Correlates of Long Sleep Duration

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Study Objective: Sleeping more than 7 to 8 hours per day has been consistently associated with increased mortality. Whether this association is causal and what pathways explain this association are unknown. We sought to identify factors that could potentially explain the association between long sleep and mortality.

Design: Cross-sectional epidemiologic survey.

Participants: Middle-aged women (n = 60,028) participating in the Nurses Health Study II who reported a habitual sleep duration of 7 hours or more.

Results: Multiple sclerosis (odds ratio [OR] = 3.7, 95% confidence interval [3.0-4.5]), antidepressant use (OR = 3.1, [2.9-3.3]), benzodiazepine use (OR = 3.0 [2.6-3.3]), and systemic lupus erythematosus (OR = 2.9, [2.3-3.6]) were the factors most strongly associated with prolonged sleep. Combining these data with prevalence information and a range of plausible associations with mortality, the confounding rate ratio was estimated. This parameter is the ratio of the unadjusted long sleep–mortality rate ratio to the rate ratio adjusted for the factor and measures the extent that the factor can alter the long sleep—mortality association, either through confounding or as a causal intermediate. Based on this parameter, psychiatric and socioeconomic factors have the greatest potential to influence the long sleep–mortality relationship. Assuming each factor doubles mortality risk, the confounding rate ratios for depression, antidepressant use, and unemployment were 1.10, 1.18, and 1.12. Lesser influential factors were benzodiazepine use, poverty, low societal status, sedentary lifestyle, and obesity.

Conclusion: Depression and low socioeconomic status are strong candidates for producing the statistical association between long sleep and mortality, either as confounders or as causal intermediates. Future causal research on the effects of long sleep should include a detailed assessment of psychiatric disease and socioeconomic status.

Keywords: Sleep duration, long sleep, depression

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INTRODUCTION

RECENT RESEARCH HAS CONSISTENTLY DEMONSTRATED THAT SLEEP DURATION CAN HAVE IMPORTANT EFFECTS ON HEALTH. OBSERVATIONAL STUDIES have found that reduced sleep is associated with an increased risk for morbidity and mortality. Experimental data suggest that sleep deprivation may alter neurohormonal regulation, thereby predisposing to disease.[1-3] Epidemiologic studies have also consistently demonstrated that prolonged sleep is statistically associated with significant morbidity as well as mortality.[4-14] In many studies, this association is even stronger than that found with short sleep.[4,7-10,12,14] Compared with the rate associated with 7 to 8 hours of sleep, the mortality rate associated with a long sleep duration is 30% to 50% greater. It is unclear whether the long sleep–mortality association is causal or simply reflects confounding by underlying factors that influence sleep habits. Unlike short sleep, there are no compelling hypotheses regarding the mechanism for the association between long sleep and disease. Moreover, there are few experimental data from which to make inferences. Nor is it clear what the causal intermediary or underlying confounder might be for this strong association. One proposed hypothesis is that depression (either as a confounder or as a causal intermediate) may explain the statistical association between long sleep and poor health.[15] Disturbed sleep patterns are a hallmark of depression, and sleep restriction has long been known to improve mood.[16] In addition, depression has become increasingly identified as an important risk factor for disease.[17-19] Comorbid sleep disorders, low socioeconomic status, preclinical medical disease, and a high level of inflammation have also been proposed as potential explanations for the association between long sleep and elevated mortality risk.

In order to better understand how prolonged sleep may impact health, we sought to better define health and social characteristics that are associated with long habitual sleep duration. We used data obtained from the Nurses Health II Study (NHS II) to investigate correlates of prolonged sleep in women. Combining measures of prevalence of these factors, the strength of their association with long sleep, and a range of plausible associations with mortality, we assessed the ability of each of these factors to produce a mathematical association between long sleep and mortality.

Disclosure Statement

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METHODS

Study Population

The NHS II is an ongoing prospective observational cohort study designed to examine associations between lifestyle factors and the occurrence of diseases in women. It was established in 1989 when 116,671 female registered nurses aged 25 to 46 years and free of cancer responded to a baseline questionnaire, representing 24% of those initially contacted. Follow-up questionnaires to ascertain lifestyle factors and occurrence of diseases have been mailed biennially since then, and the follow-up rate exceeds 90% of potential person-years.

For the current analysis, we studied responses to a questionnaire administered in 2001. This questionnaire included a question about average sleep duration. Participants were asked, "On average, over a 24-hour period do you sleep. . ." The available choices were less than 5, 5, 6, 7, 8, 9, or 10+ hours. This question has been previously validated against 1 week of sleep diaries in a similar cohort.[7] The study cohort consisted of 85,700 women who responded to this question. Because the distribution of many health and lifestyle variables has been found to have a U-shaped distribution relative to sleep duration, we restricted our analysis to the 60,028 women who reported sleeping on average at least 7 hours per day in order to identify differences between those who had long sleep (9 or 10+ hours) and those who had normal sleep patterns (7 or 8 hours).

Predictors

Psychiatric Factors

Current depressive symptoms were assessed using the 5-item Mental Health Inventory (MHI-5), 1 of the 8 health-related quality-of-life scales included in the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36).[20,21] The MHI-5 is scored from 0 to 100, in which higher-scoring participants enjoy better mental health, whereas those who score less than 52 are likely to satisfy the clinical diagnostic criteria for depression and related disorders.[22] For the present analysis, the MHI-5 score was considered a dichotomous indicator of the presence (MHI-5 score < 52) or absence (MHI-5 score ≥ 52) of depressive symptoms. Any history of depression was defined as the presence of current depressive symptoms, having had a 2-week or longer period of time when the individual felt sad, blue, or depressed every day for most of the day, or having ever sought treatment for depression from a physician or mental health specialist. Participants were also asked about current antidepressant use, either a selective serotonin reuptake inhibitor or another antidepressant, as well as benzodiazepines. Examples of each of these classes of drugs were provided on the questionnaire form.

Lifestyle Factors

Lifestyle factors included self-reported consumption of alcohol and caffeine, as well as current tobacco use. Physical activity and total caloric intake were calculated using previously validated activity and food-frequency questionnaires, respectively, and divided into quartiles.[23,24] Because dietary questionnaires were not administered on the 2001 survey, information regarding alcohol, caffeine, and caloric intake were taken from the 1999 survey.

Socioeconomic Factors

Socioeconomic factors included marital status (single, married, widowed, or divorced/separated), living situation (living alone or with others), number of children (0, 1, 2, ≥ 3), pretax household income ($< \$30{,}000$, \$30,000-\$40,000, \$40,000-\$50,000, \$50,000-\$74,999, \$75,000-\$99,999, $\geq \$100{,}000$), and employment status. The MacArthur Scale of Subjective Social Status was also used to assess socioeconomic status.[25] Briefly, participants were asked to rate their societal status by marking their ranking in society using a ladder with 10 rungs compared with both their community and with the United States as a whole. The average of these 2 scores was used as a measure of societal status, in which the higher the rung, the higher the self-perceived societal ranking.

Medical Factors

Obesity was defined as a body mass index greater than 30 kg/m^2, with the body mass index calculated from self-reported height and weight. Participants were asked whether they had ever been diagnosed by a physician as having a wide variety of medical disorders. All conditions were considered as dichotomous variables. Neurologic disorders considered included head trauma, seizures/epilepsy, cerebrovascular disease (stroke or transient ischemic attack), and multiple sclerosis. Endocrine disorders included hypothyroidism, hyperthyroidism, and diabetes. Cardiovascular disorders included hypertension and coronary artery disease (history of myocardial infarction, angina pectoris, coronary artery bypass surgery, or angioplasty). Rheumatologic conditions included systemic lupus erythematosus, rheumatoid arthritis, osteoarthritis, and herniated lumbar disk. Respiratory disorders included asthma and chronic obstructive pulmonary disease (emphysema or chronic bronchitis). Other disorders included a diagnosis of cancer (except nonmelanoma skin cancer) or inflammatory bowel disease (ulcerative colitis or Crohn disease).

Gynecologic Factors

Gynecologic factors included menopausal status, current pregnancy, and a diagnosis of premenstrual syndrome, as well as current use of either oral contraceptives or hormone replacement therapy.

Sleep Factors

Participants were asked if they had been diagnosed with restless legs syndrome, if they snored nightly, or if they performed shift work, which was defined as working a permanent night-shift schedule for more than 6 months at any time or working rotating shifts for 5 or more months in the past 2 years.

Statistical Analysis

All analyses were performed using SAS version 8.0 (SAS Institute, Cary, NC). Because our goal was to understand the increased mortality risk of long sleepers relative to normal sleepers that has been repeatedly reported in the literature, short sleepers were excluded from analyses, and binomial logistic regression was performed to identify factors associated with long sleep duration (9 or more hours), compared with normal sleep durations (7-8 hours). In order to assess the ability of each variable to alter

the association between long sleep and mortality, the confounding rate ratio (CRR) was computed. This parameter is the ratio of the unadjusted long sleep–mortality rate ratio (RR) to the adjusted RR. It should be noted that the CRR cannot distinguish between a confounder and a causal intermediate. If the variable is a confounder, then the CRR provides a measure of the degree of distortion produced by not accounting for differences in the distribution of this variable; if the variable is a causal intermediate, the CRR provides a measure of the degree of the long sleep–mortality causal association that is mediated via the intermediate variable. In either case, variables with a large CRR are of interest because they are most likely to explain the observed association in the literature. Of note, if no true causal association exists between long sleep and mortality (so that all third factors can only be confounders), the CRR is equal to the RR that will be estimated by a study that fails to account for the confounder.

The CRR is a function of the prevalence of the confounder, the degree of association between the confounder and long sleep, and the degree that the confounder increases the risk of mortality. For a dichotomous confounder:

$$CRR = \frac{q + OR \times RR^{*} \times p}{(q + OR \times p)(q + RR^{*} \times p)}$$

where p is the prevalence of the confounder, q = 1-p, OR is the odds ratio for association between the confounder and long sleep, and RR* is the mortality RR for the confounder.[26,27] This equation can be easily generalized for confounders with more than 2 categories.[28] Because our study does not provide a measure of the mortality RRs associated with the potential confounders, a sensitivity analysis was performed for a range of RRs between 1.25 and 4.0. For confounders with more than 2 categories, the range of RR of 1.25 and 4.0 was used for the comparison of the highest- to lowest-risk groups with a linear change assumed in the RRs across the intermediate categories.

RESULTS

Of the 85,700 women who reported sleep duration, 25,672 (30.0%) slept 6 hours or less per day, 55,449 (64.7%) slept 7 to 8 hours, and 4579 (5.3%) slept 9 or more hours. Average characteristics of the 3 groups are displayed in Table 1. A large number of the factors studied were found to have a U-shaped distribution with respect to sleep duration, whereby both short and long sleepers were more likely to have characteristics associated with poor health. Because our goal was to understand differences between those with a normal sleep duration and those with a long duration, subsequent analyses were restricted to the 60,028 women who reported sleeping on average at least 7 hours per day.

Psychiatric Factors

Questionnaire responses suggestive of depression were very common in this cohort (Table 2). Any history of depressive symptoms was found in 51% of the cohort, with nearly 7% of women having ongoing depressive symptoms. Depressive symptoms were strongly associated with long sleep (OR = 1.9, 95% confidence interval [CI[[1.7-2.0]). Ongoing symptoms of depression were even more strongly associated with long sleep. Those with past but not current depressive symptoms were 1.7 times more likely to have long sleep than were nondepressed women, whereas those with ongoing depressive symptoms were 2.9 times more likely to have long sleep. Depression severity was also assessed by medication use. Compared with women without depressive symptoms and not taking antidepressants, those with a history of depressive symptoms but not on antidepressant medication were 1.3 times more likely to have long sleep, and those with symptoms of depression and using antidepressants were 3.5 times more likely. Antidepressant use, itself, was also strongly associated with long sleep (OR = 3.1 [2.9-3.3]), and this association was present among those both with and without a history of depressive symptoms. The association with long sleep was similar in magnitude among those using selective serotonin reuptake inhibitors and those us-

Table 1—Baseline Characteristics

	Sleep Duration, h/day		
	≤ 6	7-8	≥ 9
Participants, no.	25,672	55,449	4579
Age, y	47.0 ± 4.6	46.7 ± 4.7	46.6 ± 4.7
Alcohol, g/d	3.5 ± 6.9	4.1 ± 7.3	4.3 ± 8.5
Smoking, %	11.2	7.6	8.4
Caffeine, mg/d	229 ± 209	218 ± 193	212 ± 194
Activity, METs/wk	17.1 ± 23.5	17.1 ± 20.5	14.8 ± 21.3
Caloric intake, kcal/d	1802 ± 574	1827 ± 552	1873 ± 580
Married, %	74.0	81.7	78.1
Children at home %	81.4	82.3	78.2
Living alone,%	10.2	7.7	9.8
Annual income < $50,000, %	18.3	15.2	23.7
Currently unemployed, %	8.2	12.5	25.6
History of depressive symptoms, %	53.1	49.6	64.7
Current depressive symptoms, %	11.0	6.1	12.2
Antidepressant use, %	15.7	16.7	38.2
Benzodiazepine use, %	3.6	2.8	7.8
Obesity, %	29.0	22.0	27.9
Diabetes, %	3.5	2.6	4.5
Hypothyroidism, %	12.3	10.9	15.0
Hyperthyroidism, %	2.2	1.9	2.0
Seizure, %	2.0	1.6	2.8
Head injury, %	12.4	10.8	13.0
Multiple sclerosis, %	0.9	0.8	2.8
Stroke, %	1.0	0.7	1.5
Coronary disease, %	2.6	1.6	3.0
Hypertension, %	21.2	16.7	20.7
SLE, %	0.9	0.7	1.9
Rheumatoid arthritis, %	3.2	2.4	3.7
Osteoarthritis, %	20.8	15.6	21.9
Herniated disc, %	9.2	6.8	9.1
Asthma, %	15.9	13.2	17.4
COPD, %	2.0	1.0	2.4
Cancer, %	5.3	5.1	6.0
IBD, %	2.4	1.6	2.7
Any medical disease, %	68.4	60.6	68.8
Pregnant, %	0.3	0.5	0.8
Postmenopausal, %	37.4	31.4	33.1
Premenstrual syndrome, %	14.3	13.0	18.5
Estrogen use, %	23.4	22.4	24.0
Restless legs syndrome, %	2.6	1.6	3.8
Snoring, %	7.7	6.5	10.1
Permanent night shift, %	13.9	7.4	9.8
Rotating night shift, %	9.3	5.2	5.7

Values expressed as percentage or mean ± SD. SLE refers to systemic lupus erythematosus; COPD, chronic obstructive pulmonary disease; IBD, inflammatory bowel disease.

Table 2—Psychiatric Factors and Long Sleep

	Prevalence, %[a]	OR	95% CI	Confounding Rate Ratio Mortality Rate Ratio[b] 1.25	1.5	2.0	4.0
Any history of depressive symptoms	49.6	1.86	1.75-1.98	1.03	1.06	1.10	1.18
Current depressive symptoms[c]	6.1	2.87	2.59-3.18				
No current depressive symptoms[c]	43.5	1.72	1.61-1.84				
Current antidepressant use[e]	15.4	3.50	3.25-3.77				
No current antidepressant use[e]	35.0	1.28	1.18-1.38				
Any antidepressant use	16.7	3.08	2.89-3.28	1.05	1.09	1.18	1.43
With history of depressive symptoms	30.6	2.75	2.54-2.97				
Without depressive symptoms	3.0	2.70	2.22-3.27				
SSRI use[d]	12.4	3.18	2.97-3.41				
Other antidepressant use[d]	5.7	3.33	3.03-3.65				
Benzodiazepine use	2.8	2.95	2.62-3.33	1.01	1.02	1.05	1.14

OR refers to odds ratio; CI, confidence interval; SSRI, selective serotonin reuptake inhibitor.
[a]Prevalence among those sleeping 7-8 hours per day.
[b]Confounding rate ratio calculated under the assumption that the mortality rate ratio (RR) for the factor in question ranges from 1.25 to 4.0.
[c]Compared with no history of depressive symptoms.
[d]Compared with no antidepressant use.

ing older antidepressants. Use of benzodiazepines, though not as common as antidepressant use, was also strongly associated with long sleep, nearly tripling the odds of this sleep characteristic. Each of these factors (depression, antidepressant use, and benzodiazepine use) was found to have a potentially substantial effect on the long sleep–mortality association. Assuming each factor doubled the risk of mortality, lack of control for depression would result in inflation of the long sleep RR for mortality by 10% and lack of control for antidepressant use would result in an 18% inflation. If these factors increased mortality risk by 4-fold, the effects would be even greater, with biases of 18%, 43%, and 14% produced from lack of adjustment in differences in depression, antidepressant use, and benzodiazepine use, respectively.

Lifestyle Factors

Lifestyle predictors of long sleep duration are presented in Table 3. No relationship between age and long sleep was found. On the other hand, a U-shaped association was found between sleep duration and alcohol consumption, in which both those who abstained from alcohol as well as heavy drinkers were more likely to be long sleepers than were those with moderate consumption. As might be expected, increasing amount of daily caffeine consumption and increasing physical activity were associated with decreasing risk of long sleep. The association between long sleep and caloric intake showed no consistent pattern, and current smoking appeared unrelated to long sleep. In general, lifestyle factors appeared to have little potential to affect any association between long sleep and mortality. Physical activity is the most

Table 3—Lifestyle Factors and Long Sleep

	Prevalence, %[a]	OR	95% CI	Confounding Rate Ratio Mortality Rate Ratio[b] 1.25	1.5	2.0	4.0
Age, y				1.00	1.00	1.00	1.01
< 40	9.6	1.00					
40-45	27.3	0.98	0.87-1.09				
45-50	35.2	0.95	0.85-1.06				
> 50	27.9	0.94	0.84-1.05				
Alcohol, g/d				1.02	1.02	1.03	1.05
0	38.0	1.00					
0-5	36.5	0.73	0.68-0.79				
5-15	19.7	0.72	0.66-0.79				
> 15	5.8	1.01	0.89-1.16				
Smoking	7.6	1.12	1.00-1.25	1.00	1.00	1.01	1.02
Caffeine				1.00	1.01	1.01	1.02
Quartile 1	25.2	1.00					
Quartile 2	24.9	0.95	0.87-1.04				
Quartile 3	25.2	0.98	0.90-1.07				
Quartile 4	24.8	0.87	0.79-0.95				
Physical activity				1.02	1.03	1.05	1.09
Quartile 1	23.3	1.00					
Quartile 2	25.1	0.71	0.65-0.77				
Quartile 3	25.9	0.63	0.58-0.68				
Quartile 4	25.7	0.60	0.55-0.65				
Caloric intake				1.01	1.01	1.02	1.03
Quartile 1	24.1	1.00					
Quartile 2	25.4	0.94	0.86-1.04				
Quartile 3	25.5	1.05	0.96-1.15				
Quartile 4	25.0	1.15	1.05-1.26				

OR refers to odds ratio; CI, confidence interval.
[a]Prevalence among those sleeping 7-8 hours per day.
[b]Confounding rate ratio calculated under the assumption that the mortality rate ratio for the factor in question ranges from 1.25 to 4.0.

influential of the lifestyle factors, with a CRR = 1.09, assuming a 4-fold greater mortality rate in the least-active to the most-active quartile.

Socioeconomic Status

In general, measures of social isolation were strongly associated with long sleep duration (Table 4). Living alone was associated with a 31% greater chance of being a long sleeper. Women who had never married were 37% more likely to have long sleep than married women, with a smaller association in women who were divorced or widowed. The likelihood of long sleep steadily decreased with an increasing number of children. Lack of employment was also strongly associated with long sleep (OR = 2.4 [2.3-2.6]), as were low income and low societal status. Women with a household income of $30,000 to $40,000 were twice as likely to have long sleep, and those making less than $30,000 were 3 times as likely as those with an income greater than $75,000. Those who perceived themselves to be in the bottom quartile of society had a 4.5 times greater odds of being a long sleeper than were those who believed they were in the top quartile. In terms of potential to affect the long sleep–mortality association, employment status was the most influential socioeconomic variable, with CRRs of 1.12 and 1.29, assuming mortality RRs of 2.0 and 4.0, respectively, for unemployment. Household income and perceived societal status had lesser potential, with CRRs of 1.05 and

Table 4—Lifestyle Factors and Long Sleep

	Prevalence, %[a]	OR	95% CI	Confounding Rate Ratio Mortality Rate Ratio[b] 1.25	1.5	2.0	4.0
Marital Status				1.01	1.01	1.03	1.06
Married	81.7	1.00					
Widowed	1.1	1.17	0.88-1.54				
Divorced	11.3	1.21	1.10-1.32				
Never married	5.9	1.37	1.22-1.54				
Children				1.01	1.02	1.03	1.07
0	17.7	1.00					
1	13.3	0.95	0.86-1.06				
2	40.6	0.77	0.71-0.84				
3 or more	28.4	0.69	0.63-0.76				
Living alone	7.7	1.31	1.18-1.45	1.01	1.01	1.02	1.05
Annual income, $				1.02	1.03	1.05	1.12
> 100,000	36.6	1.00					
75,000-100,000	21.3	1.01	0.91-1.11				
50,000-75,000	26.9	1.21	1.11-1.32				
40,000-50,000	8.6	1.43	1.27-1.61				
30,000-40,000	3.9	1.95	1.68-2.25				
< 30,000	2.7	3.07	2.65-3.55				
Unemployed	12.5	2.42	2.25-2.59	1.03	1.06	1.12	1.29
Social status, rung				1.01	1.02	1.04	1.09
7.5 -10.0	16.1	1.00					
5.0 - 7.5	70.4	0.95	0.87-1.03				
2.5 - 5.0	13.2	1.39	1.25-1.55				
0.0 - 2.5	0.4	4.46	3.36-5.92				

OR refers to odds ratio; CI, confidence interval.
[a]Prevalence among those sleeping 7-8 hours per day.
[b]Confounding rate ratio calculated under the assumption that the mortality rate ratio for the factor in question ranges from 1.25 to 4.0.

Table 5—Medical Factors and Long Sleep

	Prevalence, %[a]	OR	95% CI	Confounding Rate Ratio Mortality Rate Ratio[b] 1.25	1.5	2.0	4.0
Obesity	22.0	1.37	1.28-1.47	1.01	1.03	1.05	1.11
Diabetes	2.6	1.73	1.49-2.01	1.00	1.01	1.02	1.05
Hypothyroidism	10.9	1.45	1.33-1.58	1.01	1.02	1.04	1.09
Hyperthyroidism	1.9	1.05	0.84-1.30	1.00	1.00	1.00	1.00
Seizure	1.6	1.71	1.41-2.06	1.00	1.01	1.01	1.03
Head injury	10.8	1.24	1.13-1.35	1.01	1.01	1.02	1.05
Multiple sclerosis	0.8	3.66	2.99-4.47	1.01	1.01	1.02	1.06
Stroke	0.7	2.19	1.68-2.84	1.00	1.00	1.01	1.02
Coronary disease	1.6	1.88	1.57-2.26	1.00	1.01	1.01	1.04
Hypertension	16.7	1.31	1.21-1.41	1.01	1.02	1.03	1.08
SLE	0.7	2.87	2.27-3.64	1.00	1.01	1.01	1.04
Rheumatoid arthritis	2.4	1.57	1.33-1.85	1.00	1.01	1.01	1.04
Osteoarthritis	15.6	1.51	1.41-1.63	1.02	1.03	1.05	1.13
Herniated disc	6.8	1.37	1.23-1.52	1.01	1.01	1.02	1.06
Asthma	13.2	1.39	1.29-1.51	1.01	1.02	1.04	1.09
COPD	1.0	2.40	1.95-2.95	1.00	1.01	1.01	1.04
Cancer	5.1	1.20	1.06-1.37	1.00	1.00	1.01	1.03
IBD	1.6	1.71	1.42-2.07	1.00	1.01	1.01	1.03
Any medical disease	60.6	1.44	1.35-1.53	1.02	1.03	1.05	1.09

OR refers to odds ratio; CI, confidence interval; SLE, systemic lupus erythematosus; COPD, chronic obstructive pulmonary disease; IBD, inflammatory bowel disease.
[a]Prevalence among those sleeping 7-8 hours per day.
[b]Confounding rate ratio calculated under the assumption that the mortality rate ratio for the factor in question ranges from 1.25 to 4.0.

1.12 for income and 1.04 and 1.09 for societal status under the assumption of mortality RRs of 2.0 and 4.0.

Medical Disorders

In general, the presence of a physician-diagnosed medical condition increased the likelihood of being a long sleeper (Table 5). An exception to this rule was hyperthyroidism, in which no relationship with long sleep was found. The strongest associations with long sleep among medical disorders were observed with multiple sclerosis (OR = 3.7 [3.0-4.5]) and systemic lupus erythematosus (OR = 2.9 [2.3-3.6]). However, because of the rarity of these disorders, the CRRs of these disorders were small. The disorders with presumably the greatest mortality risk (cancer, coronary disease, and stroke) also did not have substantially high CRRs, even at a mortality RR of 4.0, due to their low prevalences. While the prevalences of disorders such as asthma and osteoarthritis were high enough to be considered important confounders, it is unlikely the mortality RRs for these disorders are greater than 1.25, resulting in CRRs of only 1.01 to 1.02. Overall, obesity appeared to be the medical condition with the greatest potential to affect the long sleep–mortality association with a CRR of 1.11 assuming obesity increases the mortality rate 4-fold.

Gynecologic Factors

Pregnancy was strongly associated with long sleep times (OR = 1.8 [1.3-2.5]), but, because of its relative rarity, it is unlikely to have an important effect on the association between long sleep and mortality (Table 6). The associations between menopausal status and sex-hormone use with long sleep were not strong enough to produce large CRRs. Based on prevalence and strength of association with long sleep, premenstrual syndrome would be of concern. However, this disorder is unlikely to greatly elevate mortality risk, so the relevant CRR is likely small. With a mortality RR as high as 1.25, the CRR is only 1.03.

Sleep Factors

Restless legs syndrome, snoring, and permanent night-shift work were all associated with long sleep, whereas working rotating night shifts was not (Table 6). Overall the moderate prevalences of the sleep factors resulted in, at most, moderate CRRs. Snoring had the greatest CRR, with values of 1.03 and 1.09, assuming mortality RRs of 2.0 and 4.0.

DISCUSSION

The presence of a U-shaped association between sleep duration and mortality rate, such that those individuals who sleep more or less than 7 hours per day are at higher risk of death, was first described more than 40 years ago.[29] Subsequently, many investigators have focused on the short-sleep portion of the curve, investigating the cognitive, psychological, metabolic, and immunologic effects of acute or chronic sleep deprivation. This research has bolstered the belief that adequate sleep is important for the maintenance of normal mental and physical function.

However, a growing number of population-based studies inves-

Table 6—Gynecologic and Sleep Factors and Long Sleep

	Prevalence, %[a]	OR	95% CI	Confounding Rate Ratio Mortality Rate Ratio[b] 1.25	1.5	2.0	4.0
Gynecologic Factors							
Pregnant	0.5	1.78	1.26-2.52	1.00	1.00	1.00	1.01
Postmenopausal	31.6	1.08	1.01-1.15	1.00	1.01	1.01	1.03
Premenstrual syndrome	13.4	1.52	1.40-1.64	1.01	1.03	1.05	1.12
estrogen use	22.5	1.10	1.02-1.18	1.00	1.01	1.01	1.03
Sleep Factors							
Restless legs syndrome	1.6	2.42	2.05-2.85	1.01	1.01	1.02	1.06
Snoring	6.5	1.62	1.46-1.79	1.01	1.02	1.03	1.09
Permanent night shift	7.4	1.36	1.23-1.51	1.01	1.01	1.02	1.06
Rotating night shift	5.3	1.09	0.95-1.25	1.00	1.00	1.00	1.01

OR refers to odds ratio; CI, confidence interval.
[a]Prevalence among those sleeping 7-8 hours per day.
[b]Confounding rate ratio calculated under the assumption that the mortality rate ratio for the factor in question ranges from 1.25 to 4.0.

tigating the effects of sleep on health have found that a prolonged sleep duration is also associated with an increased mortality risk. These findings have been replicated in the Cancer Prevention Study I and II, NHS, the first National Health and Nutrition Examination Survey, Framingham Study, and the Japan Collaborative Cohort Study.[4,6-8,10,30] In fact, in many of these studies, long sleep was associated with an even greater mortality risk than short sleep. Compared with those sleeping 5 hours, women reporting 9 hours of sleep had a 15% greater mortality risk in Cancer Prevention Study II, a 30% greater risk in NHS, and a 33% greater risk in the Japan Collaborative Cohort Study.[4,7,8]

Epidemiologic research also suggests that the association between long sleep and mortality is not limited to 1 cause of death. Both the Cancer Prevention Study II and NHS studies reported that prolonged sleep was associated with an across-the-board increase in risk over a wide range of specific causes of death.[7,8] Prolonged sleep has been linked to an increased risk for obesity, diabetes, heart disease, and stroke, suggesting several pathways may be present.[6,8,11,12,14]

The reason for these strong associations is not clear. There have been virtually no experimental studies to assess the health effects of prolonged sleep, so hypotheses on the physiologic effects of long sleep are limited. Many have speculated that this association is due to residual confounding, despite the large number of covariates that many of these studies have incorporated in their multivariate modeling. Clearly, a confounder causing such a large effect must be prevalent, strongly associated with prolonged sleep duration, and strongly associated with poor health outcomes.

This study, by combining data on the first 2 prerequisites (prevalence and association with long sleep) with a reasonable range of estimates for the third requirement (association with mortality), attempts to identify the variables that could produce the greatest alterations in the long sleep–mortality association and, therefore, result in a substantial statistical association.

One caveat that should be made clear is that this analysis, because of its cross-sectional nature, does not distinguish between causal associations, in which the third factor is on the causal pathway, and noncausal associations, in which the third factor is a confounder. The statistical meaning of the CRR is identical in either circumstance: it is the ratio of the unadjusted long sleep–mortality RR to the adjusted RR and, therefore, determines to what degree a factor is responsible for the mathematical association between long sleep and mortality. If the factor is on a causal pathway between long sleep and death (ie, long sleep causes the factor), then the CRR assesses to what degree the association is mediated through that factor. On the other hand, if the factor is a cause of long sleep, then it is a confounder, and the CRR assesses the distortion in the true causal association produced by that factor. Further biologic research is required to differentiate whether variables that importantly affect estimates of the association between long sleep and mortality are causes or consequences of long sleep duration.

The association between long sleep and mortality in the literature is fairly strong. Compared with normal sleepers, those sleeping 9 hours had an adjusted mortality RR of 1.27 to 1.29 in Cancer Prevention Study I, 1.17 to 1.23 in Cancer Prevention Study II, 1.3 in National Health and Nutrition Examination Survey I, 1.40 in NHS, 1.27 to 1.57 in Japan Collaborative Cohort Study, and 1.5 to 1.8 in the Framingham Study, with even stronger associations in those sleeping 10 or more hours.[4,6-8,10,30] Thus, if no causal association between long sleep and mortality exists, a confounder (or set of confounders) that was not adequately measured in these studies must have a CRR on the order of 1.3 to 1.5 to be responsible for the RRs that have been reported in the literature. While many factors are associated with long sleep, our analyses demonstrate that the list of factors capable of producing a CRR high enough to produce the reported long sleep–mortality associations is much more limited.

A broad range of factors was assessed for their association with long sleep, including demographic, lifestyle, socioeconomic, medical, psychological, and sleep-related variables. The a priori hypotheses were that prolonged sleep might be related to depression, social isolation, or chronic medical diseases, or a combination thereof. In each case, the relationship may be causal in either direction. Long sleep times may interfere with the development of interpersonal relationships and educational or job successes, but, alternatively, a lack of such activities would allow for more time sleeping. Chronic medical conditions may limit other activities, thereby facilitating longer sleep. In addition, inflammatory conditions might produce long sleep through the soporific effects of elevated cytokines.[31,32] However, the opposite causal relationship may also be posited. Habitual long sleepers appear to have longer biologic nights, characterized by longer times with elevated serum melatonin and increasing levels of serum cortisol, as well as more time with a depressed body temperature.[33] These differences may have adverse effects on immune function or other biologic processes. In addition, long sleep durations may lead to complications of immobility, such as a prothrombotic state.

A wide range of variables were associated with long sleep, including numerous medical conditions, pregnancy, sleep disorders, low levels of exercise, extremes of alcohol intake, and measures of social isolation. Although the magnitude of some of these associations was quite large, e.g., multiple sclerosis and lupus, the rarity of these disorders makes them unable to explain the strong association of sleep time to mortality reported in the literature. Depression-related measures, on the other hand, both because of their high prevalence and strong association with long sleep,

appear to be the most likely to have a strong effect on the long sleep–mortality association, whether as a confounder or an intermediate variable in the causal pathway. Long sleep has also been strongly associated with depression and depressive symptoms in other cross-sectional analyses.[4,7,34] In the Japan Collaborative Cohort Study, having 2 or more depressive symptoms was more than twice as likely among those sleeping 10 hours compared with 8 hours.[4]

The exact CRR for depression clearly depends on the strength of its association with mortality. Depression has been strongly associated with poor health outcomes, including an elevated risk for heart disease, cancer, and mortality, with rate ratios in the 1.5 to 2.0 range.[17-19] Thus, the CRR for depression is likely in the range of 1.06 to 1.10. Therefore, poor control of differences in the prevalence of depression between long sleepers and normal sleepers may have an important effect on estimation of the long sleep–mortality association. These data strengthen the hypothesis that depression plays a fundamental role in linking long sleep with disease. Further research is still needed to understand whether depression is a confounder or causal intermediate in the association of long sleep with mortality. An abnormal sleep pattern, including prolonged sleep, is a diagnostic criterion for depression.[35] Sleep restriction improves depression,[16, 36,37] however, and self-report of "sleeping too much" has been reported as an independent predictor for the development of major depression 1 year later.[38] These observations suggest that depression could be, to some degree, a causal intermediate between long sleep and mortality.

The use of antidepressant medications was also strongly associated with long sleep times. In this setting, antidepressant use may simply serve as a surrogate marker for more-severe depression. However, the strong association between antidepressant use and long sleep in analyses stratified for depression suggests that antidepressants may themselves have a soporific effect. Interestingly, the strength of association was similar for selective serotonin reuptake inhibitors and the older antidepressants, despite the clinical belief that older agents such as trazodone and tricyclic agents are much more sedating. Another explanation of this finding is that healthcare providers interpret long sleep as a sign of depression and try to treat this symptom with antidepressants. Clearly, more research into the relationships between sleep, depression, and antidepressant use is required.

Based on our results, measures of low socioeconomic status, such as lack of employment, low household income, or low perceived societal status, were also strongly associated with long sleep. The CRR for employment status was of similar magnitude to that of depression. Whereas the CRRs for income and perceived societal status were lower, this was in large part due to the low prevalence of the lowest classes of these variables in this relatively homogenous cohort of educated healthcare professionals. The CRRs for these factors in the general population would likely be much greater. Low socioeconomic status is also strongly associated with increased disease risk, due to both lack of access to health care as well as poorer quality of care. Thus, understanding the associations between long sleep and low socioeconomic status, as well as detailed measurements of socioeconomic status, in future epidemiologic studies of sleep duration will be vital in fully understanding whether long sleep time causes excess mortality.

Although medical disorders were associated with increased sleep time, these associations were relatively weak, except for certain rare disorders. Grouping together all medical disorders and assuming they double the mortality rate results in a CRR of only 1.05. Certain diseases such as cancer, heart disease, and stroke may be more strongly associated with death, but even assuming an RR of 4 results in CRRs of 1.03, 1.04, and 1.02, respectively, for these diseases. Although, in populations with a high prevalence of these conditions, their impact might be greater, these results make the hypothesis that the observed long sleep–mortality association is due to confounding by underlying medical disorders less likely.

There are several limitations to this study that should be noted. Sleep duration was obtained by subjective report to a questionnaire. We have previously demonstrated that questionnaire responses correlate well with sleep diaries.[7] However, whether long sleep represents an increase in actual time spent sleeping or just increased time in bed is not clear because no objective measurement of sleep was attempted. Nonetheless, because all of the published epidemiologic associations of long sleep with adverse health outcomes have been based on subjective reports of sleep, we believe this work has direct relevance in explaining those findings. Further research is needed to validate questionnaire reports of prolonged sleep with objective measures such as actigraphy.

Second, information about sleep-duration predictors was also based on questionnaire reports and so is susceptible to misclassification. However, the fact that our cohort was a medically educated population should limit the extent of this misclassification. There is also no reason to believe that there were different levels of misclassification between average and long sleepers so that the effect of misclassification would only tend to weaken associations. Thus, the true association of the measures assessed in this work with long sleep may be underestimated.

Third, we did not have actual data on the mortality RRs for the various factors considered in this study. Instead, we were forced to use a range of RR estimates between 1.25 and 4.0 to generate the CRRs. This range, we believe, covers the plausible RRs for most factors associated with disease. For example, one of the best studied risk factors for disease, cigarette smoking, had an estimated mortality rate ratio of 1.68 in the original Surgeon General's report warning on the dangers of smoking.[39] More recently in the Cancer Prevention Study II cohort, the RR for smoking was estimated at 1.8 in women and 2.1 in men.[40] Thus, although lack of knowledge on the exact mortality RR for each factor prevents us from precisely estimating the true CRR, we believe our ability to identify those variables with the capacity to importantly change the statistical association between long sleep and mortality is preserved.

Fourth, although the CRR is robust when utilized to assess the effect of a confounder, use of the CRR may provide a biased estimate of the degree to which the effect of long sleep is mediated through a causal intermediate.[41] However, because the goal of our study was to provide insight into which factors are most likely to be responsible for the long sleep–mortality association, we believe a qualitative interpretation of our results is still possible and valid.

Finally, our analyses considered the possibility of only a single confounder or causal intermediate. It is likely that multiple confounding, intermediate factors, or a combination of confounding and intermediate factors exist and that they may interact in nonlinear ways to affect the long sleep–mortality association.

Although estimating the magnitude of effect that multiple confounders would have is beyond the scope of this work, we believe that the factors with the greatest effect in univariate analyses are also the most likely to be involved in causing large changes in a scenario of multiple interacting factors.

Overall, this work suggests that there are many predictors of a prolonged sleep duration that could potentially explain the statistical association between long sleep and mortality. However, when considered from the standpoint of confounding RRs, which rely on the strength of association with long sleep, prevalence in the population, and the strength of association with mortality, the number of possible explanations is greatly narrowed. Chief among the candidates are depression and low socioeconomic status. Future research on the health effects of long sleep should focus on the relationships between sleep habits, depression, and socioeconomic status.

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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, Tasali E, Penev P, Van Cauter E. Brief communication: 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.
3. Spiegel K, Leproult R, L'Hermite-Baleriaux M, Copinschi G, Penev PD, 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.
4. Tamakoshi A, Ohno Y. Self-reported sleep duration as a predictor of all-cause mortality: results from the JACC study, Japan. Sleep 2004;27:51-4.
5. Wingard DL, Berkman LF. Mortality risk associated with sleeping patterns among adults. Sleep 1983;6:102-7.
6. Qureshi AI, Giles WH, Croft JB, Bliwise DL. Habitual sleep patterns and risk for stroke and coronary heart disease: a 10-year follow-up from NHANES I. Neurology 1997;48:904-11.
7. Patel SR, Ayas NT, Malhotra MR, et al. A prospective study of sleep duration and mortality risk in women. Sleep 2004;27:440-4.
8. Kripke DF, Garfinkel L, Wingard DL, Klauber MR, Marler MR. Mortality associated with sleep duration and insomnia. Arch Gen Psychiatry 2002;59:131-6.
9. Kojima M, Wakai K, Kawamura T, et al. Sleep patterns and total mortality: a 12-year follow-up study in Japan. J Epidemiol 2000;10:87-93.
10. Kripke DF, Simons RN, Garfinkel L, Hammond EC. Short and long sleep and sleeping pills. Is increased mortality associated? Arch Gen Psychiatry 1979;36:103-16.
11. Gottlieb DJ, Punjabi NM, Newman AB, et al. Association of sleep time with diabetes mellitus and impaired glucose tolerance. Arch Intern Med 2005;165:863-7.
12. 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.
13. 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.
14. 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.
15. Youngstedt SD, Kripke DF. Long sleep and mortality: rationale for sleep restriction. Sleep Med Rev 2004;8:159-74.
16. van den Burg W, van den Hoofdakker RH. Total sleep deprivation on endogenous depression. Arch Gen Psychiatry 1975;32:1121-5.
17. Ariyo AA, Haan M, Tangen CM, et al. Depressive symptoms and risks of coronary heart disease and mortality in elderly Americans. Cardiovascular Health Study Collaborative Research Group. Circulation 2000;102:1773-9.
18. Ferketich AK, Schwartzbaum JA, Frid DJ, Moeschberger ML. Depression as an antecedent to heart disease among women and men in the NHANES I study. National Health and Nutrition Examination Survey. Arch Intern Med 2000;160:1261-8.
19. Penninx BW, Guralnik JM, Pahor M, et al. Chronically depressed mood and cancer risk in older persons. J Natl Cancer Inst 1998;90:1888-93.
20. Ware JE, Snow KK, Kosinski M, Gandek B. SF-36 health survey: Manual interpretation and guide. Boston: Nimrod Press, 1993.
21. McHorney CA, Ware JE, Jr., Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. Med Care 1993;31:247-63.
22. Cannuscio CC, Jones C, Kawachi I, Colditz GA, Berkman L, Rimm E. Reverberations of family illness: a longitudinal assessment of informal caregiving and mental health status in the Nurses' Health Study. Am J Public Health 2002;92:1305-11.
23. Salvini S, Hunter DJ, Sampson L, et al. Food-based validation of a dietary questionnaire: the effects of week-to-week variation in food consumption. Int J Epidemiol 1989;18:858-67.
24. Wolf AM, Hunter DJ, Colditz GA, et al. Reproducibility and validity of a self-administered physical activity questionnaire. Int J Epidemiol 1994;23:991-9.
25. Adler NE, Epel ES, Castellazzo G, Ickovics JR. Relationship of subjective and objective social status with psychological and physiological functioning: preliminary data in healthy white women. Health Psychol 2000;19:586-92.
26. Flanders WD, Khoury MJ. Indirect assessment of confounding: Graphic description and limits on effect of adjusting for covariates. Epidemiology 1990;1:239-46.
27. Lin DY, Psaty BM, Kronmal RA. Assessing the sensitivity of regression results to unmeasured confounders in observational studies. Biometrics 1998;54: 948-63.
28. Greenland S. Quantitative methods in the review of epidemiologic literature. Epidemiol Rev 1987;9:1-30.
29. Hammond EC. Some Preliminary Findings on Physical Complaints from a Prospective Study of 1,064,004 Men and Women. Am J Public Health Nations Health 1964;54:11-23.
30. Gottlieb DJ, Schulman DA, Nam BH, D'Agostino RA, Kannel WA. Sleep duration predicts mortality: the Framingham study. Sleep 2002;25:A108.
31. Vgontzas AN, Papanicolaou DA, Bixler EO, Kales A, Tyson K, Chrousos GP. Elevation of plasma cytokines in disorders of excessive daytime sleepiness: role of sleep disturbance and obesity. J Clin Endocrinol Metab 1997;82:1313-6.
32. Vgontzas AN, Zoumakis E, Bixler EO, et al. Adverse effects of modest sleep restriction on sleepiness, performance, and inflammatory cytokines. J Clin Endocrinol Metab 2004;89:2119-26.
33. Aeschbach D, Sher L, Postolache TT, Matthews JR, Jackson MA, Wehr TA. A longer biological night in long sleepers than in short sleepers. J Clin Endocrinol Metab 2003;88:26-30.
34. Hartmann E, Baekeland F, Zwilling GR. Psychological differences between long and short sleepers. Arch Gen Psychiatry 1972;26:463-8.
35. Diagnostic and Statistical Manual of Mental Disorders, DSM-IV-

TR: Text Revision. Washington: American Psychiatric Publishing, Inc.; 2000.
36. Schilgen B, Tolle R. Partial sleep deprivation as therapy for depression. Arch Gen Psychiatry 1980;37:267-71.
37. Papadimitriou GN, Christodoulou GN, Katsouyanni K, Stefanis CN. Therapy and prevention of affective illness by total sleep deprivation. J Affect Disord 1993;27:107-16.
38. Ford DE, Kamerow DB. Epidemiologic study of sleep disturbances and psychiatric disorders. An opportunity for prevention? JAMA 1989;262:1479-84.
39. US Public Health Service. Smoking and Health: Report of the Advisory Committee to the Surgeon-General of the Public Health Service. US Department of Health, Education, and Welfare, Public Health Service, PHS Publication No. 1103; 1964.
40. Thum MJ, Day-Lally C, Myers et al. Trends in tobacco smoking and mortality from cigarette use in Cancer Prevention Studies I (1959 through 1965) and II (1982 through 1988). In: Shopland DR, Burns DM, Garfinkel L, Samet JM, eds). Changes in cigarette-related disease risks and their implication for prevention and control. Smoking and Tobacco Control Monograph No. 8. Bethesda: US Department of Health and Human Services, Public Health Service, National Institutes of Health, National Cancer Institute, NIH Publication No. 97-4213; 1997:305-82.
41. Robins JM, Greenland S. Identifiability and exchangeability for direct and indirect effects. Epidemiology 1992;3:143-55.