HHS Public Access

Author manuscript

Sleep Med. Author manuscript; available in PMC 2016 October 01.

Published in final edited form as:

Sleep Med. 2015 October ; 16(10): 1213–1216. doi:10.1016/j.sleep.2015.06.014.

The interactive effects of nocturnal sleep and daytime naps in relation to serum C-Reactive protein

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Abstract

Background—C-Reactive Protein (CRP) is a general marker of inflammation that has been differentially linked with sleep. Elevated CRP (i.e., high inflammation) has been associated with either short/insufficient sleep duration, long sleep duration, both, or neither. Daytime napping has also been tied to increased and decreased inflammation. We sought to unify these findings by examining the relationship between CRP and sleep duration in conjunction with napping in a healthy young adult cohort.

Participants—Young adults (mean age = 29.05 yrs, n = 2,147) from the National Longitudinal Study of Adolescent Health (Add Health) cohort, a nationally representative longitudinal sample.

Methods/Results—ANCOVA tests examined whether self-reported sleep duration (Short, Medium or Long) and nap frequency (none-few days/week; most days/week; every day) interacted in relation to CRP. Standard covariates (i.e., age, gender, race/ethnicity, body mass index, physical activity, depression, snoring, systolic blood pressure, clinical symptoms, household income) were used. There was a linear increase in CRP with increased napping (contrast estimate = .265, 95% CI [.045 to .485], p = .018). There was also an interaction between sleep duration and napping frequency in relation to CRP ($F_{4,2128}$ = 2.90, p = .021). Inflammation differed between nap groups within the long and short sleep groups.

Conclusions—Our results suggest increased napping is an independent predictor of inflammation in young adults. These results also provide evidence for interactive effects of inflammation, nocturnal sleep, and daytime naps. Our findings confirm that excess sleep, insufficient sleep, frequent napping and infrequent napping can all be linked with elevated CRP, but these relationships depend on both nocturnal and daytime sleep patterns. These analyses will guide future work to more specifically examine sleep-inflammation processes and directionality.

Keywords

sleep duration; nap; C-Reactive Protein; inflammation

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Conflicts of interest: none

1. Introduction

C-Reactive Protein (CRP) is a positive acute-phase protein synthesized in response to non-specific cell injury. It is a highly sensitive and reliable marker of inflammation due to its rapid synthesis[1] and lack of diurnal variation[2]. Elevated CRP is a known predictor of coronary events[1] and has also been tied to somatic and cognitive deficits[3,4].

There is an established, yet complex, relationship between CRP and sleep. Sleep plays an important role in the maintenance of immune health[5], and insufficient sleep triggers a global immune response[4]. It has been posited that sleep loss activates phagocytic white blood cells and inflammatory cytokines (e.g., interleukin-6 [IL-6]), which prompt production of CRP in an attempt to mediate inflammation[3].

In human studies, insufficient sleep has been linked with inflammation. For example, CRP increases with both experimental sleep deprivation[6] and poor self-rated sleep quality[4,7] in a dose-dependent manner. Contrarily, several investigations have linked long sleep (≥9 hrs/night) with higher CRP in individuals with Obstructive Sleep Apnea and type 2 diabetes[8–10]. Others, however, have found no connection between sleep duration, quality, and CRP levels[11,12].

The relationship between daytime naps and CRP is also ambiguous. For example, a large cohort investigation compared two groups of older adults (M_{age} = 69.5 yrs): those who reported napping at least once per week and those who did not nap (i.e., not differentiating between those with frequent and infrequent nap incidence)[10]. Self-reported nappers had increased CRP, and the authors suggested that frequent naps may actively elevate CRP, possibly via enhanced blood pressure upon waking. On the other hand, a recent investigation focusing on young adults (M_{age} = 27.0 yrs) who nap infrequently reported IL-6, the precursor to CRP, increases following sleep deprivation, but decreases after subsequent naps[13]. Concurrently, naps diminished elevated cortisol and norepinephrine (an IL-6 inhibitor), which may serve in ‘resetting’ inflammation to basal levels. Taken together, these results suggest that the relationship between sleep and CRP may depend on both nocturnal sleep duration and nap frequency.

Therefore, although the above results vary markedly, they might not be contradictory. We attempted to unify previous findings on sleep and inflammation by observing nap frequency in conjunction with overnight sleep duration. Using a large sample of healthy young adults, we were able to assess differing nap frequency, ranging from never napping to napping every day, and sleep duration in relation to CRP.

2. Materials and Methods

2.1 Participants

Participants were from the National Longitudinal Study of Adolescent Health (Add Health)[14], a nationally representative study of adolescent health and behavior in the United States, monitored through early adulthood. Of the 12,105 participants interviewed at Wave I (1994–1995), only those with complete datasets through Wave IV were included. Sleep and nap data were obtained at Wave III (2002), and covariates and biomarker data (e.g., CRP,

BMI) were obtained at Wave IV (2008). Only participants with complete data at were included in analyses (n = 2,147).

According to Add Health procedures, all participants provided written informed consent prior to participation in accordance with The Declaration of Helsinki.

2.2. Measures

The dependent variable was high-sensitivity C-Reactive Protein (mg/L). Extensive details on data collection, assays, and quality control are published elsewhere[15].

The independent variables were self-reported nap frequency and sleep duration. Participants were asked how often they napped in the previous 7 days: "never to a few times"($_{few}$nap), "almost every day"($_{most}$nap), and "every day"($_{all}$nap). Consistent with a previous large cohort nap investigation[10], CRP collection was performed ~6 yrs after nap data collection. Individuals reported typical sleep and rise time for weekday and weekend overnight sleep. A difference score was created and weighted: 5/7*(weekday sleep)+ 2/7*(weekend sleep) and assessed as a categorical variable: Short Sleepers (≤5 hrs/night), Medium Sleepers (5–9 hrs/night), and Long Sleepers (≥9 hrs/night)[9]. A conservative low cut-off of 5 hours was chosen to ensure extreme habitual short sleepers were captured.

We included covariates previously linked with CRP alterations[4,10,16]. Sex, age, race/ethnicity, daily physical activity, socioeconomic status, depression status, snoring, and clinical symptoms of illness were self-reported, while BMI, systolic blood pressure, and CRP were not. Physical activity was assessed with a query of how often categories of activities[14] were performed over the past 7 days with a maximum score of 7/week for each category (maximum of 49/week). This score was divided by 7 to obtain a daily activity score. Socioeconomic status was assessed using self-reported yearly household income. Participants responded yes/no to feelings of depression over the past 7 days. Self-reported snoring (yes/no) was used as a proxy for sleep-disordered breathing. Body Mass Index (BMI: weight(kg)/[height(m)]^2), systolic blood pressure (mmHg), and clinical illness symptoms (e.g., "Have you had a fever in the last 2 weeks?" with scores from 0–3, quantifying symptom count) were obtained in conjunction with CRP collection.

2.3 Statistical Analyses

All statistical tests were conduced using SPSS Version 21.0 (Armonk, NY: IBM Corp). CRP levels were log transformed ($_{log}$CRP) to obtain a normal distribution[8,9,11]. One-way ANOVAs and chi-square tests assessed descriptive differences between groups (Sleep Duration, Nap). A Pearson's correlation examined the relationship between nap frequency and sleep duration. Two-way ANCOVAs were used to examine the effect of Nap ($_{few}$nap, $_{most}$nap, $_{all}$nap) × Sleep (Short, Medium, Long) on $_{log}$CRP. Subsequently, $_{log}$CRP differences between nap groups for each level of sleep duration were examined using post-hoc one-way ANCOVAs. Polynomial contrasts, which test for linear or U-shaped patterns between groups, were applied to all ANOVAs. For these, contrast estimates and 95% Confidence Intervals (95% CI) are reported.

3. Results

3.1 Sample characteristics

In the sample, 3.5% reported napping every day, 7.3% almost every day, and 89.2% a few times or never within the last 7 days. As expected, 70.7% were Medium sleepers, 11.3% were Short sleepers, and 18.0% were Long sleepers. Descriptive statistics for these groups are presented in Table 1. Pearson's correlations showed those who napped more frequently had a significantly longer nocturnal sleep duration ($r = .03$, $p = .045$). One-way ANOVA tests found no differences in age, physical activity, systolic blood pressure, snoring, or depression between sleep duration or nap groups. However, there was a significant difference between sleep duration groups for household income; short sleepers had the lowest income ($F_{2,2128} = 3.31$, $p = .037$). A quadratic contrast showed a U-shaped curve for clinical symptoms across nap groups, such that the $_{most}$nap group had fewer symptoms than the $_{few}$nap and $_{all}$nap groups (contrast estimate = .135, 95% CI [.04-.23], $p = .007$). Finally, a chi-square test found a significant difference between gender proportion for nap groups, such that the $_{all}$nap group consisted of fewer women than the other groups ($X^2_{2,2128} = 6.34$, $p = .04$).

3.2 Sleep Duration, Nap Frequency, and $_{log}$CRP

We used a two-way ANCOVA to examine the relationship between nap frequency, sleep duration, and $_{log}$CRP. There was a main effect of nap frequency ($F_{2,2128} = 3.14$, $p = .044$), but no main effect of sleep duration ($F_{2,2128} = .53$, $p = .65$). A quadratic contrast showed there was a significant linear relationship between nap groups: more frequent nappers had higher $_{log}$CRP (contrast estimate = .265, 95 %CI [.045 to .485], $p = .018$). There was a significant interaction between sleep duration and nap frequency ($F_{4,2128} = 2.90$, $p = .021$).

To better understand this interaction, we separated the sample into sleep duration groups and examined whether nap groups had different $_{log}$CRP at each level of sleep duration. One-way ANCOVA tests found no significant differences in $_{log}$CRP between nap groups within the Medium sleep group. However, within the Short sleep group, the $_{all}$nap group had significantly higher $_{log}$CRP than the $_{few}$nap (1.68 vs. 0.87; 95% CI [.143 to 1.55]; $p = .02$) and $_{most}$nap groups (1.68 vs. 0.48; 95% CI [0.44 to 2.1]; $p = .003$). Within the Long sleepers, the $_{most}$nap group had a higher $_{log}$CRP than the $_{few}$nap group (1.21 vs. 0.66; 95% CI [-.98 to −0.37]; $p = .04$).

Figure 1 shows that Medium sleepers, regardless of nap frequency, are clustered and have relatively low $_{log}$CRP. However, $_{log}$CRP in the Short and Long sleepers varies greatly across nap groups.

4. Discussion

It has been posited that sleep loss triggers an immune cascade that ultimately activates CRP, a general marker of systemic inflammation. However, to date, there have been markedly dissimilar results, showing elevated CRP is related to short sleep[7,6], long sleep[8,9,10], both[17], or neither[11,12]. By taking nap frequency into account, we have unified these findings and demonstrated that daytime naps should be considered when assessing immune health.

This is the first study to show a relationship between increased napping and CRP in young adults. Previously, excess napping and CRP had been linked in older adults[10], a population that often exhibits inflammatory alterations[4]. The current study supports this link, and we propose that increased napping is an independent predictor of elevated CRP and, thus, inflammation in otherwise healthy young adults.

The strength of this study is the inclusion of a large number of young adults who were not affected by age-related changes in immune response[4]. We were also able to control for many CRP-affecting factors, including snoring and recent clinical symptoms. However, a limitation of this study is the lack of objective measures. For example, although self-reported snoring is a proxy of sleep-disordered breathing, polysomnography is necessary for objective screening against sleep apnea. Undetected sleep-disordered breathing may have elevated CRP in some participants[4]. Participants may also have misestimated nighttime sleep duration and nap frequency given imprecise nap categories. However, our results mirror those of a previous study with a similar self-reported nap design[10], and thus are unlikely to be biased. The current study is also limited by use of a quasi-longitudinal design such that the link between CRP and sleep/nap characteristics was assessed retrospectively. However, these analyses will be useful in guiding prospective work in an attempt to disentangle sleep-related inflammation processes and directionality.

Despite these limitations, this work is in line with former investigations of sleep and inflammation. For example, the link between insufficient sleep and CRP has been reported in numerous human studies that demonstrate a dose-dependent response to poor sleep quality. Our sample seems to mirror this relationship, as the short sleepers had the highest $_{\log}$CRP overall. However, although sleep may influence inflammation, inflammation may also directly influence sleep. Exogenous administration of IL-6 cytokine, the precursor to CRP, increases sleepiness and fatigue[16]. Moreover, increased IL-6 predicts subsequent deepened sleep (i.e., higher IL-6 leads to greater Slow Wave Sleep ‘rebound’)[18]. Finally, inflammatory diseases increase sleepiness[4]. It follows, then, that elevated CRP has been found in long sleepers, both with and without disease[8–10]. Paralleling these findings, the current study shows that long sleepers who nap almost every day have elevated $_{\log}$CRP.

Interestingly, the aforementioned influence of inflammation on sleep varies: although IL-6 in low doses induces sleepiness[16,19], high doses of IL-6 negatively affect sleep and increase sleep fragmentation[16]. In the current sample, short sleep, especially in the presence of frequent naps, could be a reflection of poor sleep quality caused by increased inflammation. Alternatively, in the long sleepers, more sleep may be necessary to compensate for shallow or fragmented sleep. Future studies would benefit from polysomnographic or actigraphic recordings to further elucidate this mechanism.

Finally, prior to this investigation, the relationship between daytime naps and CRP was ambiguous: elevated CRP was found in older adults who report habitual daytime napping[10], yet daytime naps decreased elevated levels of IL-6 in young adults who napped infrequently[13]. Likewise, we found a linear increase in CRP with nap frequency, but certain sleep/nap subsets have decreased CRP. It may be conjectured that nap habituality changes the relationship between CRP and nocturnal sleep (i.e., increased napping changes nocturnal

sleep quality, altering its link with inflammation). An alternative explanation is that two differing nap types are present in the current sample: 'replacement' naps[20], which make up for lost sleep and return CRP to basal levels, and 'essential' naps, which are a marker of increased underlying inflammation and thus linked with higher CRP. Ultimately, if causality between these factors is determined via prospective investigation, findings could prompt clinical recommendations for limiting excess daytime napping or for managing inflammation in order to restore healthy sleep habits.

Acknowledgments

We thank funding support from NIH R01 AG040133 (to RMCS).

This study uses data from Add Health, a program project directed by Kathleen Mullan Harris and designed by J. Richard Udry, Peter S. Bearman, and Kathleen Mullan Harris at the University of North Carolina at Chapel Hill. Add Health was funded by grant P01-HD31921 from the Eunice Kennedy Shriver National Institute of Child Health and Human Development, with cooperative funding from 23 other federal agencies and foundations. Special acknowledgment is due Ronald R. Rindfuss and Barbara Entwisle for assistance in the original design. Information on how to obtain the Add Health data is available on the Add Health website (http://www.cpc.unc.edu/addhealth). No direct support was received from grant P01-HD31921 for this study.

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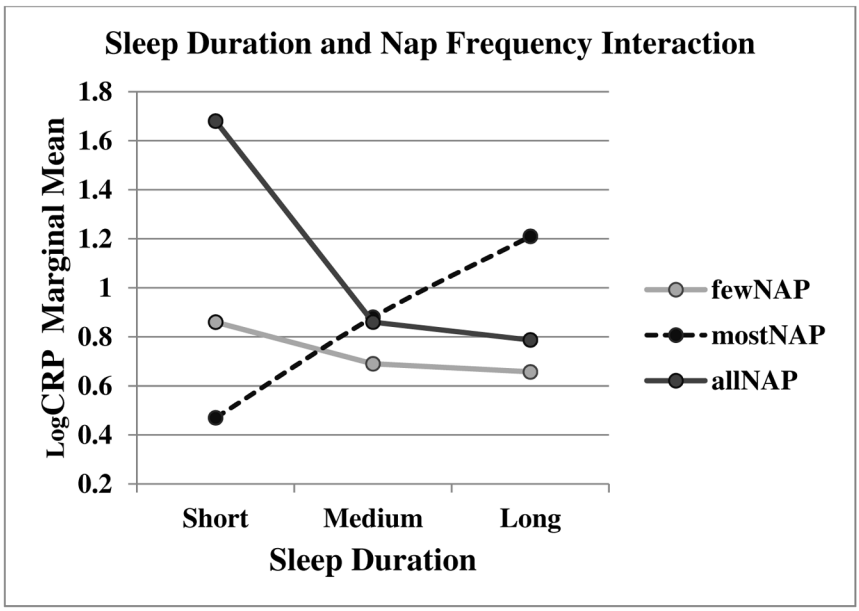

Figure 1.

Sleep duration and nap frequency differentially interact and relate to CRP. Short sleepers = 5 hours hrs/night; Medium sleepers = ≤5–9 hrs/night; Long sleepers = ≥9 hrs/night. $_{few}$nap = no naps to a few naps/week; $_{most}$nap = naps almost every day/week; $_{all}$nap = naps every day/week. Marginal means obtained from ANCOVA.

Table 1

Demographic information in the full sample and separated by sleep duration (Short, Medium, and Long) and nap groups ($_{few}$nap, $_{most}$nap, $_{all}$nap). $_{log}$CRP = log-transformed C-Reactive Protein (mg/L); BMI = body mass index; phys. activity = physical activity composite score (scale from 1 (light) to 7 (active)); BP = blood pressure, measured in millimeters of mercury.

		Sleep Duration Groups			Nap Groups		
	Total (n=2147)	**Short (n=247)**	**Medium (n=1498)**	**Long (n=402)**	**fewNap**	**mostNap**	**allNap**
$_{log}$CRP $_{few}$Nap (n=1902)	0.70±1.3	0.86±1.3	0.69±1.3	0.65±1.4	-----	-----	-----
$_{log}$CRP $_{most}$Nap (n=150)	0.95±1.4	0.37±0.85	0.95±1.5	1.47±1.5	-----	-----	-----
$_{log}$CRP $_{all}$Nap (n=76)	0.83±1.3	2.14±0.94	0.64±1.2	0.69±1.4	-----	-----	-----
Age (yr)	29.05±1.8	29.09±1.8	29.06±1.8	29.0±1.8	29.07±1.78	29.03±1.78	19.17±1.78
Income (thous/yr)	48.20±58.4	*47.17± 60.6*	*46.9±47.1*	*53.87±88.5*	48.46±64.82	48.63±52.59	42.90±31.1
BMI (kg/m^2)	29.14±7.4	29.55±7.8	29.18±7.3	28.76±7.8	29.23±7.41	29.00±7.43	29.37±7.22
Phys. Activity Score	0.91±0.8	0.94±0.83	0.91±0.83	0.89±0.88	0.93±0.85	0.89±0.83	0.89±0.84
Systolic BP (mmHg)	124.58±13.6	124.4±13.2	124.8±13.5	124.1±14.2	124.53±13.6	124.44±13.7	124.6±13.7
Clinical Symptoms (#)	0.45±0.73	0.46±0.75	0.44±0.72	0.49±0.75	*0.54± 0.73*	*0.33± 0.74*	*0.5± 0.65*
Snoring (%)	49.7	45.0	50.4	50.1	49.8	48.6	50.6
Depressed (%)	28.9	28.5	29.0	29.9	27.0	31.2	30.8
Gender (%female)	54.2	52.6	53.8	56.8	*55.0*	*54.8*	*48.4*

Italicized rows indicate respective groups differed significantly (p-value < .05).