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Sleep and Inflammation During Adolescents' Transition to Young Adulthood

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Abstract

Purpose: This study investigated the extent to which multiple sleep dimensions are associated with inflammation during adolescents' transition to young adulthood, a developmental period when sleep difficulties and systemic inflammation levels are on the rise. Additionally, the moderating roles of SES and ethnicity were explored.

Methods: A total of 350 Asian American, Latino, and European American youth participated at two-year intervals in Wave 1 (n = 316, M_{age} = 16.40), Wave 2 (n = 248 including 34 new participants to refresh the sample, M_{age} = 18.31), and Wave 3 (n = 180, M_{age} = 20.29). Sleep duration (weekday and weekend) and variability in duration (nightly and weekday/weekend) were obtained from eight nights of wrist actigraphy. Subjective sleep quality was assessed using the Pittsburgh Sleep Quality Index. Levels of C-reactive protein (CRP), a biomarker of systemic inflammation, were assayed from dried blood spots obtained from finger pricks.

Results: Multilevel models demonstrated that greater weekday/weekend sleep variability, as well as worse sleep quality, were associated with higher CRP; shorter weekend duration was associated with higher CRP only at younger ages. Shorter weekday duration was associated with higher CRP only among high-SES youth, whereas greater nightly variability was associated with higher CRP only among European American youth.

Conclusions: Aspects of poor sleep may contribute to the rise of CRP during adolescents' transition to young adulthood, especially in earlier years. In addition, some sleep-CRP associations may vary as a function of youth's SES and ethnicity.

Keywords: sleep, actigraphy, inflammation, CRP, adolescence, young adulthood, longitudinal

Implications and Contribution

This study contributes to the limited literature on sleep and inflammation during adolescents' transition to young adulthood. The findings suggest that consistent and sufficient sleep durations and good sleep quality may slow the developmental rise of systemic inflammation. The roles of SES and ethnicity should be further explored.

Introduction

The prevalence of sleep issues such as insufficient, inconsistent, and poor quality sleep increases during adolescence and the transition to young adulthood.[1,2] Given that poor sleep is associated with chronic health conditions during adulthood including cardiovascular disease (CVD),[3–6] a leading cause of mortality globally,[7] adolescents' poor sleep may have lasting consequences for adult health. Inflammatory markers such as C-reactive protein (CRP) are important markers of risk for CVD and predict development of CVD even in currently healthy individuals.[8,9] Although CVD is uncommon during adolescence, CRP levels may distinguish adolescents who are at differential risk for future CVD.[9] Thus, advancing the understanding of the link between adolescents' sleep and their CRP levels can offer insights into potential long-term consequences of problematic sleep during this key period of developmental transition.

However, sleep-CRP links in youth remain largely unknown because the majority of studies have focused on adult populations. In adults, poor sleep quality has been associated with higher CRP levels, suggesting negative repercussions of unrested sleep. Additionally, both short and long sleep durations have been associated with elevated CRP levels,[3,6,10] indicating that excessive short and long durations are both problematic in adults.

The few extant studies with adolescents have focused on sleep duration rather than quality and showed short, rather than long, duration to be associated with higher CRP levels[11,12] and likelihood of being in the high-risk CRP group.[13] Additionally, greater variability in sleep duration has been associated with higher CRP levels[14] and likelihood of being in the high-risk CRP group[13]. Yet to our knowledge, the only report of the link between sleep quality and CRP during adolescence came from the first wave of the current longitudinal study when participants were in high school (14–18 years) and showed no association between sleep quality and CRP.[14]

Based on the emerging evidence,[11–14] short and inconsistent sleep durations, but not poor sleep quality, may trigger proinflammatory processes during adolescence prior to the transition to young adulthood, but the paucity of research requires additional studies.

As a result of relatively few studies focusing on youth, two key questions remain unanswered. First, it remains unclear whether the trends continue into young adulthood, as past research captured a rather narrow age-range. The health benefits of longer sleep durations may reduce as adolescents age since the recommended sleep durations decline with age.[15] Preliminary support for this possibility was found in our aforementioned report with high school students; shorter sleep duration was associated with higher CRP for younger but not older adolescents.[14] On the other hand, sleep quality may emerge as a risk factor in the post high school years, akin to studies with adults demonstrating that sleep quality is more robustly associated with inflammation as compared with sleep duration.[6] Moreover, inconsistent sleep durations may continue to be linked with CRP, based on cross-sectional studies that reported associations between greater variability in sleep duration and higher CRP in adolescents[13,14] and adults.[16] As such, it would be valuable to examine sleep-CRP links over a longer age-span.

Secondly, whether sleep-CRP links differ by SES or ethnicity remains largely unknown.[4] The links may be more apparent among low-SES and ethnic minority youth since socioeconomic and ethnic disparities may sensitize them to the influence of inadequate sleep on inflammation. Health disparities perspectives contend that exposure to a stressor exerts stronger influences on those with more sociocultural disadvantages,[17] and low-SES and ethnic minority youth tend to face additional sociocultural disadvantages such as poverty[18,19] and discrimination.[20] Alternatively, low-SES and ethnic minority youth may show weaker sleep-CRP links if their additional sources of stressors dampen their physiological responses[21] and obscure the influence of poor sleep on inflammation. They may also have elevated baseline levels of inflammation, offering less room to shift as a function of their sleep characteristics.

To address these gaps in research, the present study investigated sleep-CRP links during adolescents' high school and post high school transitional years. We examined multiple sleep dimensions including duration, variability in duration, and quality, distinguishing weekday and weekend sleep parameters given considerable discrepancies between adolescents' weekday and weekend sleep patterns.[2,22] Furthermore, we explored the moderating roles of SES and ethnicity.

Methods

Participants

Data were obtained from 350 adolescents (57% female; 21% Asian, 31% European American, 42% Latino, 6% other ethnicity) who participated in a three-wave longitudinal project with their caregivers at two-year intervals. In Wave 1 (October 2011–June 2012), 316 adolescents (M_{age} = 16.40, *SD* = 0.74) were recruited from 10th and 11th grade classrooms at four public high schools in the Los Angeles metropolitan area. Research staff introduced the study and distributed flyers to students in the classrooms and also mailed the flyers to the students' homes. Staff then called students' homes to provide more information, answer questions, obtain verbal consent, and schedule visits for the families who wished to participate in the study. Written consents were obtained during the first visit, which took place in the family's home or a local research center depending on the family's preference.

In Wave 2 (October 2013–August 2014), 248 youth (M_{age} = 18.31, *SD* = 0.77) participated. Of the initial participants, 214 returned. Additionally, 34 new, grade-matched participants were recruited to refresh the sample and adjust for attrition bias[23]. In Wave 3

(October 2015–August 2016), 180 youth (M_{age} = 20.29, *SD* = 0.74) who participated in at least one previous wave returned.

Seventy percent of the participants returned in at least one subsequent wave. Compared to those who did not return, participants who returned had higher parental education levels (t[344] = -2.21, p = .028). Asian Americans participated in fewer waves compared with European Americans and Latinos (F[3, 346] = 4.73, p = .003). Those who returned vs. did not return did not differ in terms of sex (t[342] = -0.70, p = .488), waist circumferences (b = -.85, *SE* = 1.52, p = .578), and CRP levels (b = .33, *SE* = .31, p = .289). They also did not differ in terms of sleep duration (weekday: b = .03, *SE* = .12, p = .824; weekend: b = -.18, *SE* = .16, p = .261), variability (nightly: b = 1.07, *SE* = 3.32, p = .748; weekday/weekend: b = -.10, *SE* = 6.15, p = .987) and quality (b = -.85, *SE* = 1.52, p = .578), but those who returned reported worse sleep quality than those who did not return (b = .70, *SE* = .32, p = .031).

Previously-published studies with this sample examined whether sleep was linked to inflammation,[14] gene regulation,[24] HPA-axis functioning,[25] mood,[26] discrimination,[27] and family stress,[28] using only the first wave of the data[14,25–28] or a subset of the sample.[24] The present analyses utilized additional waves of data collected after those reports, enabling the assessment of sleep-CRP links across a longer age span into young adulthood.

Procedure

Participants wore a wrist actigraph (Micro Motionlogger Sleep Watch, Ambulatory Monitoring, Inc.; Ardsley, NY) on their non-dominant hand before going to bed for eight consecutive nights. They were told to keep it on until the following morning when they got out of bed and to press the event marker on it to indicate when they turned off the lights to go to sleep, got out of bed in the middle of the night, and got out of bed in the morning. Participants wore the actigraph for an average of 6.19 nights across waves.

Additionally, participants completed measures on subjective sleep quality, depressive symptoms, and substance use. Adolescents and their primary caregivers reported demographic information. Staff measured participants' waist circumference and obtained finger-prick blood samples. Participants completed additional measures not reported in this paper. They received $50 in Wave 1, $75 in Wave 2, and $120 in Wave 3. Additionally, two movie theater passes were provided to incentivize completion of the daily measurement protocol. All procedures were approved by the UCLA Institutional Review Board.

Measures

Actigraphy sleep duration and variability. Actigraphy data were processed using one-minute epochs and the Sadeh scoring algorithm in the software package Action 4 (Ambulatory Monitoring, Inc.; Ardsley, NY).[2,14,29–31] Sleep duration was total hours scored as sleep during adolescents' in-bed period, which began at the time of the first event marker indicating when participants turned off the lights to go to sleep, and ended at the time of the last event marker indicating when they got out of bed in the morning. Weekday sleep durations (Sunday–Thursday nights) were averaged to compute participants' mean weekday sleep duration. Friday and Saturday night sleep durations were averaged to compute their mean weekend sleep duration.

Nightly variability in sleep duration was calculated by taking the mean of the absolute differences between a participant's mean nightly sleep duration and each individual night's sleep duration.[2,14,32] Variability in weekday vs. weekend duration was computed by taking the absolute difference between a participant's mean weekday and weekend sleep duration (weekday/weekend variability).

Subjective sleep quality. Participants' sleep quality was assessed using the 18-item Pittsburgh Sleep Quality Inventory (PSQI).[33] Open-ended (e.g., usual bedtime) and 4-point Likert scale (e.g., overall sleep quality during the past month: very good, fairly good, fairly bad, very bad) questions assessed subjective sleep quality and disturbances during the past month. Using the traditional scoring approach, the items were coded to compute seven sleep components (e.g., disturbance, duration), which were summed to yield one global score (possible range: 0-21) with higher scores indicating worse sleep quality.[33,34]

CRP. CRP levels were assayed from dried blood spots, a well-validated and relatively non-invasive procedure.[35,36] A sterile, disposable microlancet was used to puncture participants' fingers that had been cleaned with alcohol. After wiping away the first drop, up to seven drops of capillary blood were allowed to fall onto standardized filter paper. Blood spot samples were dried overnight, and then stored at -80°C. Two spots per participant were shipped to the Laboratory for Human Biology Research at Northwestern University and processed to assess levels of CRP using high-sensitivity enzyme-linked immunosorbent assay. The assay had a lower detection limit of .030 mg/L. Samples were run in duplicate, and intra- and inter-assay coefficients of variation were <6.4% and <9.3%, respectively. Ten samples with CRP values above 10mg/L were excluded from analyses as they reflected temporary acute inflammatory response due to infection.[37] CRP values were log-transformed to address skewness.

Parental education. Parental education levels were used as an index of socioeconomic status (SES). Primary caregivers reported their and their spouse's highest level of education (1 = some elementary school; 11 = graduated from medical, law, or graduate school). Primary caregivers' and spouses' levels of education were averaged (M = 7.17, SD = 1.87).

Ethnicity. Participants self-reported their ethnicity from a list of 45 labels (e.g., European-American, Asian-American, Latino/a). They were also given the opportunity to self-report their ethnicity not on the list. Additionally, parents reported the birth countries of participants' parents and grandparents. The responses were then coded into pan-ethnic categories: European American (30%), Asian American (22%), and Latino (42%). The rest was coded as other ethnicity (6%).

Covariates. Age, sex, waist circumference, depressive symptoms, and substance use were included as covariates. Age was computed from parent reports of participants' date of birth. Information on sex was collected via self-reports at study entry. At each wave, waist circumference, an index of adiposity, was measured by staff. Depressive symptoms were assessed at each wave using the Center for Epidemiologic Studies Depression (CES-D) Scale, which consisted of 20 items (e.g., "You were bothered by things that usually don't bother you.") that participants self-reported on a 4-point scale (1 = rarely/none; 4 = most/all).[38] Substance use was participants' lifetime use of various types of substance including cigarette, alcohol, marijuana, LSD, and ecstacy, assessed at each wave using the Youth Self-Report (YSR) scale.[39]

Data Analysis Strategy

Using Stata SE 15.0, multilevel models were estimated to examine the associations between sleep and CRP wherein waves (Level 1) were nested within persons (Level 2). Prior to fitting the models, outliers for sleep variables (+/- 3 SD) were winsorized with highest/lowest values within the range.[2,40] Separate models were fit for each sleep parameter.

First, grand-mean centered sleep variables were entered with age, sex, parental education, ethnicity, depressive symptoms, substance use, and waist circumference as covariates to predict wave-varying CRP levels. This set of analyses leveraged all data by pooling across between- and within-person associations to examine the overall sleep-CRP link. Sleep, age, depressive symptoms, and substance use, and waist circumference (wave-varying) were modeled at Level 1. Sex, parental education, and ethnicity (person-varying) were modeled at Level 2. Age was centered around 14.5 (the youngest age), and parental education and waist circumference were grand-mean centered.

Second, within-person associations between sleep and CRP were examined in another set of multilevel models. Sleep variables were person-mean centered, such that significant effects represented associations with CRP that occurred when adolescents experienced greater than their average levels of sleep. This set of analyses examined whether changes in adolescents' sleep characteristics during their transition to adulthood would be concurrently associated with changes in their own CRP levels. Age, sex, parental education, ethnicity, depressive symptoms, substance use, and waist circumference were included as covariates. Person-mean centered sleep, depressive symptoms, substance use, and waist circumference, as well as age (centered around 14.5) were wave-varying predictors and thus were modeled at Level 1. Sex, parental education, and ethnicity (person-varying) were modeled at Level 2.

Lastly, age, parental education, and ethnicity were each added as moderators to examine whether the within-person sleep-CRP associations varied as a function of age, parental education, and ethnicity. Significant interactions were followed by tests of simple slopes where a given sleep-CRP link was estimated for different ages (14–22 years), parental education (-1SD, average, +1SD), and ethnicity (European American, Asian, Latino, and other ethnicity).

Results

Table 1 presents descriptive statistics by wave. Across waves, weekday and weekend sleep durations shortened, nightly and weekday/weekend sleep variability increased, and sleep quality worsened; CRP levels increased.

Sleep and CRP

As shown in Table 4 and Figure 1, the overall sleep-CRP association was significant for two of the five sleep dimensions; greater weekday/weekend variability (b = .18, SE = .07, p = .008) and worse sleep quality (b = .07, SE = .02, p = .003) were associated with higher CRP. Across 14–22 years when CRP increased with age (b = .14, SE = .04, p < .001), CRP was higher if weekday/weekend variability was high or sleep quality was poor. Weekday duration (b = -.04, SE = .06, p = .482), weekend duration (b = .02, SE = .04, p = .672), and nightly variability (b = .11, SE = .11, p = .329) were not associated with CRP.

As shown in Table 5, the within-person sleep-CRP association was significant for weekday/weekend variability. Increases in a given participant's weekday/weekend variability over the years were associated with increases in the participant's own CRP levels (b = .20, SE = .08, p = .019).

Age Moderation

Age moderated the within-person sleep-CRP association for weekend duration (b = .12, SE = .04, p = .003). According to tests of simple slopes, from 14 years (b = -.58, SE = .18, p = .001) to 17 years (b = -.23, SE = .08, p = .005), decreases in a participant's weekend duration were associated with increases in the participant's CRP levels. Yet from 18 years (b = -.11, SE = .06, p = .083) to 21 years (b = .24, SE = .12, p = .051), the within-person association was non-significant. At 22 years, the association flipped; increases in a participant's weekend duration were associated with increases in the participant's CRP levels (*b* = .36, *SE* = .16, *p* = .024). Figure 2 summarizes the findings.

SES and Ethnicity Moderation

Participants with lower parental education had higher CRP (*b* = -.11, *SE* = .04, *p* = .010). Asian Americans exhibited lower CRP than European Americans (*b* = .62, *SE* = .21, *p* = .003).

Two significant variations emerged concerning the moderating roles of SES and ethnicity in the within-person sleep-CRP associations. First, the weekday duration interacted with parental education in predicting CRP (*b* = -.09, *SE* = .04, *p* = .037). As shown in Figure 3a, tests of simple slopes revealed that for those with high parental education levels (+1SD mean), decreases in a given participant's weekday duration was associated with increases in the participant's own CRP levels (*b* = -.28, *SE* = .11, *p* = .013). However, the within-person association was non-significant for average-parental education (*b* = -.11, *SE* = .08, *p* = .167) and low-parental education participants (*b* = .06, *SE* = .11, *p* = .609).

Second, the within-person association between nightly variability and CRP differed significantly between Latino and European American participants (*b* = .89, *SE* = .37, *p* = .016). As shown in Figure 3b, tests of simple slopes revealed that increases in a participant's nightly variability was associated with increases in the participant's own CRP levels only among European American youth (*b* = .62, *SE* = .31, *p* = .044). The slopes were non-significant not only for Latino (*b* = -.28, *SE* = .21, *p* = .190) but also for Asian (*b* = .14, *SE* = .39, *p* = .712) and other ethnicity (*b* = -.28, *SE* = .65, *p* = .664) youth.

Discussion

The present study examined associations between five dimensions of sleep and CRP during adolescents' transition to young adulthood, leveraging three waves of data that spanned five years from 10th grade to three years post high school. Direct sleep-CRP associations were found for two sleep dimensions (weekday/weekend variability and quality), whereas the other three dimensions (weekday duration, weekend duration, and nightly variability) had different associations with CRP as a function of age, SES, or ethnicity. Certain experiences of poor sleep may augment the rise of CRP during adolescents' transition to young adulthood, and adolescents younger in age or with high-SES and European American backgrounds may be more sensitive to the influence of inadequate sleep on CRP as compared to their peers.

The link between greater weekday/weekend variability and higher CRP indicates that altering sleep durations based on the type of days may trigger heightened proinflammatory responses during the transition from adolescence to young adulthood. Although the directionality cannot be ascertained in our study, discrepant weekday vs. weekend sleep durations may disrupt youth's sleep regulation that plays an important homeostatic role in immunity regulation.[5,41] The finding also builds upon our previous paper when the youth were 14–18 years of age; at the time, greater nightly variability in sleep duration was associated with higher CRP,[14] but weekday/weekend variability was not examined. In the current paper, weekday/weekend variability but not nightly variability was associated with CRP across adolescents' high school and post high school years. Therefore, it raises the possibility that for older youth, weekday/weekend variability may be more meaningful than nightly variability in considering their inflammation levels. For instance, as parental monitoring declines and autonomy increases during the transition to young adulthood,[42] youth may not only obtain shorter sleep durations but also develop more extreme sleep habits such as engaging in greater catch-up sleep on weekends to make up for insufficient amounts of weekday sleep, which has been associated with elevated CRP levels.[5,13] Indeed, our participants showed a pattern of increases in their sleep variability across the waves despite overall declines in their sleep durations, and their weekday/weekend variability was somewhat greater than their nightly variability. Our findings imply the importance of promoting consistent sleep practices across weekdays and weekends during adolescents' transition to young adulthood.

Additionally, our findings suggest that sleep quality may emerge as an important risk factor for inflammation in late adolescence and young adulthood. Sleep quality has been consistently associated with markers of inflammation in adults,[6] but sleep quality was unassociated with CRP in our prior analyses when adolescents were 14–18 years of age.[14] Although the link between sleep quality and inflammation in adolescents warrants more investigations due to the paucity of research, the current literature suggests that health consequences of poor sleep quality may be evident in adulthood rather than in adolescence. A potential explanation may be increasing vulnerability with the normative process of aging. Sleep quality as measured by PSQI taps the extent to which participants experience sleep disturbances such as difficulty falling asleep and use of medications, experiences that are more commonly reported in older adults.[34] Similarly, aging is associated with elevated systemic inflammation.[43]

On the other hand, the role of sleep duration in systemic inflammation may decline as adolescents transition to young adulthood. Unlike past studies with younger adolescents where short sleep durations were associated with higher CRP,[11–14] neither weekday nor weekend durations had direct associations with CRP in the current study with older youth. However, we found that age moderated the within-person association between weekend duration and CRP such that decreases in duration was associated with increases in CRP only up to 17 years of age. Interestingly, longer duration was associated with higher CRP in later years (22 years), similar to the pattern found in older adults.[44] Implications of sleep duration for inflammation may vary across the lifespan, potentially due to the declines in ideal amounts of sleep durations over the years.[15] For instance, insufficient amounts of sleep may be a risk factor in early years when longer sleep is needed,[15], but prolonged sleep durations may signal medical conditions or sedentary lifestyles at older ages.[45]

In exploratory analyses, we found significant moderations by SES and ethnicity for two of the five sleep dimensions' links with CRP. For high-SES youth, there was a significant within-person association between shorter sleep and higher CRP, but the association was non-significant for low- and average-SES youth. Additionally, the within-person association between greater nightly variability and higher CRP was evident in European American youth, but not in Asian and Latino youth. These findings suggest that the protective function of longer and consistent sleep for youth's physical health may be limited to youth from more advantaged backgrounds. Low-SES and ethnic minority youth may suffer from additional sources of elevated inflammation such as poverty[18,19] and discrimination,[20] which may blunt and obscure the influence of sleep issues on inflammation. Additionally, low-SES youth had higher CRP compared to high-SES youth, suggesting that low-SES youth's systemic inflammation may have little room to move regardless of their sleep durations. Although further replication research is needed, our findings are in line with the only other study with adolescents that examined the moderating role of ethnicity in sleep-inflammation links; short weekday sleep duration was associated with elevated CRP risks in White, but not Black, adolescents in the stratified analyses by race.[13]

Our study required separate tests to avoid multicollinearity in examining the extent to which different sleep dimensions were associated with CRP. In this context, it is important to keep in mind that the sleep-CRP associations documented in our study were specific to certain dimensions of sleep. Additionally, the strengths of the associations were modest while some of our control variables such as sex and waist circumference had stronger associations with CRP. Therefore, future studies should examine the roles of sex and adiposity in considering sleep-CRP links. For instance, adiposity may be one pathway through which poor sleep contributes to elevated levels of CRP. Additionally, given that we did not examine clinical outcomes in this study, the findings provide limited clinical significance despite demonstrating some associations between sleep and inflammation.

During the transition from adolescence to young adulthood, sleep difficulties[2] and CRP[43] are both on the rise. Our study demonstrates that certain aspects of sleep issues may heighten the rise of CRP during this developmental period. By utilizing multiple waves of data and examining various sleep dimensions, our findings provide a complex picture of dimension- and context-specificity in sleep-CRP associations in youth, rather than suggesting that poor sleep generally and consistently contributes to youth’s pro-inflammatory responses. Nonetheless, the significant sleep-CRP links found in the present study advocates for consistent sleep practices across days, identifying and reducing distractors for good quality sleep, and greater attention to the roles of age and contextual factors in sleep health.

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