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Brain Behav Immun. Author manuscript; available in PMC 2010 July 26.

Published in final edited form as:
Brain Behav Immun. 2009 March ; 23(3): 351–354. doi:10.1016/j.bbi.2008.10.008.

Disturbed sleep is associated with increased C-reactive protein in young women

Michele L. Okun[a,*], **Mary Coussons-Read**[b], and **Martica Hall**[a]

[a] University of Pittsburgh, Western Psychiatric Institute and Clinic, 3811 O'Hara Street, Room E-1116, Pittsburgh, PA 15213, USA

[b] Department of Psychology, University of Colorado at Denver and Health Sciences Center, Denver, CO USA

Abstract

Evidence links disturbed sleep with an exaggerated inflammatory response and increased risk of adverse health outcomes. An emerging risk factor for many adverse health outcomes is chronic, low-grade inflammation. An exaggerated inflammatory response could provide a biological link between disturbed sleep and adverse health outcomes. The relationship between sleep and chronic, low-grade inflammation has been sparsely examined in otherwise healthy, young women. We evaluated cross-sectional relationships between self-reported sleep and three inflammatory markers. Participants were community dwelling nonpregnant women ($N = 43$, 28.2 ± 5.2 years of age). Measures included the Pittsburgh Sleep Quality Index (PSQI), sleep diaries, and serum levels of IL-6, TNF-α and C-reactive protein. Poor sleep quality and continuity were associated with higher CRP levels after controlling for covariates. No significant relationships were observed between PSQI scores and IL-6 or TNF-α; sleep duration was not related to any of the inflammatory markers. Poor sleep, in young adulthood, may contribute to the chronic, low-grade inflammation associated with an increased risk for future adverse health outcomes. Future work should longitudinally evaluate how these relationships may affect development of gender-specific diseases in apparently healthy young women.

Keywords

Sleep; Sleep quality; Inflammation; C-reactive protein; Women; Cytokine

1. Introduction

Sufficient sleep is essential for immunocompetence (Born, 1999; Irwin, 2002) and for overall health (Alvarez and Ayas, 2004; Ancoli-Israel, 2006). Emerging evidence links short sleep duration, poor sleep continuity, and poor sleep quality with increased risk of adverse health outcomes, including depression (Breslau et al., 1996) (Okun et al., in press) and hypertension (Gangwisch et al., 2006). Although the precise mechanism for this association is not known, several epidemiological studies suggest that increased inflammation is an important risk factor in these relationships (Benderly et al., 2007; Cesari et al., 2003; Sesso et al., 2007).

Chronic, low-grade inflammation, rather than acute increases, is an emerging risk for disease (Benderly et al., 2007; Cesari et al., 2003; Ridker, 2004). It promotes a diseased

*Corresponding author. Fax: +1 412 246 5300. okunml@upmc.edu (M.L. Okun).

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environment through increased endothelial dysfunction (Diamanti-Kandarakis et al., 2006), plaque rupture (Cesari et al., 2003), and insulin resistance (Yudkin et al., 1999). Epidemiologic data report that older women who developed hypertension (Sesso et al., 2007) or Type 2 diabetes (Ridker, 2004) had higher baseline levels of interleukin 6 (IL-6) and/or C-reactive protein (CRP) than women who remained healthy.

Exaggerated inflammatory activation could provide a link between disturbed sleep and adverse health outcomes. The bulk of the evidence stems from sleep restriction studies which indicate that poor sleep is associated with an exaggerated inflammatory response indicated by increased circulating concentrations of the proinflammatory cytokines, IL-6 and tumor necrosis factor (TNF)-α (Irwin et al., 2006; Redwine et al., 2003; Vgontzas et al., 2004; von Kanel et al., 2006), and CRP (Liukkonen et al., 2007; McDade et al., 2006; Meier-Ewert et al., 2004; Shamsuzzaman et al., 2002). The relationship between naturalistic sleep patterns and inflammation, along with its potential long-term consequences has not been extended to younger women of childbearing age.

The present study is a secondary analysis evaluating the relationship between subjective sleep and inflammation in a community sample of young women. Women of childbearing age may be at increased risk of adverse health outcomes later in life as a consequence of significant sleep disturbances experienced during this period. We hypothesized that decreased sleep duration, poor sleep continuity, and poor sleep quality would be associated with increased circulating levels of the inflammatory markers IL-6, TNF-α, and CRP.

2. Methods

2.1. Participants

Participants were nonpregnant women ($N = 43$) recruited as a comparison group (Okun and Coussons-Read, 2007). The participants were not seeking medical treatment and free of any self-reported illness. No clinical assessment was performed; thus no data were available for BMI, presence of sleep disorders, or medications used. Participants were young (mean = 28 ± 5 years of age), well educated (mean = 17.6 ± 2.8 years), and primarily single (60.5%).

2.2. Procedures

Participants completed questionnaires, provided a venous blood sample and completed a sleep diary for 2 weeks. *The Pittsburgh Sleep Quality Index* (PSQI) (Buysse et al., 1989) assessed habitual sleep complaints over the previous month and characterized *sleep quality*. Higher scores reflected poorer overall sleep quality. *The Additional Sleep Problems Questionnaire* (ASDQ) is a compilation of questions used to evaluate the presence (yes/no) of sleep-related symptoms, such as snoring, sleep apnea, periodic limb movements (PLMS), or restless legs syndrome (RLS). The *Center for Epidemiological Studies-Depression scale* (CES-D) (Radloff, 1977) was administered to capture a unitary measurement of current depressive symptomatology. Scores ≥ 16 are suggestive of clinical depression. Lastly, prospective sleep patterns were ascertained from *The Daily Sleep Diary* (DSD). *Sleep continuity* was characterized by wake after sleep onset (WASO). S*leep quantity* was characterized by minutes of sleep obtained during the nocturnal sleep period. Both variables were averaged from 14 daily sleep diary values. These variables were chosen given the link between sleep fragmentation and sleep duration and inflammation (Irwin, 2002).

2.3. Inflammatory markers

Non-fasting venous blood samples were collected through routine venipuncture. Every effort was made to collect blood samples during a midday window (11 a.m.–2 p.m.), although due to variability in subject availability, some collection times ranged from 10 a.m. to 4 p.m.

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Samples were centrifuged and 0.5 ml aliquots were frozen at −70° C until analysis. Serum cytokine levels of IL-6 and TNF-α were determined using commercially available ultra sensitive ELISA kits (Biosource, Europe). Sensitivity for IL-6 was <.104 pg/ml and coefficients of variation (CV) was ≤ 7.8%; sensitivity for TNF-α was <.09 pg/ml and CV was ≤ 9.7%. Samples were assayed in duplicate and according to the manufacturer's instructions. CRP was detected via EIA (DSL, Webster, TX) with an enzymatically amplified 'two-step' sandwich type immunoassay. Sensitivity for CRP was <1.6 ng/ml and CV was <4.2%. Samples were diluted by 1:100 and assayed in duplicate according to manufacturer's instructions.

2.4. Data analysis

All statistical assessments were performed using Statistical Packages for the Social Sciences (SPSS) (SPSS Inc. v15). Immune-dependent variables were normalized using log-10 transformation. Outliers ($n = 2$) >2 SDs above the mean were removed from analyses (1 TNF, 1 CRP). WASO was normalized using square root transformation. One participant had missing data for the CES-D, one had missing IL-6, and one was missing sleep diary information. Pearson product moment correlations or point bi-serial correlations were used as appropriate. Sleep variables from PSQI and sleep diaries were assessed as continuous. Sleep disorder variables from the ASDQ were dichotomized. Linear regression analyses were conducted as warranted evaluating the relationship between sleep variables (sleep quality, sleep continuity and sleep quantity) and the three inflammatory markers. Possible covariates included: marital status, children at home, years of education, oral contraceptive use, menstrual phase, responses from the ASDQ, and CES-D scores. Results were statistically significant if $p < 0.05$.

3. Results

3.1. Subject characteristics

Demographic characteristics of the sample, as well as data pertaining to the primary sleep disorders of snoring/sleep apnea, PLMS and RLS, are shown in Table 1. Among those who reported or were told they snore, only one participant reported snoring *frequently*. No woman reported having sleep apnea. Only five (11.9%) women positively endorsed RLS. The average CES-D score (5.8 ± 5.1) indicated minimal endorsement of depressive symptoms. However, three women had a CES-D score >20. Table 1 also shows that the sleep of these young women was well within normal range. The PSQI averaged 4.02 ± 2.6 with a range of 0–11, wake after sleep onset averaged 10.9 ± 10.1 min with a range of 0–37.3 min, and sleep duration averaged 448.7 ± 47.4 min (approximately 7½ h) with a range of 369–569 min (6–9½ h). Although average PSQI scores were low, 19% of the participants had PSQI scores >5 which suggests poor sleep quality (Buysse et al., 1989).

We assessed the relationship between the three inflammatory markers, given that CRP is produced in response to circulating IL-6 and TNF-α (Ridker, 2004). IL-6 and CRP were correlated (r =.32, p <.05). TNF-α was not correlated with either IL-6 or CRP. Inflammatory levels for all participants were within normal ranges (IL-6 =.54 ±.3 pg/ml; TNF-α = 3.9 ± 1.8 pg/ml; and CRP = 27.5 ± 32.0 ng/ml), although IL-6 levels were lower than previously reported (Maier et al., 2005; Mills et al., 2007; Vgontzas et al., 2005).

3.2. Associations between covariates and inflammatory markers

Only one significant bivariate correlation was found between any of the demographic characteristics and the inflammatory markers. Women taking oral contraceptives exhibited higher levels of CRP even after partialling out the menstrual phase (37.0 ± 38.1 ng/ml vs 27.0 ± 52.0 ng/ml, r =.36, p =.03). There were no differences in any of the sleep or

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inflammatory markers when assessed by menstrual phase. No significant bivariate correlations were found between responses from the ASDQ or the CES-D and any of the inflammatory markers.

3.3. Linear regression analyses

Table 2 illustrates the data from linear regression analyses. We controlled for oral contraceptive use, having children at home, and CES-D scores. Although having children at home and CES-D scores were not associated with the inflammatory markers, we chose to include them as a covariates in the regression models since women with children at home report more disturbed sleep than those without (Lee, 1992) and depressive symptoms are associated with increased inflammation (Cyranowski et al., 2007).

Due to the small sample we ran two regression models for each inflammatory marker. The first regression model controlled for oral contraceptive use and having children at home. The second controlled for CES-D scores. Significant relationships were found for CRP only. Table 2 shows that poor sleep continuity (WASO) and poor sleep quality (PSQI) are associated with increased CRP levels in both regression models.

4. Discussion

Our findings show that sleep continuity and sleep quality are associated with increased levels of CRP, but not IL-6 or TNF-α. No association was found between sleep duration and any of the inflammatory markers. These findings complement existing data (Friedman et al., 2005; Liukkonen et al., 2007; McDade et al., 2006; Okun and Coussons-Read, 2007; Suarez, 2008). They are also interesting and thought provoking given the evidence that inflammation, and in particular chronic, low-grade inflammation, is a risk factor for future medical disease, especially those that are more prevalent in women, such as preeclampsia, polycystic ovarian syndrome, cardiovascular disease and Type 2 diabetes (Benderly et al., 2007; Freeman et al., 2004; Pradhan et al., 2001; Vgontzas et al., 2006). Persistent poor sleep, likely originating in young adulthood, and continuing into middle adulthood, may increase chronic, low-grade inflammation and the risk for inflammatory-related illnesses later in life. This relationship needs further examination in young women.

We did not corroborate the relationship between sleep duration and inflammation. This may reflect differences in methodologies as previous studies evaluated experimentally induced sleep restriction (Irwin et al., 2006; Meier-Ewert et al., 2004; Vgontzas et al., 2004). Women in this study naturalistically slept an average of 7½ (range 6–9½) h per night over the course of 2-weeks. These values and the variability (standard deviations) are well within expected ranges for young adult women (Baker and Driver, 2004; Tworoger et al., 2005). Women with restricted sleep periods, possibly due to family or career obligations, may exhibit similar inflammatory responses to those observed in laboratory settings.

Sleep data reported here are both in agreement and at odds with other studies looking at subjective sleep of nonpregnant women (Baker and Driver, 2004; Tworoger et al., 2005). Similar to Baker and Driver (Baker and Driver, 2004), menstrual phase did not influence sleep. This is in contrast to Manber and Bootzin (1997) who found that the luteal phase was associated with poorer sleep quality compared to follicular phase (Manber and Bootzin, 1997). Age could partially explain the difference in results (Lee, 1992). The average age in our study was 28 years compared to 38 years in the Manber and Bootzin (1997). Taken together, these few studies indicate that sleep in young women is extremely variable and susceptible to any number of confounding factors, including age (Baker and Driver, 2004).

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A modulating factor of interest is oral contraceptive (OC) use. OC have immunomodulatory effects (Cauci et al., 2008; Giraldo et al., 2008; Salkeld et al., 2001). However, in agreement with a recent report (Giraldo et al., 2008), we found no difference in IL-6 or TNF-α between OC users and non-users. We did observe a differential effect of OC use on CRP which is consistent with a report by Cauci et al. (Cauci et al., 2008). The menstrual phase was also examined since inflammatory markers fluctuate during the menstrual cycle (O'brien et al., 2007). There was no affect of menstrual phase on any of the inflammatory markers which may be due to the small sample.

In accordance with other studies, we propose that CRP may be more sensitive to behavioral modifications, such as moderate sleep disturbances, than circulating cytokines (Meier-Ewert et al., 2004; Sesso et al., 2007; Shamsuzzaman et al., 2002); and this, along with the fact that CRP does not exhibit a diurnal variation (Meier-Ewert et al., 2001), may partially account for our current findings.

Even though our preliminary findings are interesting, we acknowledge certain limitations. We did not screen out for sleep disorders, assess current infections or ascertain BMI at enrollment. All of which can influence inflammatory markers (Vgontzas et al., 2000). Solely relying on subjective indices of sleep does not allow for a complete evaluation between two physiological processes. However, there is sufficient evidence that the subjective experience (i.e. sleep quality) is as important to alterations in inflammatory markers as physiologic measures (i.e. polysomnography) (Opp, 2006). Another limitation is the one blood sample collected at the convenience of the participant. Having such variability in collection times, in addition to the fact that cytokines levels are lowest during the day (Vgontzas et al., 2005), may partially explain why we found no relationship between sleep quality and IL-6 or TNF-α. Levels may have been too low to detect. In fact, our average IL-6 level (.54 pg/ml) was substantially lower than levels reported by Mills et al. (1.58 pg/ml for women) (Mills et al., 2007).

Finally, we recognize that the demographics of our sample limits the generalizability of the findings. Given that children are a source of sleep disruptions (Lee, 1992) and only 21% of our sample had children at home, we cannot extend these findings to all women. Future studies need to assess naturalistic sleep patterns in a representative cohort of women concomitantly with multiple blood draws in order to examine the relationship between poor sleep quality and continuity and chronic, low-grade inflammation.

In summary, we found that young, healthy women who have poor sleep continuity and quality have higher levels of CRP than women with few sleep complaints. We speculate that these increased, low levels of inflammation may contribute to increased disease risk in otherwise healthy women. Understanding this relationship among women may be especially important given that gender is an important factor in inflammation (O'connor et al., 2007) and inflammation plays a role in several diseases that commonly afflict women, including polycystic ovary syndrome (PCOS) (Vgontzas et al., 2006) and preeclampsia (Qiu et al., 2004). Future work should longitudinally evaluate how these relationships may affect development of chronic disease in apparently healthy young women.

Acknowledgments

This work was supported by the Training Grant MH-16804 from the National Institutes of Health. All recruitment was conducted at the University of Colorado at Denver.

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Table 1

Demographic characteristics of 43 nonpregnant women.

	Mean ± SD
Age	28.1 ± 5 years
Education	17.6 ± 2.8 years
	N (%)
Marital status–married	17 (39.5)
Employment–full/part Time	43 (100)
Menstrual phase–follicular	26 (60)
% with children at home	9 (21)
% Caucasian	37 (86)
% Using oral contraceptives	23 (53.5)
ASDQ	
Snore or been told snore	18 (41.9)
Snoring (frequently)	1 (.05)
PLMS	16 (38.1)
RLS	5 (11.9)
CES-D*	5.8 ± 5.1
PSQI	4.02 ± 2.6
Wake after sleep onset	10.9 ± 10.1
Sleep duration (sleep diary)	448.7 ± 47.4

ASDQ, Additional Sleep Disorders Questionnaire; CES-D, Center for Epidemiological Studies–Depression; PSQI, Pittsburgh Sleep Quality Index.

1 participant had missing data.

*Three women scored >20 which is suggestive of depression.

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Table 2

Regression analyses of sleep parameters on inflammatory markers.

	Sleep quality		Sleep continuity[¥]	
IL-6				
Unadjusted	β =.04	p =.81	β = −.01	p =.94
Adjusted[*]	β = −.01	p =.94	β = −.06	p =.76
Unadjusted	β =.03	p =.84	β = −.01	p =.95
Adjusted[#]	β = −.03	p =.88	β = −.07	p =.70
TNF-α				
Unadjusted	β = −.01	p =.94	β =.08	p =.63
Adjusted[*]	β =.08	p =.66	β =.02	p =.92
Unadjusted	β =.09	p =.57	β =.08	p =.64
Adjusted[#]	β =.22	p =.23	β =.10	p =.57
C-Reactive protein				
Unadjusted	β =.47	p = 002	β =.34	p =.03
Adjusted[*]	β =.41	p =.01	β =.33	p =.04
Unadjusted	β =.46	p = 002	β =.34	p =.03
Adjusted[#]	β =.40	p =.02	β =.36	p =.03

Sleep Quality assessed by Pittsburgh Sleep Quality Index.

Sleep continuity = Wake after sleep onset from sleep diary.

[*] β coefficients are adjusted for oral contraceptive use and children at home.

[#] β coefficients are adjusted for CES-D scores, 1 participant had missing data.

[¥] 1 participant had missing sleep data.