, "Did you exercise long enough to work up a sweat or get your heart thumping?" "If yes, "For how many minutes did you exercise?" For smoking, "Did you smoke any tobacco product?" If yes, "How many cigarettes, cigars, bowls of tobacco?" For alcohol consumption, "Did you consume any alcoholic drinks?" If yes, "How many (a glass of wine, a 12 ounce beer, or a shot of hard liquor each equal 1 drink)?" Scores for each behavior were computed as the arithmetic mean across the 14 days.

Psychological variables that were assessed by questionnaire included a 10-item measure of the perceptions of stress in the participant's life[12]; the perceived socioeconomic rank as assessed by the participants placing themselves on a 9-rung ladder in terms of where they stand in their country on income, education, and occupation[9]; and extraversion and agreeableness using the modified 5-item versions of the subscales from Goldberg's[13] "Big Five." Positive emotional style was assessed as the extent to which respondents reported feeling happy, calm, full of pep, lively, and cheerful during each of the 14 interview days, averaged across days.[11]

VIRAL CULTURES AND ANTIBODY RESPONSE

Virus-specific neutralizing antibody titers were measured in serum samples collected before and approximately 28 days after virus exposure[14]; the results were expressed as reciprocals of the final dilution of serum. Daily nasal lavage samples were frozen at −80°C and later cultured for RV using standard techniques.[14]

SIGNS AND SYMPTOMS

On each quarantine day, the participants rated the severity (during the previous 24 hours) of each of 8 illness symptoms (nasal congestion, sneezing, runny nose, earache, sinus pain, sore throat, cough, and chest congestion) on a scale of 0 (none) to 4 (very severe).[15] Daily mucus production was assessed by collecting used tissues in sealed plastic bags.[16] The bags were weighed, and the weight of the tissues and bags was subtracted. Nasal mucociliary clearance function was assessed as the time required for the dye that was administered into the anterior area of the nose to reach the nasopharynx.[16] Baseline-adjusted daily scores for each measure were calculated by subtracting the appropriate baseline score from each postexposure daily score. Negative adjusted scores were reassigned a value of 0. Total adjusted scores for symptoms, mucus weight, and nasal clearance were calculated by summing the respective adjusted daily scores over the postchallenge quarantine days.

The participants were considered to have a clinical cold if they were both infected and met illness criteria. Infection was defined as the recovery of the challenge virus on any of the postchallenge days or a 4-fold or greater increase in the virus-specific serum neutralizing antibody titer (preexposure to 28 days postexposure).[16] We used an objective illness criterion in the primary analyses that required a total adjusted mucus weight of 10 g or more or a total adjusted nasal clearance time of 35 minutes or more.[6] By this criterion, the mean (SD) total adjusted subjective symptom score was 36.07 (22.36) for participants with clinical colds compared with 11.52 (13.47) for those without colds ($t_{151}=-8.48$; $P<.001$). We also reported analyses using an illness criterion based on subject self-report. This modified Jackson criterion requires a total adjusted symptom score of 6 or more in addition to the participants either reporting having a cold or reporting rhinorrhea on 3 or more days of the 5-day period.[14]

STATISTICAL ANALYSES

Body mass index, total symptom, mucus weight, and nasal clearance scores were logged (base 10) to normalize each distribution. Logistic regression was used to predict colds (1, yes; 0, no), and multiple linear regression was used to predict continuous markers of objective illness and total subjective symptom scores. Sleep measures were treated as continuous variables, and we reported regression coefficients as well as their standard errors and probability levels. To help clarify the nature of the relationships and to provide a clearer estimate of effect sizes, we also fit regression equations using categorical measures of sleep (tertiles) and reported odds ratios (ORs) and 95% confidence intervals (CIs). In the primary analyses, we reported the association of sleep habits and both objective and subjective cold criteria, but the remaining analyses focused on the objectively determined outcome.

RESULTS

RATES OF INFECTION AND COLDS

Of the 153 subjects, 135 (88.2%) were infected; 54 (35.3%) developed a cold defined as infection and the objective cold criterion; and 66 (43.1%) developed a cold defined as infection and the subjective (Jackson) criterion.

SLEEP SCORES

The mean (SD) average sleep scores were 7.45 (1.33) hours for duration, 94% (0.06) for efficiency, and 77% (0.22) for the percentage of nights the participants felt rested. The average sleep scores were only moderately intercorrelated: $r=0.37$ for efficiency and duration; $r=0.22$ for efficiency and percentage of nights rested; and $r=0.29$ for duration and percentage of nights rested (all P values <.01). Approximate tertiles for duration were as follows: low, less than 7 hours of sleep (n=58); middle, 7 to 8 hours of sleep (n=52); and high, 8 or more hours of sleep (n=43). For efficiency, they were low, less than 92% (n=48); middle, 92% through 98% (n=53); and high, more than 98% (n=52).

BASELINE SLEEP AND COLD SUSCEPTIBILITY

Because of their traditional associations with cold susceptibility, we included age and viral-specific antibody titers as controls in all the primary analyses. We then conducted a series of analyses, each entering 1 of the 16 separate control variables. By trimming the number of covar-

iates, we reduced risk of "overfitting" the model[17]; however, including all covariates in a single model yielded the same conclusions.

When sleep habits were treated as continuous variables, and age and antibody titers were entered as controls, both shorter sleep duration and lower sleep efficiency were associated with increased risk for the development of a cold by both objective (B=−0.39 [SE, 0.15], $P<.02$ for duration; and B=−8.93 [SE, 2.97], $P<.003$ for efficiency) and subjective (B=−0.36 [SE, 0.15], $P<.02$ for duration; and B=−12.33 [SE, 3.35], $P<.001$ for efficiency) criteria. The percentage of nights that the participants felt rested was unrelated to either cold criterion ($P>.17$).

Using tertiles of the sleep variables to predict objectively defined colds illustrates that the relationships between sleep variables and colds were graded for both duration (for low, OR, 2.94; 95% CI, 1.18-7.30; for middle, OR, 1.63; 95% CI, 0.63-4.19; and for high, 1 [reference]) and efficiency (for low, OR, 5.50, 95% CI, 2.08-14.48; for middle, OR, 3.94; 95% CI, 1.50-10.37; and for high, 1 [reference]) (**Figure**).
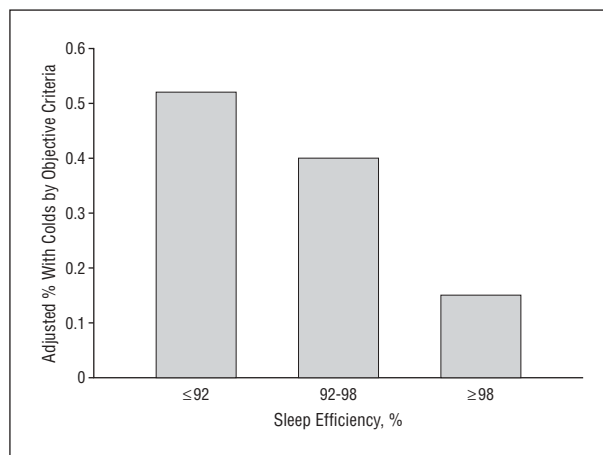
To determine whether sleep duration and efficiency were independent predictors, we entered both into the same equation predicting the objective cold criterion. Sleep efficiency (B=−7.34 [SE, 3.14], $P<.02$) but not duration (B=−0.27 [SE, 0.16], $P>.10$) remained a significant predictor, suggesting that there was an overlap between the 2 predictors and that sleep efficiency accounted for a greater part of the effect.

It is common to consider sleep efficiencies of 85% or less as abnormal. Only 8.5% of our sample fell below this norm. To provide a risk estimate based on this common cutoff, we compared the participants with sleep efficiencies of 85% or less (n=13) with the remaining participants (dummy coded). Those with efficiencies of 85% or less were at a substantially increased risk of getting a cold relative to the rest of the sample (OR, 5.37; 95% CI, 1.51-19.1).

In a second set of regressions, each analysis contained a single control variable along with either sleep duration or sleep efficiency (32 analyses). In all cases, the sleep variables' associations with colds remained significant (lowest $P<.03$), indicating that the sleep effects were independent of all of the controls. Finally, in models including all 16 control variables, both duration (β=−0.39 [SE, 0.18], $P<.03$) and efficiency (β=−6.93 [SE, 3.37], $P<.04$) remained independent predictors.

BASELINE SLEEP AND INDIVIDUAL SIGNS AND SYMPTOMS OF ILLNESS

In additional analyses, we used individual signs and symptoms as the outcomes instead of clinical illness. After age and antibody titer were controlled for, poor sleep efficiency (β=−1.11 [SE=0.42], $P<.01$) but not reduced sleep duration ($P>.11$) was associated with increased mucus weight. Neither efficiency nor duration predicted the average increase in nasal clearance time (P values >.54). Sleep efficiency (β=−1.51 [SE=0.40], $P<.001$) but not sleep duration ($P>.11$) was associated with the total symptom score.

Figure. Sleep efficiency (percentage of time in bed asleep) averaged over a 14-day period before virus exposure is associated with the percentage of persons who subsequently developed a cold. The percentage of colds is based on predicted values (adjusted for prechallenge antibody and age).

COMMENT

Poorer sleep efficiency and shorter sleep duration as assessed by self-report over a 2-week period in the 23 days before exposure to an RV were associated with increased probability of developing a cold. Both associations were graded. They were also robust in the face of 16 control variables: prechallenge viral-specific antibody titers, age, body mass index, race, income, education, sex, season of exposure, psychological factors (perceived stress, perceived social status, positive emotional style, extraversion, and agreeableness), and health practices (smoking, alcohol consumption, and physical activity). Associations of sleep duration and sleep efficiency overlapped, with efficiency being the primary and independent predictor. Interestingly, while measures estimating when a participant was sleeping (duration and efficiency) were predictive, the more evaluative sleep measure—feeling rested—was not.

Much of what we know about sleep and health derives from prospective cohort studies that have used 1 or 2 retrospective questions to assess habitual sleep duration. These studies suggest that the lowest morbidity (coronary heart disease) and mortality generally occur among persons who report sleeping approximately 7 to 8 hours a night.[18,19] Our findings on risk for the common cold suggest that there is a substantial risk associated with getting less than 7 hours of sleep per night. However, unlike some of the mortality studies,[18,19] we found that increases in sleep duration above 8 hours are associated with better (rather than poorer) health. One explanation for elevated mortality among long sleepers is that longer-duration sleep is merely a symptom of depression, itself a risk factor for mortality. Our participants were screened for psychiatric disorders; therefore, depression is not likely to be at play here. Another issue is that our sample was relatively young (mean age, 37 years; maximum age, 55 years) and healthy, while evidence for longer sleep being detrimental derives from samples that have included a large segment of older adults, many of whom have chronic illnesses.

The data were quite consistent across outcome measures, with the exception of nasal clearance function. The reason for this anomaly is not clear, although we found surprisingly little variability (as compared with mucus weights or symptoms) in the day-to-day measures of nasal clearance, suggesting a potential insensitivity of this measure.

What mechanisms might link sleep to cold susceptibility? When the components of clinical illness (infection and signs or symptoms) were examined separately, sleep efficiency but not sleep duration was associated with signs and symptoms of illness. However, neither was associated with infection (data not reported). This study was designed to maximize the infection rate (participants selected for low antibody levels) and was not powered to fairly test whether sleep is associated with infection (>88% were infected). Consequently, no conclusions about the role of sleep in infection can be made from this null effect. However, the evidence is consistent with increased clinical illness among individuals with poorer sleep being attributable to symptom expression. A possible explanation for this finding is that sleep disturbance influences the regulation of proinflammatory cytokines, histamines, and other symptom mediators that are released in response to infection.[1]

The relative ease of assessing self-reported sleep makes these findings particularly useful to physicians and patients, giving them an approximate indicator on which they can act. Studies of both 17- to 30-year-olds and 32- to 59-year-olds have found that about two-thirds report sleeping 7 to 8 hours a night and approximately three-fourths report 7 hours or more of sleep.[20,21] Similar to the mortality studies,[18,19,22] the data reported herein support the argument that 7 to 8 hours of sleep is a reasonable target. However, they also suggest that even a minimal habitual sleep disturbance (sleep losses of 2%-8%, 10-38 minutes for an 8-hour sleeper) is associated with 3.9 times the risk of developing a cold.

Evidence from actigraphy studies suggests that self-reported sleep slightly underestimates both duration and total number of nocturnal wakenings.[23-25] Therefore, we may want to be cautious about the exactness of self-reported estimates of sleep duration and efficiency and treat them as broad relative indicators. However, the actigraphy studies suggesting self-report bias were conducted in persons with sleep disorders and other psychiatric and physical problems.[23-25] Self-report biases are likely less marked in healthy samples with less disturbed sleep. Moreover, if there are actually biases in self-reports of duration and efficiency, these same biases would enter into patients' attempts to meet specific sleep targets and hence have little significance for clinical intervention. Finally, since existing suggestions about what constitutes health-promoting sleep are based on studies of self-reported sleep habits, our data can be more readily compared with earlier evidence on other morbidities and mortality.

That viral-challenge trials results are applicable to natural colds is supported by concordant evidence of these trials, with epidemiologic data and by the close fit between symptom timing and severity patterns and those found in epidemiologic studies.[10,26] Generalization of results using RV-39 to those using other cold viruses is pro-

vided by challenge studies showing that associations hold across multiple upper respiratory viruses,[10,11] including an earlier study of sleep efficiency and colds.[6]

In sum, according to our study results, measures of sleep predicted susceptibility to the development of a cold. Although both shorter sleep duration and lower sleep efficiency were associated with risk for illness, duration did not predict independently of efficiency, which was a stronger overall correlate of illness. Although the prospective design does not allow causal inference, it does eliminate reverse causation as an explanation. Because of the prospective design and the controls for multiple confounding factors, these results strongly suggest the possibility of sleep playing a causal role in cold susceptibility. Moreover, the use of a maximally reliable multiple day assessment of sleep habits increases our confidence in the findings of this study.

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