Correlates of Serum C-Reactive Protein (CRP) – No Association With Sleep Duration or Sleep Disordered Breathing

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Study Objectives: Increasing evidence suggests that alterations in sleep duration are associated with cardiovascular disease (CVD) and mortality. Additionally, sleep disordered breathing (SDB), which is associated with disturbed nighttime sleep and hypoxemia, may be an independent risk factor for CVD. The inflammatory marker, C-reactive protein (CRP), is an important predictor of CVD. We investigated potential associations between circulating CRP, sleep duration, and SDB.

Design: Cross-sectional Study.

Population: Participants were 907 adults from the Wisconsin Sleep Cohort Study (WSCS).

Measurements and Results: CRP was measured after overnight polysomnography. The relationships between CRP and sleep parameters were evaluated using multiple linear regression with and without controlling for age, sex, and body mass index (BMI) and other potential confounders. CRP was found to be higher for women and had a strong positive correlation with age and BMI. CRP showed a significant positive association with current smoking, waist-hip ratio (WHR), LDL-cholesterol, triglycerides, leptin, and insulin, independent of age, sex, and BMI. Significant independent negative associations for CRP were observed with HDL-cholesterol (HDL), insulin sensitivity (quantitative insulin sensitivity check index [QUICKI]), and hours of exercise. There was a significant positive association between CRP levels and the apnea-hypopnea index (AHI, the measure of SDB), but these relationships were not significant after adjustment for age, sex, and BMI. No significant association between CRP levels and measures of sleep duration (polysomnographic and self-reported) were found.

Conclusion: There was no significant association between CRP levels and sleep duration. The lack of an independent association between CRP levels and SDB suggests that the reported relationship between these 2 variables may be primarily driven by their association with obesity.

Keywords: C-reactive protein (CRP), sleep duration, sleep disordered breathing (SDB), apnea-hypopnea index (AHI), obesity

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INTRODUCTION

With increasing recognition that inflammation plays a key role in atherosclerosis, there has been great interest in the study of inflammatory factors in cardiovascular disease.[1,2] The acute phase response protein, C-reactive protein (CRP), has emerged as an important measure of cardiovascular risk.[3] CRP is a 120kDa pentamer whose circulating levels reflect presence and severity of inflammation.[4] CRP is highly stable and its levels do not show any significant diurnal variation.[5] CRP levels within the normal range ("high sensitivity" CRP; hsCRP) correlate with components of the metabolic syndrome and allow cardiovascular risk stratification.[3,6]

Although the precise physiological functions of sleep are unknown, both short and long sleep duration have been associated with increased mortality.[7] Short sleep duration has been associated with obesity, insulin resistance, and increased cardiovascular risk in both small controlled laboratory studies and large population studies.[8-15] A recent study reported an association between acute sleep deprivation and elevated CRP in healthy male volunteers.[16] Sleep disordered breathing (SDB) is characterized by snoring and repeated airway collapse (apneas) and partial collapse (hypopneas), resulting in hypoxemia and sympathetic nervous system activation during sleep.[17-19] Frequent arousals cause sleep disruption at night and daytime sleepiness. SDB is highly prevalent in adults in Western countries.[17,18 20,21] Although SDB is strongly correlated with obesity, several studies have hypothesized that it carries an independent predisposition to cardiovascular disease.[22] In particular, SDB is associated with hypertension independent of body mass index (BMI).[23] SDB-related hypoxemia has also been suggested to contribute to endothelial dysfunction.[24] Small studies, however, have reported conflicting associations between SDB and elevated CRP levels.[25-28]

To explore the putative association between short sleep duration, SDB, and a pro-inflammatory state, we examined associations between sleep measures and CRP in the Wisconsin Sleep Cohort Study (WSCS), an ongoing longitudinal study of sleep habits and disorders in the general population.[15,21] We first examined all potential correlates of CRP in our study population. Next, we examined any association between CRP levels, sleep duration, and SDB, correcting for the correlates of CRP identified in our initial analysis.

METHODS

The Wisconsin Sleep Cohort Study (WSCS)

The institutional review board of the University of Wisconsin Medical School approved the study protocols. Informed consent was obtained from all participants. The WSCS has recently been

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described in detail elsewhere.[15] Briefly, WSCS is an ongoing longitudinal study of sleep and its disorders in the general population.[21] Recruitment began in 1989 initially through mailed surveys (repeated at 5-y intervals) on sleep habits, health, and demographics sent to all employees aged 30–60 y of four state agencies in south central Wisconsin. From respondents, a stratified random sample, based on risk for SDB, was recruited for an extensive overnight protocol including polysomnography. Weighted analysis is used when estimates based on the original population are desired and, in this analysis, to check for potential bias in associations. Exclusion criteria for the WSCS included pregnancy, unstable cardiopulmonary disease, airway cancers, and recent upper respiratory tract surgery.

Because baseline studies were staggered, study entry and follow-up time vary within the cohort. Follow-up studies have been conducted at 4-year intervals, with up to 3 follow-up studies to date. Collection of morning fasted blood after polysomnography began in 1995.

Sleep duration data included polysomnographic measures of sleep the night previous to blood sampling and measures of self-reported sleep duration from questionnaires. Before polysomnography, questionnaires on lifestyle and health history were administered. Height, weight, other anthropometric variables, and blood pressure were measured. Participants set their own sleep and rise times. A fasting blood sample was collected shortly after awakening from polysomnography.

Polysomnography

An 18-channel polysomnographic system was used to assess sleep, respiratory, and cardiac variables. Sleep was studied using electroencephalography (EEG), electro-oculography, and chin electromyography (Grass Instruments, Quincy, MA, USA). SDB was assessed by continuous measurement of arterial oxyhemoglobin saturation by pulse oximetry (Ohmeda, Englewood, CO, USA), oral and nasal airflow, nasal air pressure, and thoracic cage and abdominal respiratory motion (Respitrace Ambulatory Monitoring, Ardsley, NY, USA). Each 30-s epoch of the polysomnographic record was scored for sleep stage and SDB using standard criteria. Sleep state and respiratory event scorings were performed by trained sleep technicians and reviewed by an expert polysomnographer. The average number of apneas and hypopneas per hour of measured sleep, the apnea-hypopnea index (AHI), was the measure for SDB. For analyses including AHI, participants were excluded if they had short sleep studies (<3 h of usable polysomnography, or <4 h of polysomnography if <20 min REM sleep was recorded), or if they were receiving CPAP treatment and chose to use it during the sleep study.

Sleep Measures

The sleep measures used in this analysis included:

A. Total sleep time (TST): Total hours of polysomnographically defined sleep;

B. Usual sleep was estimated from the following questions: how many hours of sleep do you usually get in (a) a workday night? (b) a weekend or non-work night? These questions were included in all mailed surveys and were added to questionnaires completed at the overnight study in 1998. For participants studied after 1998, data from questionnaires administered at the overnight study were used (58%); for the remainder of the sample, data from the mailed survey closest in time to the overnight study were used. Usual sleep was calculated as (5 × workday sleep + 2 × weekend sleep)/7.

Hormone Assays

Following overnight fasting, serum was collected soon after awakening and stored at -70 °C. All samples were assayed blindly in duplicate. It was not possible to assay samples from all participants in all assays because of the volume of serum available; this particularly affected the ghrelin assay, which required the most volume.[15] Serum CRP was measured in duplicate using a highly sensitive enzyme-linked immunoassay (Alpha Diagnostic International, San Antonio, TX, USA).[30] Both intra- and inter-assay variations were less than 10%. Internal controls were used in all assays. Subjects with CRP levels greater than 10 mg/L (127 studies from 74 subjects) were excluded, since this may have reflected acute inflammation. Inclusion of these subjects, however, did not alter any of our findings. The other assays used have been previously described.[15] Leptin and insulin were determined using enzyme-linked immunoassays (ELISA; Linco Research, St. Charles, MO, USA). Total ghrelin and adiponectin were measured by radioimmunoassay (Linco Research).[15] The quantitative insulin sensitivity check index (QUICKI) was calculated as previously described.[31-33] Genotyping for apolipoprotein E4 (ApoE4) was carried out in a previous study.[35]

Data Analysis

All analyses were cross-sectional and performed using SAS/STAT 9.1. All relationships were examined using single and multiple observations from 907 participants. Data presented are for the first CRP measurement, but all tested relationships were similar when multiple observations were used (28% of participants had multiple CRP measurements). All relationships were examined unadjusted and adjusted for age, sex, and BMI. Relationships with sleep disordered breathing and sleep duration were further adjusted for variables with significant relationships to CRP, SDB, or both. Mixed modeling techniques (SAS *PROC MIXED*) were used to account for within-subject correlation for participants with multiple visits. All reported P values are two-sided.

CRP, leptin, ghrelin, adiponectin, triglycerides, insulin, and glucose were log transformed based on the distribution of residuals from multivariate regression models. One was added to CRP (mg/L) before log transformation to avoid excessive separation of values <1 (log(CRP+1). Relationships with categorical variables were evaluated using least squares means and 95% confidence intervals for transformed CRP (SAS *PROC GLM*), which were transformed back to the original scale for ease of interpretation (Table 2). Relationships of log(CRP+1) with continuous variables were examined using Pearson correlation coefficients, and partial correlation coefficients adjusted for sex, age, and BMI (SAS *PROC CORR*).

We evaluated the relationship between CRP and multiple variables: anthropometric (waist-hip ratio [WHR]), metabolites (HDL-cholesterol, LDL-cholesterol (LDL), triglycerides, glucose), hormones (leptin, ghrelin, adiponectin, insulin), measures of insulin sensitivity (QUICKI, diabetes, hypertension), lifestyle factors (hours of self-reported exercise,[34] alcohol consumption,

Table 1—Description of Sample

Variable	N	Mean (SD)	Median (interquartile range)	Category N (%)
A. General				
Male	907[a]			500 (55.1%)
Age (y)		52.5 (8.1)		
Body mass index [b] (Kg/m^2)			29.1 (25.9,33.4)	
Waist-hip ratio (waist girth/hip girth)		0.90 (.09)		
B. Sleep duration				
i. Polysomnography-derived				
Total sleep time (h)		6.3 (1.0)		
ii. Self-reported				
Usual sleep (h)	906	7.1 (1.0)		
C. Sleep-disordered breathing				
i. Apnea-hypopnea index (AHI)				
AHI < 5				623 (68.7%)
AHI 5-15				173 (19.1%)
AHI ≥ 15				111 (12.2%)
ii. Habitual snoring	899			418 (46.5%)
D. Hormones & Metabolites				
C-reactive protein (mg/L)			2.4 (1.1, 5.0)	
Leptin (ng/ml)	903		12.7 (6.3, 24.1)	
Insulin (ng/dl)	899		9.9 (6.6, 15.1)	
Glucose (mg/dl)	906		94 (88, 102)	
E. Insulin sensitivity, diabetes, and cardiovascular disease				
QUICKI [b]	864	0.34 (.04)		
Diabetes	906			58 (6.4%)
Hypertension	906			346 (38.2%)
Cardiovascular disease	906			48 (5.3%)
F. Lifestyle				
Current Smoking	906			120 (13.3%)
Alcohol (drinks/wk)	906	3.7 (5.2)		
Exercise: none	901			330 (36.6%)
H. Medications				
Cholesterol-lowering				126 (13.9%)
Anti-inflammatory				243 (26.8%)
Estrogen or oral contraceptive				114 (12.6%)

[a] N = 907 unless indicated otherwise
[b] BMI: body mass index; QUICKI: quantitative insulin sensitivity check index

smoking), and ApoE4[35] genotype. The diabetes group was defined as those with a self-reported physician diagnosis of diabetes. In all analyses, participants with diabetes were included, but their exclusion did not alter the results. The hypertension group included those with systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg or on antihypertensive medications. We also examined the use of medications that are known to affect CRP level: anti-inflammatories, cholesterol-lowering medication, and estrogen from either hormone replacement therapy or oral contraceptives.

Multivariable regression (SAS PROC GLM) was used to model the relationship of transformed CRP with sleep disordered breathing and sleep duration. We modeled the relationship between CRP and SDB in several ways, including modeling AHI categorically (AHI <5, 5-15, ≥15 events/hour) and continuously (transformed: log[AHI + 1]). We also tested any potential relationship between CRP and extremes of AHI (≥20 events/hr and ≥30 events/hr). Measures of sleep duration were modeled continuously with quadratic (squared) terms were added to examine possible nonlinear relationships. As a further check, categorical models of sleep duration were also examined. The fully adjusted models in Table 4 were also examined using sampling weights to test for bias in the association; no significant differences from the models presented were found.

RESULTS

Table 1 shows the characteristics of the sample. CRP was found to be higher for women (see Table 2) and had a strong positive correlation with age and BMI (partial correlation coefficients: age = 0.152, P <0.0001 (adjusted for sex and BMI); BMI = 0.404, P <0.0001 (adjusted for sex and age). Table 2 shows the means and 95% confidence intervals for CRP and statistical comparisons for potential related variables.

In unadjusted models, CRP levels were found to be significantly greater for women, habitual snorers, smokers, those who undertook less frequent physical activity, diabetics, and those with hypertension. After adjustment for age, sex, and BMI, the differences that remained significant were for physical activity and current smokers vs. nonsmokers. No significant relationship between CRP levels and cardiovascular disease was noted, but only 5.3% of the sample had any known cardiovascular disease (Table 1).

Table 2—Mean CRP by Category

Effect	Categories	Unadjusted Models[a] Least squares mean (95% CI)	Unadjusted Models[a] P-value	Adjusted Models[a,b] Least squares mean (95% CI)	Adjusted Models[a,b] P-value
Sex	M*	2.20 (2.03, 2.39)	--	2.25 (2.09, 2.41)	--
	F	2.96 (2.73, 3.21)	<0.0001	2.90 (2.69, 3.12)	<0.0001
Snoring	Rare/Occasional*	2.23 (2.06, 2.42)	--	2.49 (2.31, 2.67)	--
	Habitual	2.90 (2.67, 3.14)	<0.0001	2.65 (2.45, 2.86)	0.25
Smoking	Never*	2.29 (2.10, 2.48)	--	2.39 (2.21, 2.57)	--
	Past	2.71 (2.47, 2.97)	0.0071	2.58 (2.37, 2.80)	0.18
	Current	2.97 (2.54, 3.44)	0.0036	3.24 (2.83, 3.69)	0.0001
Hypertension	No*	2.23 (2.07, 2.40)	--	2.49 (2.32, 2.66)	--
	Yes	3.06 (2.80, 3.34)	<0.0001	2.68 (2.45, 2.92)	0.22
Diabetes	No*	2.48 (2.33, 2.63)	--	2.56 (2.43, 2.70)	--
	Yes	3.30 (2.66, 4.06)	0.013	2.54 (2.05, 3.11)	0.95
Exercise (hrs/week)	0*	3.11 (2.84, 3.40)	--	2.89 (2.66, 3.14)	--
	1-3	2.17 (1.89, 2.47)	<0.0001	2.25 (1.99, 2.53)	0.0006
	4-6	2.28 (2.07, 2.51)	<0.0001	2.45 (2.24, 2.66)	0.0063
	7+	2.09 (1.66, 2.58)	0.0006	2.35 (1.93, 2.83)	0.048
Cardiovascular disease	No*	2.50 (2.35, 2.65)	--	2.55 (2.42, 2.69)	--
	Yes	3.01 (2.35, 3.80)	0.15	2.65 (2.10, 3.30)	0.76
APOE4 allele	Absent*	2.52 (2.34, 2.72)	--	2.55 (2.39, 2.73)	--
	Present	2.30 (2.03, 2.60)	0.21	2.32 (2.07, 2.59)	0.14

[a] Transformed CRP (log(CRP + 1)) was used for all estimates; means and 95% confidence intervals were back-transformed (exponentiated, 1 subtracted) to return estimates to original CRP units (mg/L).
[b] The adjusted model for sex included age and body mass index. All other models included adjustment for sex, age, and body mass index.
* Reference category

Table 3 shows the relationships between CRP levels and anthropometric measures, metabolites, hormones, insulin sensitivity measures, and lifestyle factors. Significant positive correlations were observed between CRP levels and waist-hip ratio (WHR), glucose, LDL-cholesterol, triglycerides, insulin, and leptin. Significant negative correlations were observed with HDL-cholesterol, QUICKI, and hours of exercise. The relationships that remained significant after adjustment for age, sex, and BMI included those with WHR, LDL-cholesterol, triglycerides, leptin, insulin, QUICKI, and hours of exercise. The relationship between CRP and WHR remained significant despite correction for BMI. No association between adiponectin (which is highly correlated with insulin sensitivity)[36] and CRP levels was observed.

Table 3—Correlation of CRP [a] with Continuous Covariates

	Pearson correlation r	Pearson correlation P-value	Partial Pearson correlation [b] r	Partial Pearson correlation [b] P-value
Anthropometric				
WHR	0.101	0.002	0.137	<0.0001
Metabolites				
Glucose [c]	0.163	<0.0001	0.009	0.79
HDL	-0.070	0.03	-0.064	0.06
LDL	0.077	0.02	0.073	0.03
Triglycerides[c]	0.260	<0.0001	0.161	<0.0001
Hormones				
Leptin [c]	0.433	<.0001	0.202	<0.0001
Ghrelin [c]	-0.026	0.48	-0.051	0.17
Adiponectin [c]	-0.024	0.48	-0.021	0.54
Insulin [c]	0.275	<0.0001	0.122	0.0003
Insulin Sensitivity				
QUICKI	-0.280	<0.0001	-0.108	0.0014
Lifestyle				
Exercise (hrs/week)	-0.140	<0.0001	-0.077	0.021
Alcohol (drinks/week)	-0.033	0.32	0.040	0.23

[a] All correlations were calculated using log(CRP + 1).
[b] Partial correlations were adjusted for age, sex, and BMI
[c] Variables were log-transformed

After adjustment for age, sex, and BMI, we observed no significant association between AHI and CRP levels when AHI was expressed categorically (Table 4). There was also no observed relationship when AHI was examined as a continuous variable, or at extremes of AHI (data not shown). As shown in Table 4, this lack of relationship was still observed after controlling for multiple factors that were associated with alteration in AHI or CRP (including WHR, lifestyle factors [smoking, alcohol consumption, exercise], medications [anti-inflammatories, cholesterol-lowering medications, estrogens], hypertension, and diabetes). Additional control for metabolites, other body habitus measures, and APOE4 genotype, and/or excluding individuals on various medications did not change the (non)significance of the relationship.

Table 4 also shows the relationship between CRP levels and measures of sleep duration before and after adjustment for age, sex, and BMI and the covariates listed above. No significant relationship between CRP and sleep duration variables (polysomnographic or self-reported) was observed. Control for factors associated with CRP (as listed above) and exclusion of those taking medications did not alter these relationships. Because the relationship between sleep duration and mortality and cardiovascular risk is U-shaped, we examined quadratic terms for both total sleep time (tst^2) and usual sleep ($usual^2$) and found no significant relationship (data not shown). Examining sleep duration categorically also yielded no significant associations (data not shown).

Table 4—Relationship of CRP to Sleep Disordered Breathing and Sleep Duration

Apnea-Hypopnea Index (AHI)

	Unadjusted Models[a]		Adjusted Models[a,b]	
	Least squares mean (95% CI)	**P-value**	**Least squares mean (95% CI)**	**P-value**
AHI <5	2.32 (2.16, 2.49)	—	2.68 (2.38, 3.00)	—
AHI 5-15	2.73 (2.40, 3.09)	0.03	2.50 (2.12, 2.92)	0.32
AHI ≥ 15	3.51 (3.02, 4.07)	<0.0001	2.61 (2.17, 3.10)	0.76

Sleep Duration

	Unadjusted Models[a]		Adjusted Models[a,b]	
	Coefficient	**P-value**	**Coefficient**	**P-value**
Total sleep time (h)	-0.003	0.90	0.004	0.83
Usual sleep (h)	0.012	0.57	0.028	0.15

[a] The natural log of (CRP + 1) was used as the response in all models.
[b] Models were adjusted for age, sex, and BMI, WHR, smoking status (current, past, never), alcoholic drinks per week, hours of exercise per week, diagnosed diabetes, hypertension (systolic ≥ 140 or diastolic ≥ 90 mmHg or antihypertensive medication), cholesterol-lowering medication and supplemental estrogen (hormone replacement therapy or oral contraceptives).

DISCUSSION

The importance of sleep to morbidity and mortality is increasingly recognized. Both short and long sleep duration have been associated with increased mortality and cardiovascular disease, but the mechanisms involved remain to be determined.[7,9] Several population studies have shown a significant relationship between short sleep duration, metabolic dysfunction, and obesity.[8,10-15] The association between short sleep duration and obesity may be due to increased food intake triggered by low leptin and high ghrelin, but the precise mechanisms remain to be determined.[13-15,37,38] While sleep duration may by itself affect health, SDB, which is associated with disrupted nighttime sleep, has been proposed to be a major risk to cardiovascular health. SDB results in sympathetic nervous system activation and hypoxemia, and is associated with hypertension independent of BMI.[23,39,40] Hypoxemia has been suggested to contribute to endothelial dysfunction.[24] Several authors have suggested that SDB confers an additional risk to that of the metabolic syndrome, which is frequently observed in association with SDB.[19,39]

CRP may be a mediator and/or marker of the association between alterations in sleep duration and quality, and cardiovascular disease. This is the first large population-based study to comprehensively examine the putative association between sleep duration (polysomnographic and self-reported), SDB, and serum CRP levels. The study, although cross-sectional, benefits from a large and well-characterized population-based sample, attention to bias and confounding factors, and extensive in-laboratory polysomnographic data. Our results confirm previous reports in identifying visceral obesity, insulin sensitivity, smoking, and exercise as important correlates of CRP.[3,41] The relationship between CRP and WHR and body fat was still significant despite correction for BMI confirming that BMI may not fully express central fat deposition, which is key to the metabolic syndrome. Indeed, the strongest correlates of CRP were WHR and QUICKI (a measure of insulin sensitivity). Interestingly, no association between adiponectin (which is highly correlated with insulin sensitivity)[15,36] and CRP levels was observed. This lack of association suggests that these 2 markers may be involved in independent pathophysiological mechanisms associated with the metabolic syndrome. However, further study is necessary with measurement of different adiponectin complexes. Our study also confirmed the correlation of CRP with leptin, independent of BMI,[42] which may reflect the closer association of these hormones with visceral obesity than body weight per se.

A recent study of young healthy male adults under laboratory conditions has reported elevations in CRP levels with total and partial sleep deprivation.[16] In our study we found no association between CRP levels and both concurrent (polysomnographic) and usual (self-reported) measures of sleep duration. Although the above recent study remains to be confirmed, an explanation of the changes observed may be related to the study of individuals much younger than the WSCS cohort. Also, the young volunteers underwent a greater degree of sleep deprivation than observed in our cohort.

Reports of associations between SDB and CRP levels are conflicting.[25-28] An association between SDB and CRP was originally reported by a small study, which controlled for BMI, but did not control for central adiposity, which may particularly important in individuals with SDB.[27] Furthermore, only individuals with severe SDB were studied. Another small study found higher CRP levels in individuals with moderate to severe SDB compared to obese controls, but the SDB group was significantly heavier.[28] A larger study, including participants with severe SDB, did not find any association between SDB and CRP.[25]

We now report that there is no association between CRP levels and SDB after controlling for age, sex, and BMI. Excess body weight clearly contributes to the incidence and progression of SDB.[19,43] Excess body weight is also strongly associated with insulin resistance, the metabolic syndrome, and alterations in metabolic hormone levels (CRP, leptin, and insulin).[6] Our results suggest that the association with excess body weight may primarily drive any relationship between SDB, CRP, and cardiovascular health.

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Drs. Taheri, Young, and Mignot designed the study. Drs. Taheri, Nieto, Young, Mignot, and Ms. Austin analyzed the data. Drs. Taheri, Ling, and Mignot performed the experiments. Dr. Young enrolled participants. Drs. Taheri, Ling, Young, Neito, Mignot, and Ms. Austin contributed to writing the paper.

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