Sleep Duration and Biomarkers of Inflammation

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Introduction: Extremes of sleep duration have been associated with adverse health outcomes. The mechanism is unclear but may be related to increased inflammation. We sought to assess the association between sleep duration and inflammatory biomarkers.

Methods: A total of 614 individuals from the Cleveland Family Study completed questionnaires about sleep habits and underwent polysomnography. A morning fasting blood sample was assayed for 5 inflammatory cytokines.

Results: In this cohort, mean (SD) habitual sleep duration based on self-report was 7.6 (1.6) h and mean sleep duration by polysomnography (PSG) on the night prior to blood sampling was 6.2 (1.3) h. After adjusting for obesity and apnea severity, each additional hour of habitual sleep duration was associated with an 8% increase in C-reactive protein (CRP) levels (P = 0.004) and 7% increase in interleukin-6 (IL-6) levels (P = 0.0003). These associations were independent of self-reported sleepiness. In contrast, PSG sleep duration was inversely associated with tumor necrosis factor alpha (TNFα) levels. For each hour reduction in sleep, TNFα levels increased by 8% on average (P = 0.02). Sleep duration was not associated with IL-1 or IL-10.

Conclusions: Increases in habitual sleep durations are associated with elevations in CRP and IL-6 while reduced PSG sleep duration is associated with elevated TNFα levels. Activation of pro-inflammatory pathways may represent a mechanism by which extreme sleep habits affect health.

Keywords: Sleep duration, inflammation, cytokine, C-reactive protein, interleukin-6, tumor necrosis factor

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MOUNTING EVIDENCE FROM BOTH OBSERVATIONAL AND EXPERIMENTAL RESEARCH SUGGESTS SLEEP DURATION PLAYS AN IMPORTANT ROLE IN HEALTH. Studies suggest both short and extended durations of sleep are associated with increased risk for all-cause mortality, coronary heart disease, diabetes, and obesity.[1-5] The mechanisms by which altered sleep duration affects health are unclear, but experimental studies suggest altered sleep may impact levels of cytokines known to be important in regulating inflammation. Experimental sleep deprivation has been shown to acutely elevate pro-inflammatory cytokine levels including C-reactive protein (CRP) and interleukin-6 (IL-6).[6-8] However, it is not clear whether this pro-inflammatory effect observed with short-term sleep deprivation experiments persists chronically. While one week of modest sleep restriction has been associated with elevations in IL-6 and tumor necrosis factor alpha (TNFα),[9] a large population based study found no relationship between habitual sleep duration in the long term and CRP levels.[10] Because chronic elevations in cytokines such as CRP and IL-6 are associated with an increased risk of adverse health outcomes such as diabetes and heart disease,[11-13] any effect of sleep duration on regulation of these cytokines could have important long-term health effects.

In this study, we sought to use a well-characterized cohort with standardized polysomnography (PSG) that allowed careful adjustment for sleep apnea severity, to examine whether an association exists between sleep duration and inflammatory mediators that might explain the associations between sleep duration and disease.

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METHODS

Subjects

The Cleveland Family Study is a longitudinal family-based epidemiological cohort designed to study the genetics of obstructive sleep apnea (OSA). Details on recruitment of this cohort have been previously described.[14,15] Briefly, index probands with a laboratory confirmed diagnosis of OSA and neighborhood controls, along with their spouses and relatives were recruited. A subset of 735 individuals was selected for detailed phenotyping based on expected genetic informativity by choosing pedigrees where siblings had extremes (either high or low) of apnea hypopnea index (AHI). A more detailed explanation of the selection scheme has been previously published.[16] Participants younger than 16 years of age and those with comorbid conditions that might influence inflammation were excluded from this analysis. The protocol was approved by the University Hospitals Case Medical Center institutional review committee, and all participants provided written informed consent.

Phenotype Collection

Sleep duration was assessed in 2 ways. Self-reported habitual sleep time was calculated based on the response to the question, "How many hours of sleep do you usually get at night?" Separate responses were obtained for weekdays and weekends and a weighted measure was calculated as: 5/7*(weekday sleep) +

2/7*(weekend sleep). Standardized attended 14-channel overnight laboratory PSG was performed, using both oronasal thermocouple and nasal pressure to assess airflow and inductive plethysmography to assess respiratory effort (Compumedics E series, Abbotsford, AU). Sleep stages were manually scored in 30-sec epochs using standard criteria.[17] PSG sleep time was obtained by summing the time spent in epochs scored as any stage of sleep during the period from "lights off" (approximately 20:00) to "lights on" (approximately 07:00). Apneas and hypopneas were defined using Sleep Heart Health Study criteria, modified to include consideration of the nasal pressure signal.[18] The AHI was computed by dividing the number of respiratory events, each associated with a 3% desaturation, by the total sleep time.

Measurements of height and weight as well as waist circumference were made in duplicate and averaged. Body mass index (BMI) was computed as the ratio of weight to height squared. Medical history and medication use were obtained by self-report. Participants with fasting glucose ≥ 126 mg/dL, 2 hour glucose ≥ 200 mg/dL on oral glucose tolerance testing, or taking hypoglycemic medications were classified as having diabetes. The Epworth Sleepiness Scale (ESS) was used to assess levels of sleepiness.[19]

Venous blood sampling was performed between 07:00 and 08:00 following the polysomnogram and an overnight fast. Samples were centrifuged, aliquoted, and stored at −80°C until assayed for CRP, IL-6, TNFα, interleukin-1β (IL-1), and interleukin-10 (IL-10) at the University of Vermont Clinical Biochemistry Laboratory. A high sensitivity immunonephelometric assay (Dade Behring BN II; Deerfield, IL) was used to measure CRP with an interassay coefficient of variation (CV) of 4.8%. IL-6 was measured by ultra-sensitive ELISA (R&D Systems, Minneapolis, MN) with an interassay CV of 18.0%. TNFα was measured using the Human Serum Adipokine Panel B LINCOplex Kit (Linco Research, Inc.; St. Charles, MO) while IL-1 and IL-10 were measured using the Human Cytokine/Chemokine LINCOplex Kit. Interassay CV ranges from 9.5% to 21% for TNFα, 11.3% to 19.9% for IL-1, and 12% to 22% for IL-10.

Statistical Analysis

All cytokine levels were log transformed prior to analysis to approximate a normal distribution. The ability of each of the 2 sleep duration variables, habitual sleep duration based upon sleep questionnaire and total sleep time ascertained by PSG on the night prior to phlebotomy, to predict biomarker levels was considered through the use of linear mixed effects models in which family was included as a random effect to account for intra-familial correlation. All regression models were adjusted for age, sex, race, BMI, waist circumference, and AHI. Because sleep duration has been reported to have a parabolic relationship with obesity,[5] a BMI squared term was also included in all analyses. In addition, a sleep duration squared term was used to test for a quadratic relationship between sleep duration and cytokine levels. To further investigate a possible nonlinear relationship between sleep duration and cytokine levels, analyses were also performed modeling the sleep duration measures as categorical variables using generalized estimating equations with an exchangeable within-family correlation structure. Habitual sleep duration categories were defined as short (< 7 h), average (7-8 h), and long (> 8 h); PSG sleep duration categories were also defined as short (< 6 h), average (6-7 h) ,and long (> 7 h). The cutpoints used to define short, average, and long categories for each sleep measure were chosen to approximate tertiles. For the categorical models, post hoc comparisons were made to the average sleep duration group only if the global P-value was significant at $P < 0.05$. All results were back transformed from the log scale in order to provide slopes (the percent change in cytokine level per hour of sleep) for linear models and geometric means for the categorical models. All analyses were conducted with SAS version 9.1.3 (Cary, NC).

RESULTS

Of the 735 participants, 91 were excluded for age < 16 years, 16 for the presence of severe comorbid diseases (collagen vascular disease, multiple sclerosis, cirrhosis, end-stage renal disease), and 14 for use of oral steroids, leaving 614 subjects available for analysis. Demographic characteristics of the study population by sleep duration are displayed in Table 1. Mean (SD) habitual sleep duration was 7.6 (1.6) h and mean PSG sleep duration on the night prior to blood sampling was 6.2 (1.3) h. The distribution of habitual sleep duration was 31% short, 36% average, and 33% long, while for PSG sleep duration, the distribution was 41% short, 37% average, and 22% long. Of note, habitual sleep duration did not predict PSG sleep duration ($P = 0.66$). Those with long sleep durations, assessed by self-report or PSG, were significantly younger. With respect to habitual sleep duration, both short and long sleepers were heavier than 7-8 hour sleepers. In contrast, long sleep duration during PSG was associated with less obesity. While no clear association was found between habitual sleep duration and medical comorbidity, short PSG sleep duration was associated with an increased prevalence of diabetes, hypertension, and OSA.

In analyses adjusted for age, sex, race, BMI, waist circumference, and AHI, longer habitual sleep duration was associated with elevated levels of pro-inflammatory cytokines (Table 2). For every additional hour in sleep duration, CRP levels increased by 8% ($P = 0.004$) and IL-6 levels increased by 7% ($P = 0.0003$). In addition, TNFα levels increased by 5% for each additional hour of sleep, although this effect was of borderline statistical significance ($P = 0.057$). No evidence for a U-shaped association was found, in that the quadratic sleep term was not significant in any of these models. No significant relationship between habitual sleep duration and IL-1 or IL-10 levels was observed. Adjusted geometric means for CRP, IL-6, and TNFα by sleep duration category are shown in Table 3. Again, CRP and IL-6 levels were found to increase in a linear fashion with increasing sleep duration ($P = 0.01$ and $P = 0.002$ for tests of linear trend respectively).

Several secondary and sensitivity analyses were performed to assess the robustness of these associations. First, because elevated cytokine levels have been proposed to lead to an increased sleep drive,[20] we assessed whether the association between increased habitual sleep durations and elevated levels of CRP and IL-6 could be explained by sleepiness. In fact, the strength of association was unaffected by adjustment for Epworth score. In ESS-adjusted analyses, each additional hour of sleep was associated with an 8% increase in CRP levels (P =

Table 1—Subject Characteristics Stratified by Both Habitual and PSG Sleep Duration

	Habitual Sleep Duration				PSG Sleep Duration			
	Short: < 7 h (n=189)	Average: 7-8 h (n=218)	Long: > 8 h (n=202)	P-value	Short: < 6 h (n=249)	Average: 6-7 h (n=227)	Long: > 7 h (n=135)	P-value
Age	46.1 ± 14.4	47.5 ± 17.4	41.3 ± 18.4	0.0007	52.3 ± 17.1	41.4 ± 15.4	37.6 ± 14.9	< 0.0001
Male gender	90 (47.6%)	99 (45.4%)	86 (42.6%)	0.48	123 (49.4%)	98 (43.2%)	55 (40.7%)	0.15
African American race	120 (63.5%)	109 (50.0%)	106 (52.5%)	0.27	134 (53.8%)	124 (54.6%)	81 (60.0%)	0.41
BMI (kg/m^2)	34.9 ± 9.7	32.1 ± 8.7	33.9 ± 9.1	0.018	34.1 ± 8.8	34.2 ± 10.0	31.5 ± 8.1	0.005
Waist circumference (cm)	103.1 ± 20.1	98.5 ± 20.7	100.7 ± 19.2	0.06	103.4 ± 20.1	100.9 ± 20.3	95.3 ± 18.8	0.0006
Obese (BMI ≥ 30 kg/m^2)	126 (66.7%)	113 (51.8%)	130 (64.4%)	0.015	167 (67.1%)	137 (60.4%)	67 (49.6%)	0.003
Diabetes mellitus	42 (22.2%)	48 (22.0%)	40 (20.0%)	0.81	74 (29.7%)	39 (17.3%)	16 (11.9%)	< 0.0001
Cardiovascular disease	28 (15.0%)	28 (12.9%)	29 (14.6%)	0.81	39 (15.8%)	27 (12.0%)	19 (14.4%)	0.54
Hypertension	70 (37.0%)	90 (41.3%)	71 (35.2%)	0.30	122 (49.0%)	76 (33.5%)	33 (24.4%)	< 0.0001
Lipid lowering agents	31 (16.4%)	29 (13.3%)	25 (12.4%)	0.47	44 (17.7%)	27 (11.9%)	13 (9.6%)	0.05
ESS Score	10.0 ± 5.1	8.5 ± 4.6	8.5 ± 5.1	0.004	8.5 ± 4.8	8.9 ± 5.1	10.0 ± 4.9	0.03
ESS ≥ 10	78 (41.3%)	68 (31.2%)	68 (33.7%)	0.14	78 (31.3%)	77 (33.9%)	59 (43.7%)	0.08
AHI				0.09				0.001
0-5	75 (39.6%)	118 (54.4%)	101 (50.0%)		96 (38.6%)	122 (53.7%)	76 (56.3%)	
5-15	57 (30.2%)	46 (21.2%)	45 (22.3%)		75 (30.1%)	39 (17.2%)	35 (25.9%)	
≥ 15	57 (30.2%)	53 (24.4%)	56 (27.7%)		78 (31.3%)	66 (29.1%)	24 (17.8%)	
Habitual sleep duration (h)	5.9 ± 1.1	7.5 ± 0.3	9.3 ± 1.1	—	7.5 ± 1.7	7.6 ± 1.6	7.7 ± 1.7	0.40
PSG sleep duration (h)	6.2 ± 1.2	6.0 ± 1.3	6.2 ± 1.3	0.81	5.0 ± 1.0	6.5 ± 0.3	7.7 ± 0.6	—
Percent slow wave sleep	17.5 ± 10.6	18.0 ± 10.5	18.3 ± 10.9	0.64	17.5 ± 11.6	17.8 ± 10.2	18.6 ± 9.6	0.22

Habitual sleep duration data were missing for 5 subjects. Mean ± standard deviation or n (proportion) reported for each variable. AHI: apnea-hypopnea index; BMI: body mass index; ESS: Epworth sleepiness scale; PSG: polysomnography.

Table 2—Association Between Continuous Measures of Sleep Duration and Cytokine Levels

Cytokine	Habitual Sleep Duration				PSG Sleep Duration			
	Unadjusted		Adjusted*		Unadjusted		Adjusted*	
	Slope (95% CI)	P-value	Slope (95% CI)	P-value	Slope (95% CI)	P-value	Slope (95% CI)	P-value
CRP	1.06 (0.99, 1.13)	0.09	1.08 (1.03, 1.14)	0.004	0.88 (0.81, 0.95)	0.002	0.98 (0.91, 1.06)	0.68
TNFα	1.04 (0.99, 1.09)	0.15	1.05 (1.00, 1.10)	0.057	0.88 (0.82, 0.93)	< 0.0001	0.92 (0.86, 0.98)	0.02
IL-1	1.02 (0.95, 1.11)	0.55	1.01 (0.93, 1.10)	0.79	1.12 (1.01, 1.24)	0.04	1.02 (0.91, 1.14)	0.74
IL-6	1.05 (1.01, 1.09)	0.02	1.07 (1.03, 1.10)	0.0003	0.91 (0.87, 0.96)	0.0004	0.99 (0.94, 1.04)	0.64
IL-10	0.98 (0.90, 1.06)	0.59	0.98 (0.90, 1.07)	0.65	1.00 (0.90, 1.11)	0.99	0.98 (0.87, 1.10)	0.70

All analyses model the effect of each additional hour of sleep on the log of cytokine levels. Thus, slopes represent the multiplicative change in cytokine level associated with an additional hour of sleep. PSG: polysomnography; CRP: C-reactive protein; TNFα: tumor necrosis factor alpha; IL: interleukin.
*Adjusted for age, sex, race, body mass index, body mass index squared, waist circumference, and apnea hypopnea index.

0.004) and 6% increase in IL-6 levels ($P < 0.001$). Because statin drugs can lower both CRP and IL-6 levels, additional analyses were done adjusting for use of lipid lowering agents and excluding the 85 subjects taking one of these medications. No change in the strength of the association was found with either analysis. Similarly, excluding those with diabetes had no appreciable effect.

The relationship between cytokine levels and PSG sleep duration differed substantially to that found with habitual sleep duration (Table 2). In unadjusted analyses, each hour reduction in PSG sleep duration was associated with a 12% elevation in both CRP and TNFα levels, as well as a 9% elevation in IL-6 levels. However, after adjusting for covariates (particularly obesity), PSG sleep duration was no longer associated with CRP or IL-6 levels. In contrast, reduced PSG sleep durations remained associated with elevations in TNFα levels. The relationship appeared linear, in that the quadratic sleep term was not significant. For every hour reduction in sleep, TNFα levels were 8% greater ($P = 0.01$). Categorical analyses confirmed this linear relationship (Table 3). Including habitual sleep duration as a covariate had no impact on these findings.

To ensure the associations were not due to residual confounding by sleep apnea, secondary analyses were performed restricted to the 387 individuals with AHI < 15. Results were similar in this subgroup. For every additional hour of habitual sleep, CRP increased 9% ($P = 0.03$) and IL-6 increased 8% ($P = 0.002$), while for every hour reduction in PSG sleep duration, TNFα levels increased by 9% ($P = 0.04$).

Table 3—Association Between Categorical Measures of Sleep Duration and Cytokine Levels

Cytokine	Habitual Sleep Duration					PSG Sleep Duration				
	Short: < 7 h (n=189)	Average: 7-8 h (n=218)	Long: > 8 h (n=202)	Overall P-value	Linear trend P-value	Short: < 6 h (n=249)	Average: 6-7 h (n=227)	Long: > 7 h (n=135)	Overall P-value	Linear trend P-value
CRP (μg/mL)	1.77 (1.49, 2.10)	2.13 (1.82, 2.51)	2.35 (1.99, 2.77)	0.03	0.01	2.11 (1.79, 2.47)	2.00 (1.71, 2.35)	2.09 (1.71, 2.56)	0.87	0.97
IL-6 (pg/mL)	2.01 (1.81, 2.24)	2.22 (2.01, 2.45)	2.51 (2.26, 2.79)	0.009	0.002	2.30 (2.08, 2.54)	2.17 (1.96, 2.39)	2.27 (2.00, 2.59)	0.66	0.89
TNFα (pg/mL)	2.96 (2.57, 3.42)	2.69 (2.35, 3.08)	3.26 (2.83, 3.75)	0.14	0.34	3.26 (2.86, 3.73)	2.87 (2.52, 3.28)	2.60 (2.19, 3.10)	0.11	0.04

The geometric mean and 95% confidence interval of each cytokine level are displayed by sleep duration category adjusted for age, sex, race, body mass index, body mass index squared, waist circumference, and apnea-hypopnea index. PSG: polysomnography; CRP: C-reactive protein; TNFα: tumor necrosis factor alpha; IL: interleukin.

DISCUSSION

In this study, a positive linear association was observed between habitual sleep duration and levels of 2 pro-inflammatory cytokines, CRP and IL-6. In addition, a similar trend was seen for TNFα levels. These findings were independent of OSA severity, and persisted in the subgroup of individuals without moderate to severe apnea. These results are consistent with findings from the Nurses Health Study, in which women reporting habitual sleep times ≥ 9 hours had 44% greater CRP levels than women sleeping 8 hours.[21] IL-6 is the primary stimulus for CRP production by the liver, so the association between sleep duration and CRP may well be secondary to the effect on IL-6. Activation of this key acute phase pro-inflammatory pathway may have important consequences. Elevations in both CRP and IL-6 levels have been found to predict an increased risk for adverse health outcomes such as myocardial infarction and diabetes.[11-13] Habitual sleep durations > 8 hours have been associated with similar adverse outcomes. In the Nurses Health Study, sleeping ≥ 9 hours on a regular basis was associated with a 57% increased risk of incident cardiac events and a 47% increased risk for incident diabetes.[3,4]

Because of the cross-sectional nature of this study, the causal direction between habitual sleep duration and cytokine levels cannot be definitively established. Given the reported somnogenic effects of IL-6 and other cytokines,[20] it is possible that elevated cytokine levels predispose to increased habitual sleep durations. However, adjusting for ESS produced no appreciable reduction in the magnitude of association between long habitual sleep durations and either CRP or IL-6 levels.

Another possibility is that an underlying condition predisposes to both increased habitual sleep durations and elevated cytokine levels. To minimize this possibility, we excluded individuals with inflammatory diseases such as connective tissue diseases from this study. In addition, our findings persisted in secondary analyses adjusting for diabetes and lipid lowering therapy. However, the possibility of subclinical disease causing residual confounding cannot be excluded.

In contrast to these findings, we found reduced PSG sleep duration was associated with elevated TNFα levels.[9] This is in keeping with prior experimental studies that found elevations in circulating TNFα levels and TNFα gene expression in monocytes following sleep restriction.[9,22] In contrast to prior experimental studies but in agreement with observational findings from the Wisconsin Sleep Cohort,[10] we did not find elevations in other inflammatory cytokines with reduced PSG sleep time after adjusting for covariates. This may be due to differences in the mechanisms for reduced sleep. The effect of externally imposed sleep deprivation as has been done in experimental studies may not be relevant to those who sleep less spontaneously in a controlled laboratory setting.

The association of reduced PSG sleep times with elevations in TNFα levels but not with related cytokines such as IL-1 may reflect differential effects of sleep on individual components of inflammatory pathways, differing half-lives of each of these mediators, or differences in the performance characteristics of the assays used to measure the different cytokines. In addition, the possibility that this isolated association may represent a false positive finding cannot be excluded.

The differing patterns of association with cytokine levels suggest self-reported habitual sleep duration and PSG-measured sleep duration on one night are measuring different constructs. The lack of correlation between these 2 measures supports this interpretation. One potential explanation for the different patterns of association with cytokine levels is that the questionnaire measure of sleep time is assessing chronic sleep exposure while the PSG measure is assessing an acute exposure. Thus differences in the relationships found with cytokine levels may be due to compensatory effects that occur only with long-term exposure to sleep deprivation. For example, similar to our findings and in contrast to short-term sleep deprivation protocols, prolonged exposure to sleep deprivation for 40 h in a recent experimental study led to reductions in CRP and IL-6 levels.[23] In addition, work in patients with chronic insomnia suggests that chronic alterations in sleep patterns can lead to changes in the diurnal pattern of cytokine secretion.[24] Another possibility is that the 2 sleep duration measures may be differentially influenced by some underlying predictor of sleep habits not measured in this work (e.g., level of stress, mood) that has a direct effect on cytokine levels.

It is interesting to note that while sleep duration has been found to have a U-shaped association with diseases such as obesity, diabetes, heart disease, and mortality,[1-5] none of the relationships between sleep duration and cytokine levels found in this study demonstrated evidence of a U-shaped relationship. This is in keeping with results for CRP in the Nurses Health Study.[21] Similarly, the association between sleep duration and the pro-inflammatory hormone, leptin, has been linear in sever-

al epidemiologic cohorts.[5,25] These data suggest the mechanisms by which sleep duration promotes disease are different in short versus long sleepers. However, the finding that depending on the measure of sleep duration considered, both long and short sleep are associated with elevations in inflammatory cytokine levels, suggests that inflammation may play a role in predisposing to morbidity at both ends of the sleep duration spectrum.

It should be noted that both sleep measures have limitations in assessing sleep exposure. Because of the reliance on self-report, habitual sleep time may overestimate true sleep exposure, particularly in those with sleep disorders. PSG sleep time, on the other hand, may not represent the typical nightly exposure due to the first night effect of sleeping in an unfamiliar environment. In addition, the use of a fixed lights out period (20:00 to 07:00) may have artificially curtailed PSG sleep time in those whose habitual sleep times fell outside this window.

In summary, our findings suggest independent of potential confounders such as OSA and obesity, the IL-6/CRP inflammatory pathway is elevated in those who report habitually long sleep times, while those with short PSG sleep times demonstrate elevations in TNFα. These data suggest the interrelationships between sleep duration and inflammation are complex, with disparate effects depending on the measure of sleep duration used and the components of the inflammatory response studied. However, this work supports a role for inflammation in mediating the adverse health effects of both short and long sleep, and indicates these associations are unlikely to be mediated by unrecognized sleep apnea.

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DISCLOSURE STATEMENT

This was not an industry supported study. Dr. Jenny has financial interests in Haematologic Technologies, a company that manufactures products for blood coagulation research. Dr. Tracy is owner of Haematologic Technologies. Dr. Redline has received the use of CPAP machines provided by Respironics for an NIH sponsored study. The other authors have indicated no financial conflicts of interest.

REFERENCES

1. Kripke DF, Garfinkel L, Wingard DL, Klauber MR, Marler MR. Mortality associated with sleep duration and insomnia. Arch Gen Psychiatry 2002;59:131-6.
2. Patel SR, Ayas NT, Malhotra MR, et al. A prospective study of sleep duration and mortality risk in women. Sleep 2004;27:440-4.
3. 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.
4. 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.
5. Taheri S, Lin L, Austin D, Young T, Mignot E. Short sleep duration is associated with reduced leptin, elevated ghrelin, and increased body mass index. PLoS Med 2004;1:e62.
6. Shearer WT, Reuben JM, Mullington JM, et al. Soluble TNF-alpha receptor 1 and IL-6 plasma levels in humans subjected to the sleep deprivation model of spaceflight. J Allergy Clin Immunol 2001;107:165-70.
7. Meier-Ewert HK, Ridker PM, Rifai N, et al. Effect of sleep loss on C-reactive protein, an inflammatory marker of cardiovascular risk. J Am Coll Cardiol 2004;43:678-83.
8. Haack M, Sanchez E, Mullington JM. Elevated inflammatory markers in response to prolonged sleep restriction are associated with increased pain experience in healthy volunteers. Sleep 2007;30(9):1145-52.
9. 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.
10. Taheri S, Austin D, Lin L, Nieto FJ, Young T, Mignot E. Correlates of serum C-reactive protein (CRP)--no association with sleep duration or sleep disordered breathing. Sleep 2007;30:991-6.
11. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. N Engl J Med 1997;336:973-9.
12. Ridker PM, Rifai N, Stampfer MJ, Hennekens CH. Plasma concentration of interleukin-6 and the risk of future myocardial infarction among apparently healthy men. Circulation 2000;101:1767-72.
13. Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. JAMA 2001;286:327-34.
14. Redline S, Tishler PV, Tosteson TD, et al. The familial aggregation of obstructive sleep apnea. Am J Respir Crit Care Med 1995;151:682-7.
15. Buxbaum SG, Elston RC, Tishler PV, Redline S. Genetics of the apnea hypopnea index in Caucasians and African Americans: I. Segregation analysis. Genet Epidemiol 2002;22:243-53.
16. Palmer LJ, Buxbaum SG, Larkin E, et al. A whole-genome scan for obstructive sleep apnea and obesity. Am J Hum Genet 2003;72:340-50.
17. Rechtschaffen A, Kales A. A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. Washington, DC: US Government Printing Office; 1968.
18. Redline S, Sanders MH, Lind BK, et al. Methods for obtaining and analyzing unattended polysomnography data for a multicenter study. Sleep Heart Health Research Group. Sleep 1998;21:759-67.
19. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991;14:540-5.
20. 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.
21. Williams CJ, Hu FB, Patel SR, Mantzoros CS. Sleep duration and snoring in relation to biomarkers of cardiovascular disease risk among women with type 2 diabetes. Diabetes Care 2007;30:1233-40.
22. 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.
23. Frey DJ, Fleshner M, Wright KP, Jr. The effects of 40 hours of total sleep deprivation on inflammatory markers in healthy young adults. Brain Behav Immun 2007;21:1050-7.
24. Vgontzas AN, Zoumakis M, Papanicolaou DA, et al. Chronic insomnia is associated with a shift of interleukin-6 and tumor necrosis factor secretion from nighttime to daytime. Metabolism 2002;51:887-92.
25. Chaput JP, Després JP, Bouchard C, Tremblay A. Short sleep duration is associated with reduced leptin levels and increased adiposity: results from the Québec Family Study. Obesity 2007;15:253-61.