Sleep Health 8 (2022) 283–287

Contents lists available at ScienceDirect

Sleep Health

Journal of the National Sleep Foundation

journal homepage: sleephealthjournal.org

Childhood adversity is associated with heightened inflammation after sleep loss

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ARTICLE INFO

Article History:
Received 4 November 2021
Revised 8 March 2022
Accepted 24 March 2022

Keywords:
Childhood adversity
Sleep restriction
Inflammation
C-reactive protein

ABSTRACT

Objectives: To investigate whether childhood adversity exacerbates the relationship between sleep restriction and inflammation.
Methods: Participants (N = 46) were randomly assigned to an experimental sleep restriction group (n = 25) or a night of typical sleep (n = 21). Participants provided a dried blood spot sample the morning before and after the experimental night.
Results: A significant interaction emerged between childhood adversity and group assignment on C-reactive protein (CRP) after the experimental night (Beta = −0.02, SE = 0.01, P = .03, 95% CI: −0.05, −0.002). Sleep restriction resulted in an increase in CRP at high levels of childhood adversity (+1 SD; Effect = −0.57, SE = 0.15, P< .001; 95% CI: −0.87, −0.26) but not low levels of childhood adversity (Effect = −0.08, SE = 0.10, P = .40; 95% CI: −0.29, 0.12).
Conclusion: Childhood adversity may amplify the effect of sleep loss on markers of inflammation.

Individuals who experience childhood adversity are at increased risk for poor adult health.[1-5] Dysregulation of the immune system and associated chronic immune system inflammation is believed to be a likely biological mediator of this relationship. Meta-analyses indicate that childhood adversity contributes to a proinflammatory state in adulthood.[6,7] This biological profile is implicated in chronic conditions which disproportionately affect individuals who experienced adversity during childhood.[1]

The behavioral pathways which may contribute to the observed relationship between childhood adversity and inflammation are less understood. One health behavior or process which is consistently linked to inflammation is sleep.[8,9] Sleep disturbances and short sleep duration are linked to higher levels of markers of immune system inflammation, and childhood adversity relates to poor sleep quality across the lifespan.[10-12] While most work on sleep and inflammation use correlational designs and examine habitual sleep patterns,[10-12] observational and experimental studies indicate that acute sleep restriction results in increases in levels of markers of immune system inflammation.[13,14] Emerging research suggests that substantial trait-like differences exist in how individuals respond to sleep restriction or deprivation,[15,16] but the psychological characteristics or experiences that contribute to this variability are largely unknown.[15] To our knowledge, to date, no experimental studies have specifically investigated whether childhood adversity affects the degree to which sleep restriction negatively impacts biomarkers or other health outcomes. In previous work, childhood adversity amplified links between disease burden and inflammation,[17] and associations between stress and health.[18] In a previous experimental sleep deprivation study, observed changes in immune blood cells mirrored those which are typically observed following exposure to stress.[19] Since childhood adversity is linked to more pronounced immune system inflammatory responses to stress,[20-22] and since as noted above sleep restriction has been shown to have similar effects on the immune system to stress exposure,[19] it is possible that childhood adversity may similarly amplify the effects of acute sleep restriction on inflammation.

In the current preliminary investigation, based on literature documenting a relationship between naturalistic patterns of sleep and childhood adversity,[12] and a body of work focused on the relationship between childhood adversity and inflammation,[6,7] we investigated whether childhood adversity moderates the relationship between mild sleep restriction and changes in a marker of inflammation. Based on previous work indicating that acute stressors are linked to rises in markers of immune system inflammation,[23] and more specifically work indicating a link between sleep restriction and increases in C-reactive Protein (CRP),[24] we chose to focus on CRP as our inflammatory outcome in this work. In addition, in our previous work, compared to other inflammatory markers (eg, Interleukin-6), we were more able to successfully detect levels of CRP in samples

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https://doi.org/10.1016/j.sleh.2022.03.006
2352-7218/

comprised of individuals free from chronic health conditions.[25] We hypothesized that individuals who reported high levels of childhood adversity would exhibit larger increases in CRP following one night of sleep restriction, compared to individuals who reported low levels of childhood adversity.

Method

Participants

Participants included 53 young adults living in the northwestern United States who took part in a larger study on sleep and socioemotional functioning. Participants were required to be between the ages of 18-30 years, and they were ineligible if they were a smoker/nicotine user, had a BMI of >30, had a lifetime history or current psychiatric disorder or substance use disorder diagnosis, had any medical conditions that may impact sleep and/or mood, were diagnosed with or had a suspected diagnosis of a sleep disorder (eg, insomnia, circadian rhythm disorders), were currently pregnant or lactating, or used medication known to impact sleep and/or mood. Some participants were not excluded at the intake assessment for the larger study, but were excluded from the present analyses because they opted out of the blood spot collection (n = 3) or had invalid CRP data (n = 2). Additionally, one participant had an autoimmune disorder that may impact CRP levels (n = 1) and another participant became ill during the experimental night and did not complete the study (n = 1) resulting in the final analytic sample of 46 (M_{age} = 19.46, SD_{age} = 2.10; 82.6% female; 91.3% white, 2.2% Asian, 2.2% American Indian/Alaskan Native, 4.3% biracial or multiracial; 6.5% Hispanic/Latino). Sample characteristics by group are reported in Table 1.

Procedures

All study procedures were approved by Montana State University's Institutional Review Board. Participants were recruited from a university subject pool based on responses to electronic self-reported eligibility screener questions. Initial screening questions for the subject pool included questions about age, medication use, lifetime history of psychiatric disorders, sleep disorders, and body mass index. Based on these pre-screener questions, participants who met initial eligibility criteria were provided with option to sign up for the study, where eligibility criteria were confirmed at the initial intake assessment completed by a study staff member (ie, undergraduate research assistant). During the intake assessment, participants completed informed consent, questionnaires, and to confirm eligibility, height and weight were measured. Eligible participants were provided with an actigraph and a blood sample collection kit. In the week leading up to the experimental night, participants were asked to refrain from altering their typical caffeine or alcohol use. Participants were also asked to maintain their regular sleep schedule, which was verified using actigraphy. Participants wore the actigraph on their nondominant wrist (Micro Motionlogger, Ambulatory Monitoring, Inc.) and completed a sleep diary[26] to assist in the identification of sleep-wake periods for at least 1 week at home prior to returning to the lab for the experimental night. Actigraphy data was collected using the zero crossing mode in 1-minute epochs and scored using the Cole-Kripke algorithm. On the day that participants returned to the lab for the experimental night, they were asked to refrain from napping, altering their sleep schedule or regular caffeine use, or using any alcohol or drugs. On the morning before participants reported to the lab for the experimental night, they collected their first blood sample at 9:00.

Upon arrival to the lab on the experimental night (at 22:00), participants were randomly assigned to the experimental sleep restriction group (n = 25; 4-hour time in bed opportunity from 4:00 to 8:00), or a night of typical sleep (n = 21; 8-hour time in bed opportunity from 24:00 to 8:00). These times in bed opportunities were based on normative sleep time data collected from the student population at this University. Participants were randomized using a random number generator, with a 1:1 ratio. Participant randomization sequence was kept in a password protected file only accessible to the principal investigator (CAP), and participants and research staff were masked to participant condition until the evening of the lab visit. In the lab, participants were not permitted to engage in physical activity, or to consume caffeine, nicotine, stimulants, or alcohol. Participants wore the actigraph for the duration of the lab visit and were continuously monitored by study staff to ensure compliance with the assigned sleep condition. Standardized snacks, breakfast, and water were provided. On the morning after the experimental night, participants completed the second blood sample at 9:00. All participants received course credit for participating, and nonresearch options for earning credit were available as an alternative. All participants completed the study in 2019.

Table 1
Demographics and descriptive statistics by group.

	Sleep restriction group M (SD) / n (%)	Control group M (SD) / n (%)
Age	19.64 (2.08)	19.24 (2.14)
Sex (% female)	20 (80)	18 (85)
Race/Ethnicity		
White	22 (88)	20 (95.2)
Asian	0 (0)	1 (4.8)
American Indian/Alaskan Native	2 (8)	0 (0)
Multiracial	2 (8)	0 (0)
Hispanic	2 (8)	1 (4.8)
RFQ	27.24 (12.25)	20.86 (4.51)
Baseline TST	445.32 (45.92)	461.08 (45.81)
Experimental night TST	222.88 (15.23)	438.80 (26.58)
Baseline CRP	1.08 (0.84)	1.06 (0.98)
Post-experimental night CRP	1.45 (0.90)	1.05 (0.98)

RFQ, Risky Family Questionnaire; TST, total sleep time, measured by actigraphy and reported in minutes; CRP, C-Reactive Protein, reported in mg/L.

Assessments

Risky family questionnaire. Participants reported on their childhood adversity using the 13-items Risky Family Questionnaire (RFQ).[27] The RFQ captures the degree to which an individual's childhood (age 5-15) was characterized by high conflict, low warmth, or unpredictability (α = 0.92). Participants reported on how true each statement was for them on a scale from 1 (*not at all*) to 5 (*very often*).

CRP. Immune system inflammation was assessed using dried blood spots (DBS) collected on the morning before and the morning after the experimental night.[28] Samples were collected by puncturing a finger using a microlancet, and spots of capillary blood were collected onto filter paper, which were dried overnight and transferred to a −20°C freezer for storage. DBS samples were then assayed in duplicate using a CRP high sensitivity enzyme-linked immune-sorbent assay following methods used in prior work.[29] CRP levels are reported in mg/L. CRP analyses were performed by the Principal Investigator of the Stress, Adversity, Resilience, and Health Lab on the Montana State University campus. The principal investigator was trained to perform the referenced validated protocol by investigators at the University of Pittsburgh.

Analytic plan

First, preliminary analyses examined differences in total sleep time using independent samples t-tests to ensure that there were no differences in sleep duration between participants randomly assigned to the control group and the experimental group in the week leading up to the overnight visit. An independent samples t-

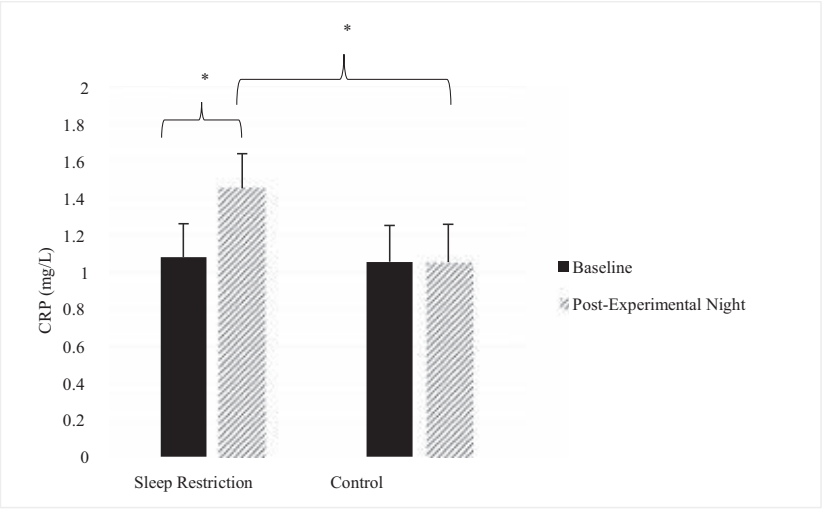

Fig. 1. Sleep restricted participants experienced increased CRP compared to participants in the control group. The asterisks denote a statistically significant difference. CRP, C-reactive protein.

test was also conducted to ensure that participants in the sleep restriction group slept less than participants in the control group on the experimental night. As an additional manipulation check, a mixed effects ANOVA was conducted to examine changes in CRP for the sleep restriction group, with group as the between-subjects factor and measurement time (pre- and postexperimental night) as the within-subjects factor. We additionally tested between-subjects differences in post-experimental night CRP by group using an ANCOVA, while adjusting for pre-experimental night CRP.

Finally, to test our primary hypothesis, a linear regression model was conducted using the PROCESS macro for SPSS.[30] Post-experimental night CRP was included as the dependent variable, and childhood adversity, group assignment, and the interaction between childhood adversity and group assignment were entered as predictors. Pre-CRP was entered as a covariate. A post-hoc sensitivity power analysis using G*Power version 3.1.9.7 was conducted.[31] This sensitivity analysis indicated that with 80% power and an α error probability of .05, our sample size would allow us to detect an effect size of $f^2 = 0.29$ or larger, which is a medium effect size. All analyses were conducted using SPSS version 25.

Results

Descriptive statistics for all variables of interest are reported in Table 1. An independent samples t-test suggested that participants in the sleep restriction group slept for a shorter duration based on actigraphy on the experimental night compared to the control group ($t(43) = -34.25$, $P < .001$; 95% CI: −228.64, −203.20). There were no differences in average actigraphy-measured sleep duration during the baseline week for sleep restricted or control participants ($t(43) = -1.15$, $P = .26$, 95% CI: −43.40, 11.88). A mixed effects ANOVA examining changes in CRP indicated that there was a significant interaction between time (pre-post experimental night) and group (sleep restriction or control; $F(1,44) = 23.22$, $P < .001$). There was a significant increase in CRP from baseline to after the experimental night for those in the sleep restriction group ($P < .001$, 95% CI: −0.48, −0.27), suggesting that CRP was higher after sleep restriction. There was no significant difference in the control group between baseline and CRP collected after the experimental night ($P = .98$, 95% CI: −0.12, 0.11). Additionally, we compared group differences in CRP after the sleep restriction night using an ANCOVA, while adjusting for baseline CRP. Results indicated that there was a significant between-subjects effect on CRP ($F(1, 43) = 22.72$, $P < .001$, 95% CI: 0.22, 0.53). The sleep restriction group had significantly higher CRP than the control group after the experimental night. These group-level differences are displayed in Fig. 1.

A regression model was conducted examining post-experimental night CRP (controlling for pre-CRP), with group assignment, childhood adversity, and the interaction between childhood adversity and group assignment as predictors. The overall model was significant ($R^2 = 0.96$, $P < .001$), and a significant interaction emerged between childhood adversity and group assignment (Beta = −0.02, SE = 0.01, $P = .03$, 95% CI: −0.05, −0.002). Simple slopes indicated that at high (+1 SD; Effect = −0.57, SE = 0.15, $P < .001$; 95% CI: −0.87, −0.26) levels of childhood adversity, but not low levels of childhood adversity (−1 SD; Effect = −0.08, SE = 0.10, $P = .40$; 95% CI: −0.29, 0.12), sleep restriction resulted in an increase in CRP. This is displayed in Fig. 2.

Discussion

To our knowledge, this work is the first to examine whether childhood adversity amplifies the consequences of sleep restriction for immune system inflammation. Similar to previous work, we found that levels of CRP, a marker of immune system inflammation, rise following acute sleep restriction. Our data extend this work by showing that the relationship between sleep restriction and increased CRP is particularly evident for those reporting high levels of adversity during childhood. Emerging research suggests that there is substantial interindividual variation in responses to sleep loss.[15,16] To our knowledge, our study is the first to provide preliminary evidence to suggest that childhood adversity is one experience that may affect vulnerability to the negative physiological consequences of sleep loss.

Our findings corroborate work indicating that in adulthood, the impact of stressors and challenging experiences on health-relevant outcomes is particularly pronounced for individuals who experienced high levels of childhood adversity compared to those who experience less childhood adversity. For example, in previous work, childhood adversity predicted more pronounced declines in sleep quality during the first year of college.[32] Separately, the relationship between daily life stressors and levels of inflammatory markers was more pronounced for individuals with child abuse history compared to those with no history of abuse during childhood.[33] Childhood adversity also appears to impact the magnitude of inflammatory responses to a

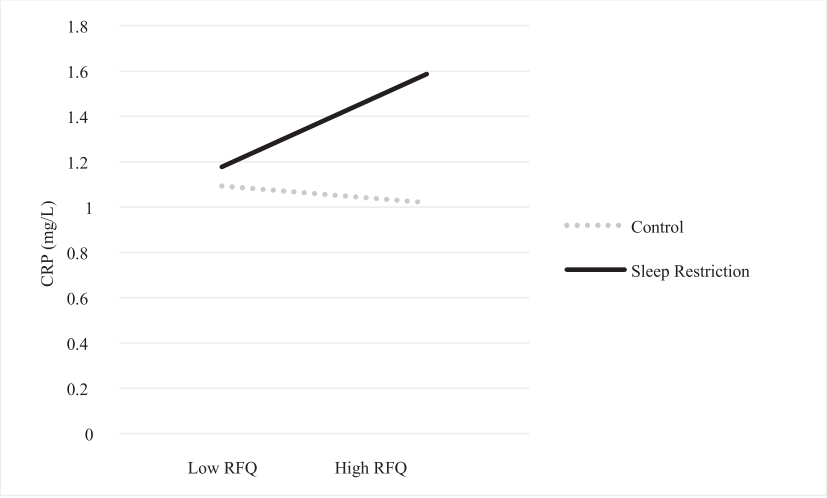

Fig. 2. Higher scores (+1 SD) on the RFQ predict increased CRP for participants undergoing sleep restriction compared to those with lower scores on the RFQ (−1 SD). CRP, C-reactive protein; RFQ, risky family questionnaire.

social stressor.[21,22] Separately, prior work found that childhood abuse moderates the effect of current trauma on structural integrity in the brain.[34] To our knowledge, the current work is the first to investigate whether childhood adversity similarly magnifies the negative consequences of sleep restriction on markers of levels of markers of immune system inflammation. The conceptual framework of the current study is similar to the frameworks used in this body of work in that it tests whether the prior experience of adversity during childhood amplifies the negative consequences of future challenges or stressors on a health-relevant outcome. The current investigation is different in that the stressor we focus on is not a psychological stressor, or a recent trauma exposure, but is rather a biological stressor.

According to the early life sensitivity model, childhood and adolescence are periods of heightened sensitivity, with high levels of plasticity. During these sensitive periods, both cognitive and biological systems undergo programming informed by an individual's environment which is designed to prepare the individual for the future environment they are likely to inhabit.[35,36] If the early environment is characterized by high levels of adversity, this acts as a signal that future environments are likely to be similarly risky and or challenging. At the level of biological systems, it is believed that early adversity calibrates systems, including the immune system, to be more vigilant and responsive to any challenge it faces.[35] The findings from the current study can be interpreted in the context of this model. Specifically, it is possible that the hypervigilant immune system profile associated with childhood adversity, contributes to an exaggerated inflammatory response in response to the experience of sleep loss. The less pronounced increases in inflammation (ie, levels of CRP) for individuals who had less childhood adversity in our sample may be explained in a similar way. Since their early environments were characterized by less challenge and adversity, their immune systems may have been programmed to be less responsive to future challenges.

In the future, findings should be replicated in a larger sample. Additionally, our participants were all university students, and predominantly Non-Hispanic White females, so investigating these associations in other samples who have experienced childhood adversity would provide data on the generalizability of these findings. A more comprehensive assessment of inflammatory markers should be obtained in future studies to understand whether this relationship is evident across multiple pro-inflammatory cytokines and anti-inflammatory cytokines. Future research should examine how childhood adversity may confer vulnerability to sleep loss in other domains, such as emotional reactivity or neurobehavioral performance. In addition, it would be useful to understand the additive and cumulative effects of multiple nights of sleep restriction on markers of inflammation as well as understand the duration of the effect. Finally, this study examined retrospective reports of childhood adversity, but understanding how ongoing adversity may influence vulnerability to sleep loss during childhood may be an important future direction, as sleep undergoes dramatic developmental changes across childhood, and youth may already experience heightened sensitivity to sleep loss compared to adults.[37]

Overall, we provide initial evidence that acute sleep restriction may contribute to a more pronounced inflammatory response for individuals who experienced high levels of childhood adversity (compared to those who experienced less childhood adversity), which may contribute to increased risk for conditions which involve inflammatory processes including cardiovascular disease, diabetes, and depression. Thus, increased inflammatory reactivity to sleep disturbances could be a pathway through which childhood adversity imparts disproportionate risk for inflammatory diseases in adulthood. These preliminary findings suggest that childhood adversity should be considered when tailoring personalized sleep recommendations and when developing sleep interventions. Promoting adequate sleep duration may be particularly important for those with high levels of childhood adversity.

Declaration of conflict of interest

The authors have declared no conflicts of interest.

Funding

Research reported in this publication was supported by the National Institute of General Medical Sciences of the National Institutes of Health under Award Numbers P20GM103474 and U54GM115371. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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