Sleep Medicine 100 (2022) 103–111

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Duration, timing, and consistency of sleep in relation to inflammatory cytokines in Mexican adolescents

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ARTICLE INFO

Article history:
Received 6 April 2022
Received in revised form
4 August 2022
Accepted 8 August 2022
Available online 17 August 2022

ABSTRACT

Objective: To evaluate whether sleep duration, timing, and variability were associated with inflammatory cytokines in a cohort of Mexico City adolescents.
Methods: The analytic sample comprised >500 adolescents who were part of an ongoing longitudinal study in Mexico City. At two time points during mid-to-late puberty (average age 14, n = 391) and late-to-post puberty (average age 16, n = 345), adolescents completed a follow-up visit that included 7-day wrist actigraphy and clinical assessment of plasma inflammatory cytokines (high-sensitivity C-reactive protein, Interleukin 1β, Interleukin 6, and Tumor Necrosis Factor α). Sleep characteristics included weekday and weekend sleep duration and midpoint (median of bed and wake time), as well as sleep variability (SD of sleep duration across 7 days) and social jetlag (midpoint difference from weekdays to weekends). At each time point, multivariable linear regression models were run with log inflammatory levels as the outcome and categories of sleep characteristics as predictors, while adjusting for potential confounders (specific to each model). Analyses were run unstratified and sex-stratified.
Results: In the mid-to-late pubertal visit, weekday sleep duration was inversely associated with natural log hs-CRP after adjustment (Q4 vs Q1: β = -0.41, 95% Confidence Interval (CI) −0.81 to −0.01) and later sleep midpoint was positively associated with log hs-CRP (Q4 vs Q1: β = 0.55, 95% CI 0.13 to 0.97). Sleep duration variability was associated with higher IL-1β among boys, while in girls social jetlag was associated with higher IL-1β and weekend sleep duration was inversely associated with IL-6. At the late-to-post pubertal visit, there were few associations except for a positive association between weekday sleep duration and hs-CRP among boys (β = 0.60, 95% CI 0.04 to 1.16) and a non-linear positive association between social jetlag and hs-CRP among girls (β = 0.80, 95% CI 0.22 to 1.37 comparing 2 to 3 h of social jetlag vs <1 h).
Conclusion: Later timing, shorter duration, and inconsistency of sleep were related to higher levels of inflammatory biomarkers, but associations were more evident at the mid-to-late pubertal visit than the late-to-post pubertal visit.

1. Introduction

Adolescents are among the populations most vulnerable to poor sleep health [1]. Over half of adolescents worldwide are estimated

Abbreviations: C-reactive protein-CRP, Early Life Exposure in Mexico to Environmental Toxicants-ELEMENT; National Institute of Public Health of Mexico (INSP), interleukin 1 beta- IL-1β; interleukin 6- IL-6, tumor necrosis factor alpha-TNF-α.

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https://doi.org/10.1016/j.sleep.2022.08.007
1389-9457/

to fall short of the recommended nightly sleep duration [1]. Timing and consistency of sleep are also important sleep health components for adolescents, with earlier and more consistent sleep typically associated with better health outcomes [2] in this age period [3,4]. Yet adolescents often have late bedtimes, due in part to pubertal circadian changes that delay sleep onset [5]. Further, sleep loss during the weekdays often means they sleep in on weekends, resulting in markedly different sleep patterns from weekdays to weekends (i.e., social jetlag) [6].

Poor sleep health contributes to a number of adverse health outcomes among youth, both physical and mental [7]. One potential contributor to these relationships is chronic inflammation, which has been implicated in many neuropsychiatric and cardiovascular conditions in adolescence, including depression, obesity, type 2 diabetes, and metabolic syndrome [8–11]. Indeed, short and long sleep duration have each been associated with increased inflammation in adolescents [12]. However, a limitation with most prior work on sleep and inflammation among adolescents is the lack of consideration of potential effect modification by sex or developmental stage. Males and females follow very different hormonal and developmental trajectories [13], and sleep habits and characteristics also diverge by sex at this age [14]; for example, adolescent females are more likely to suffer from insomnia symptoms [15]. Finally, inflammatory cytokines have been shown to differ according to pubertal stage in a sex-specific manner [16]; to highlight, more advanced pubertal status was associated with higher C-reactive protein (CRP) among girls while CRP levels among boys did not differ by pubertal status in a sample of 155 US adolescents. In support of differences in the sleep and inflammation relationship by sex, one longitudinal study among 10,744 American adolescents showed that higher level of high-sensitivity C-reactive protein (hs-CRP) was related to longer sleep duration in girls but shorter sleep duration in boys [17]. Further, in support of age-specific associations, within a sample of 350 US adolescents/young adults [18], higher weekday-weekend variability was associated with higher hs-CRP across multiple stages of follow-up, but the association between weekend sleep duration and inflammation was different across ages (inverse at 14–17, no association at 18–21, and positive at 22). To our knowledge, no study has considered both age and sex as potential modifiers. Therefore, we aimed to examine the associations of multiple sleep characteristics including sleep duration, timing, and variability with a set of inflammatory cytokines in a cohort of adolescents living in Mexico City. We examined sex-specific relationships between sleep and inflammation during two follow-up visits, one that occurred when participants were in mid-to-late puberty (mean age of 14) and another that occurred when participants were in late-to-post puberty (mean age of 16). We hypothesized that shorter sleep duration, later sleep timing, and higher sleep variability would be associated with higher inflammation, with stronger associations among females.

2. Methods

2.1. Study sample

The analytic sample included adolescents from two birth cohorts of the Early Life Exposure in Mexico to Environmental Toxicants (ELEMENT) Study [19]. Between 1997 and 2004, 1,079 pregnant women obtaining care from public maternity clinics of the Mexican Social Security Institute in Mexico City were recruited during the first trimester of pregnancy, and their children were followed periodically from birth through childhood and adolescence.

There were two follow-up studies conducted during the adolescent and emerging adulthood period for which we collected both sleep and inflammatory cytokines. In 2015, 558 participants between the ages of 9 to 17 years participated in a study visit (henceforth called the “mid-to-late pubertal visit”) that included collection of basic health and demographic information, anthropometric assessments and blood draw during a clinic visit, as well as an objective-sleep assessment (wrist-actigraphy) over seven consecutive days following the clinic visit. Of the 558 adolescent participants who completed this follow-up visit, 391 adolescents had complete information on inflammatory cytokines and sleep collected from that visit. In 2017, 519 participants of 558 completed the second clinic visit when participants were between 11 and 21 years of age (henceforth called the "late-to-post pubertal visit”), and 345 adolescents had complete information on inflammatory cytokines and sleep.

The National Institute of Public Health of Mexico (INSP) Research, Ethics, and Biosafety Committees (CI-599-9-15102014) and the University of Michigan Human Subjects Committee (HUM00034344) approved all research protocols and procedures, and all participants provided informed consent.

2.2. Sleep measures

We measured sleep duration, midpoint, and fragmentation using wrist-actigraphy devices (ActiGraph GT3X-BT; ActiGraph LLC, Pensacola, FL) that adolescent participants wore on the non-dominant wrist for seven consecutive days. Participants also kept a nightly sleep diary to record their bedtimes and wake times. Nightly sleep measures were estimated from the actigraphy data using a pruned dynamic programming algorithm developed in R (R Foundation for Statistical Computing, Vienna, Austria) that was validated against polysomnography, the gold standard for sleep assessment [20]. The self-reported bedtimes and wake times were used to ascertain whether the sleep times estimated from the accelerometer data fell within a similar time frame. If not, the data (both the diary and the accelerometry) were manually checked and cleaned if needed. We conducted analyses separately for weekdays and weekends because sleep habits are known to vary, with adolescents having more freedom to choose their sleep schedule on the weekends. We included weekday (Sunday through Thursday) and weekend sleep duration (Friday and Saturday; in minutes), and weekday and weekend sleep midpoint (the median of sleep onset and wake time; reported in decimal hours). We also investigated sleep duration variability, calculated as the standard deviation of the 7-day sleep durations, and social jetlag, calculated as the difference between weekend and weekday sleep midpoint. Sleep characteristics were split into quartiles for analysis, except for social jetlag, which was categorized as <1 h difference, 1–2 h difference, 2–3 h difference, and >3 h difference.

2.3. Inflammatory measures

Venous whole blood was taken during the clinic visit after an overnight fast (at least 8 h), and immediately separated and stored at −80°C. The following cytokines were measured in serum at the Michigan Diabetes Research Center's Chemistry Laboratory (MDRC) at University of Michigan: CRP, interleukin 1 beta (IL-1β), interleukin 6 (IL-6), and tumor necrosis factor alpha (TNF-α). High sensitivity CRP (hs-CRP) was measured via the highly sensitive CRP Ultra-Wide Range Reagent kit (Sekisui Diagnostics, Inc., Prince Edward Island, Canada), a latex-enhanced turbidimetric in vitro immunoassay, using a Randox RX Daytona analyzer (Randox, Kearneysville, WV). We followed all manufacturer's recommended protocols. The detectable levels of CRP ranged from 0.1 to 160 mg/L. The other three cytokines, IL-1β, IL-6, and TNF-α, were assayed via the MILLIPLEX® MAP Human High Sensitivity T Cell Magnetic Bead

kit (Millipore Corporation, Billerica, MA) using the Luminex-200 instrument (Luminex Corporation, Austin, TX, USA). Values were reported as pg/ml. For these 3 cytokines, the intra-assay laboratory coefficients of variation (CV) were less than 7% and the inter-assay CV were less than 8%. Data were log transformed prior to analysis to improve normality.

2.4. Confounders

Possible baseline confounders were selected based on a priori knowledge and included sex (in non-sex-stratified models), age, puberty status, height-for-age Z scores, physical activity, screen time, smoking status (ever/never), alcohol consumption, and maternal education. Trained research assistants measured height in cm (Tonelli E120 A), and height for age Z scores (HAZ) were calculated based on the World Health Organization growth references. [21] Pubertal status was determined by physicians via Tanner staging and orchidometers (for males) following standard techniques [22]. Girls were also asked about whether menarche had occurred. For analysis, pubertal status was analyzed dichotomously as earlier (defined as premenarcheal for girls and testicular volume <15 mL for boys) vs later (had started menarche for girls and testicular volume ≥15 mL for boys). Physical activity information was obtained from the actigraphs using Chandler's vector magnitude cutoffs [23] and classified as moderate minutes/day. Total screen time per week was assessed with a self-reported questionnaire adapted for and validated in Mexican adolescents [24], and was divided into quartiles. Smoking behavior was self-reported with a single question "Have you ever tried smoking?" and alcohol consumption was self-reported regarding whether they had consumed alcohol at all in the past year. Both questions were categorized dichotomously. Maternal education was reported by mothers at baseline and was classified into 4 categories: < 8 years, 9–11 years, 12 years, and >12 years.

2.5. Statistical analysis

All analyses were run separately for the two study visits, with the consideration that the visits represented different developmental stages. For each visit, the analyses proceeded in the following manner:

We first estimated the means and standard deviations of sleep duration on weekdays and weekend, total sleep variability, and total sleep midpoint according to the demographic and lifestyle characteristics. P values were obtained from ANOVA tests. In addition, we also estimated the medians and interquartile ranges (IQR) of hs-CRP, IL-1β, IL-6, TNF-α by categories of main characteristics. P values were obtained from Kruskal-Wallis test.

We then estimated the medians and interquartile ranges of hs-CRP, IL-1β, IL-6, TNF-α according to categories of sleep characteristics (quartiles for sleep duration on weekdays and weekend, sleep variability, sleep midpoint on weekdays and weekends; and the following categories for social jetlag: <1 h difference, 1–2 h difference, 2–3 h difference, or >3 h difference). P values were obtained from Kruskal-Wallis tests.

The associations between sleep characteristics (sleep duration on weekdays and weekend, sleep variability, sleep midpoint on weekdays and weekends, and social jetlag) and inflammatory indicators (hs-CRP, IL-1β, IL-6, TNF-α) were examined by linear regression models. Due to the skewed distribution, levels of inflammatory indicators were natural log-transformed and then used as dependent variables. Sleep characteristics were categorized in the same way as mentioned above. Models were adjusted for the potential confounders that were associated with both sleep and inflammatory biomarkers, which included sex, age, smoking status, height-for-age z score, and month of measurement. Due to positive correlations between sleep duration and midpoint, sleep duration models included midpoint as a potential confounder and vice versa. In the model for social jetlag, both sleep duration on weekdays and weekends were treated as continuous variables. BMI was considered as a potential mediator and was not included in final models since our goal was to estimate the total effect.

In addition, we performed all the analyses stratified by sex. All analyses were run in R Studio version 1.3.1073 (PBC, MA). Statistical significance was set as two-tailed P< 0.05.

3. Results

3.1. Mid-to-late pubertal visit

At the mid-to-late pubertal visit, the study sample included 391 adolescents, of whom 50.6% were female (Table 1). The mean ± standard deviation of age was 13.8 ± 1.9 years. The mean sleep durations on weekdays and weekend were 515.28 ± 72.97 min (Supplemental Fig. 1) and 549.67 ± 74.42 min (Supplemental Fig. 2), respectively. The sleep midpoints on weekdays and weekend were 3:43 ± 1:19 (Supplemental Fig. 4) and 4:41 ± 1:16 (Supplemental Fig. 5), respectively. Girls' average sleep duration on weekend was almost 30 min longer than that of boys (P<0.001).

The median (IQR) of hs-CRP, IL-1β, IL-6 and TNF-α were 0.62 (1.23) mg/L (Supplemental Fig. 7), 0.86 (0.40) pg/mL (Supplemental Fig. 8), 3.21 (8.90) pg/mL (Supplemental Fig. 9) and 4.78 (2.95) pg/mL (Supplemental Fig. 10), respectively. Girls' median of IL-1β was significantly higher than that of boys, but the relationship was reversed for TNF-α. Significantly higher medians of TNF-α were observed in girls who had not experienced menarche and adolescents who had not ever smoked cigarettes (Table 2).

There were multiple associations between sleep and inflammatory biomarkers observed in bivariate analysis (Supplemental Table 1), and these associations persisted upon adjustment (Table 3). Sleep duration on weekdays was inversely associated with the log hs-CRP after adjusting for sex, age, smoking status, height-for-age z score and sleep midpoint on weekdays (Q4 vs Q1: β = -0.41, 95% Confidence Interval (CI) −0.81 to −0.01, p = 0.046; Table 3). Later sleep midpoint on weekdays was also associated with higher level of log hs-CRP after confounder adjustment (Q4 vs Q1: β = 0.55, 95% CI 0.13 to 0.97, p = 0.01). Associations did not vary by sex (Supplemental Table 3).

There was a non-linear positive association between total sleep variability and log IL-1β after confounder adjustment. This association was found exclusively among boys, such that those in Q3 had 0.26 higher log IL-1β compared to Q1 (95% CI 0.09 to 0.44, p = 0.004; Supplemental Table 4). For girls, those with social jetlag between 2 and 3 h had higher log IL-1β than those with <1 h of social jetlag (β = 0.21, 95% CI 0.04 to 0.38, p = 0.01).

Finally, there was an inverse dose-response relationship between weekend sleep duration and log IL-6 among girls (Supplemental Table 5). To illustrate, girls in Q4 had 0.84 higher log IL-6 compared to Q1 (95% CI -1.35, −0.32, p = 0.002).

There were no associations of sleep measures with TNF-α, either in unstratified or sex-stratified models (Table 3 and Supplemental Table 6).

3.2. Late-to-post pubertal visit

At the late-to-post pubertal visit, the study sample included 345 adolescents, of whom 51.6% were female (Table 1). The mean ± standard deviation of age was 15.8 ± 2.0 years. The mean of sleep duration on weekdays and weekend were 509.31 ± 86.90 min

Table 1
Sleep characteristics of adolescents across study visits.

	Mid-to-late pubertal visit (ages 9–18) (n = 391)			Late-to-post pubertal visit (ages 11–21) (n = 345)		
Sleep duration on weekdays (min), Mean ± SD	515.28	±	72.97	509.31	±	86.90
Sleep duration on weekend (min), Mean ± SD	549.67	±	74.42	538.85	±	86.32
Sleep variability (min), Mean ± SD	87.00	±	38.49	93.73	±	39.36
Sleep midpoint on weekdays (hour:min), Mean ± SD	3:43	±	1:19	4:09	±	1:28
Sleep midpoint on weekend (hour:min), Mean ± SD	4:41	±	1:16	4:54	±	1:19
Social Jetlag (difference between weekend and weekdays midpoints, in hours), Mean ± SD	1.20	±	0.93	1.07	±	0.86

(Supplemental Fig. 11) and 538.85 ± 86.32 min (Supplemental Fig. 12), respectively. The sleep midpoint on weekdays and weekend were 4:09 ± 1:28 (Supplemental Fig. 14) and 4:54 ± 1:19 (Supplemental Fig. 15), respectively.

Associations between potential confounders and inflammation were similar in late-to-post pubertal visit compared to the mid-to-late pubertal visit, with associations noted for sex, age, and cigarette smoking (data not shown).

The medians of inflammatory biomarkers were greater in the late-to-post pubertal visit than the mid-to-late pubertal visit for all inflammatory biomarkers and were 0.74 (1.64) mg/L (Supplemental Fig. 17), 3.19 (1.92) pg/mL (Supplemental Fig. 18), 6.18 (23.34) pg/mL (Supplemental Fig. 19) and 10.66 (4.42) pg/mL (Supplemental Fig. 20) for hs-CRP, IL-1β, IL-6 and TNF-α, respectively.

Overall, there were very few associations between sleep and inflammatory cytokines in late adolescence (Table 4). Among boys, there was a positive association between weekday sleep duration and hs-CRP, such that those in the highest quartile of sleep duration had 0.55 higher log hs-CRP compared to those in the lowest quartile of sleep duration (95% CI 0.03, 1.07, p = 0.04; Supplemental Table 7). There was also a positive association between social jetlag and hs-CRP, and this association was stronger among girls. To illustrate, girls with 2 to 3 h of social jetlag had 0.8 higher log hs-CRP than girls with <1 h of social jetlag (95% CI 0.22 to 1.37, p = 0.01; Supplemental Table 7). No other associations of sleep with inflammatory measures were statistically significant, either in non-sex-stratified or sex-stratified models (Table 4 and Supplemental Tables 8–10).

4. Discussion

In this study of Mexican adolescents, sleep characteristics were associated with inflammatory cytokines in mostly the expected direction during peri-puberty, but associations were largely null during young adulthood. Specifically, during the mid-to-late pubertal visit, short sleep duration and delayed sleep timing were related to higher hs-CRP, an overall indicator of inflammation. A few other associations were apparent for individual cytokines in a sex-specific manner. For boys, sleep variability was positively associated with IL-1β. Among girls only, social jetlag was associated with IL-1β, and longer sleep duration on the weekends were associated with lower IL-6. None of these associations held in the late-to-post pubertal visit, although there was evidence of a few different associations with hs-CRP (long sleep duration and social jetlag).

The fact that sleep duration was associated with CRP is in line with several other studies. Short sleep duration was associated with higher CRP in a sample of 250 US adolescents [25]. Other studies have observed a similar association, but within certain subgroups. Short sleep trajectories were associated with higher log hs-CRP in young adult males [17]. Shorter weekday sleep duration was associated with higher CRP in a US sample of older adolescents, but only within the lower-SES group [18].

We also found that later sleep timing at the mid-to-late pubertal visit was associated with higher hs-CRP levels, and that this association was independent of sleep duration. To our knowledge, no other studies have examined sleep midpoint in relation to inflammation, although some other studies in pediatric samples have linked delayed sleep timing with adiposity and cardiometabolic outcomes [26,27].

Several plausible mechanisms exist to explain the relationships between sleep duration and timing with CRP that we observed in the mid-to-late pubertal visit. Shorter sleep duration and later sleep timing have been linked to higher levels of adiposity [28,29], as well as lifestyle behaviors such as lower intake of fruits and vegetables and reduced physical activity [30,31]; factors that in turn are also related to higher overall inflammation [32,33]. Another related pathway could be via alterations in gut microbes [34].

Associations were also noted between inconsistent sleep patterns and inflammation, again primarily during the earlier study visit. At the mid-to-late pubertal visit, sleep duration variability was associated with higher IL-1β among boys, while social jetlag (marker for variability in timing) was associated with higher IL-1β in girls. At the late-to-post pubertal visit, social jetlag was associated with higher hs-CRP, also in girls. Although not sex-specific, a few US studies have found positive links between sleep variability and inflammation in adolescents. To illustrate, greater weekday/weekend variability has been associated with higher CRP within a US study of adolescents followed multiple times over the ages of 16 and 20 [18]. Further, catch-up sleep on the weekend, which is one way to look at variability of sleep duration, has been associated with higher CRP [25]. The potential mechanisms to explain relationships between inconsistent sleep duration and timing with inflammation could include lower quality diets [35] (e.g., eating more calorie-dense foods on days with short duration or altered timing) and lower physical activity [36]. Further, constantly shifting sleep patterns can also alter the metabolic profile, particularly increasing adiposity [37], which would also increase inflammation levels [38].

Although we found that social jetlag was associated with one cytokine at the mid-to-late pubertal visit and with hs-CRP at the late-to-post pubertal visit among girls, we were expecting this finding to be more robust (i.e. associated with greater number of cytokine and/or higher magnitude associations). Yet, while findings on social jetlag are fairly consistent in adult studies [39], the relationship may not be as straightforward among adolescents. For example, a recent study among Hispanic youth in the US found that higher social jetlag was related to lower adiposity and healthier behaviors [40]. Further examination of social jetlag in adolescents is needed; it is possible that the benefits of catch-up sleep on weekends outweighs the circadian misalignment resulting from stark changes in sleep patterns from weekdays to weekends. In line with this explanation, we found that longer sleep duration ("catch-up sleep") on the weekends was associated with lower IL-6 in girls.

Table 2
Inflammatory indicators of adolescents according to sociodemographic predictors.

Adolescents at the mid-to-late pubertal visit									
Sociodemographic predictors	N[a]	hs-CRP (mg/L)		IL-1β (pg/mL)		IL-6 (pg/mL)		TNF-α (pg/mL)	
		Median	IQR	Median	IQR	Median	IQR	Median	IQR
Total	391	0.62	1.23	0.86	0.40	3.21	8.90	4.81	2.95
Sex									
Male	193	0.60	1.17	0.81	0.38	2.85	12.52	5.32	3.33
Female	198	0.65	1.40	0.91	0.37	3.30	7.05	4.25	2.76
P value[b]		0.66		<0.001		0.39		<0.001	
Age group									
9.5 to <12 y	86	0.63	0.96	0.90	0.37	3.26	12.05	5.19	2.32
12 to <14 y	150	0.49	1.15	0.87	0.40	3.37	12.52	4.79	3.17
14 to <16 y	81	0.65	1.20	0.83	0.36	3.21	9.21	4.74	3.26
16 to 18 y	74	0.81	1.41	0.87	0.39	2.45	3.25	4.32	2.85
P value		0.13		0.37		0.21		0.30	
Testicular volume (boys)									
<15 mL	40	0.79	1.67	0.83	0.29	3.84	8.69	5.32	3.52
≥15 mL	144	0.59	0.97	0.82	0.40	2.77	12.59	5.35	3.04
P value		0.36		0.88		0.95		0.71	
Menarche status (girls)									
Had not experienced	37	0.64	0.90	0.86	0.42	2.90	4.20	4.46	2.91
Had experienced	159	0.66	1.53	0.92	0.36	3.30	7.04	3.96	2.69
P value		0.64		0.53		0.88		0.01	
Mother's education, years									
8 y or less	43	0.65	0.93	0.89	0.52	2.90	12.51	4.94	3.97
9 to 11 y	153	0.63	1.10	0.87	0.41	3.20	7.37	4.58	3.01
12 y	136	0.66	1.45	0.86	0.36	3.13	9.09	4.79	2.67
>12 y	55	0.55	1.65	0.86	0.42	3.62	18.38	5.21	1.83
P value		0.78		0.78		0.69		0.61	
Moderate physical activity, quartiles									
Q1, 14.96 to 56.67 min/day	95	0.63	1.39	0.84	0.45	3.49	12.37	4.71	2.84
Q2, 56.67 to 72.81 min/day	95	0.55	1.16	0.86	0.33	3.19	4.33	4.32	2.93
Q3, 72.81 to 92.89 min/day	95	0.76	1.58	0.90	0.51	2.75	5.20	4.83	2.79
Q4, 92.89 to 173.75 min/day	95	0.59	0.78	0.89	0.36	3.65	15.16	4.97	3.05
P value		0.39		0.60		0.21		0.91	
Screen time, quartiles									
Q1, 1 to 22.5 h/wk	114	0.59	1.10	0.88	0.35	3.40	7.21	4.82	2.82
Q2, 23 to 32.5 h/wk	106	0.58	1.18	0.84	0.42	3.12	6.18	4.81	3.38
Q3, 33 to 48 h/wk	98	0.67	1.31	0.87	0.44	3.20	16.30	4.80	2.64
Q4, 48.5 to 116 h/wk	70	0.76	1.59	0.83	0.34	2.70	8.99	4.70	2.92
P value		0.59		0.37		0.38		0.65	
Consumed alcohol									
Not in the past year	232	0.64	1.30	0.88	0.41	2.92	6.72	4.59	2.80
Yes, within the past year	45	0.62	0.76	0.83	0.37	4.32	14.69	5.01	3.69
P value		0.42		0.76		0.05		0.07	
Ever smoked cigarettes									
No	321	0.60	1.26	0.86	0.40	3.29	8.53	4.95	2.99
Yes	64	0.74	1.03	0.88	0.47	2.57	13.21	3.97	2.26
P value		0.23		0.79		0.62		0.00	
Height-for-age z score[c]									
<-1	75	0.75	1.29	0.84	0.33	2.63	4.46	4.31	2.92
−1 to 0	135	0.50	0.98	0.87	0.38	3.20	6.27	4.62	3.09
0 to <1	142	0.64	1.79	0.88	0.45	3.29	14.70	4.97	2.83
≥1	35	0.80	0.85	0.90	0.37	3.77	14.58	5.29	3.48
P value		0.20		0.36		0.06		0.20	
Adolescents at the late-to-post pubertal visit									
Sociodemographic predictors	N	hs-CRP (mg/L)		IL-1β (pg/mL)		IL-6 (pg/mL)		TNF-α (pg/mL)	
		Median	IQR	Median	IQR	Median	IQR	Median	IQR
Total		0.74	1.64	3.19	1.92	6.18	23.34	10.66	4.42
Sex									
Male	167	0.56	1.04	1.04	1.93	5.28	26.31	11.78	4.91
Female	178	1.08	2.07	3.35	1.89	7.25	19.25	9.96	3.71
P value		<0.001		0.001		0.03		<0.001	
Age group									
11 to <15 y	104	0.65	1.06	3.13	1.93	7.63	31.33	10.65	4.48
15 to <17 y	133	0.65	1.35	3.11	1.88	6.18	19.39	10.65	4.22
17 to <19 y	66	0.72	2.02	3.32	1.89	7.99	32.71	10.49	4.49
19 to 21 y	42	1.63	2.27	3.26	2.10	5.15	5.61	11.32	3.77
P value		<0.001		0.89		0.27		0.49	
Mother's education									
8 y or less	37	1.36	2.78	3.66	1.29	7.00	24.04	10.38	3.78
9 to 11 y	142	0.79	1.45	3.11	1.83	6.30	13.67	10.94	4.69
12 y	115	0.68	1.43	3.03	1.91	5.86	22.68	10.53	4.59
>12 y	50	0.64	1.25	3.39	1.94	5.98	34.45	10.55	3.47

(*continued on next page*)

Table 2 (*continued*)

Adolescents at the mid-to-late pubertal visit									
Sociodemographic predictors	N[a]	hs-CRP (mg/L)		IL-1β (pg/mL)		IL-6 (pg/mL)		TNF-α (pg/mL)	
		Median	IQR	Median	IQR	Median	IQR	Median	IQR
P value		0.21		0.17		0.67		0.65	
Moderate physical activity, quartiles									
Q1, 0 to 46.93 min/day	80	0.84	1.67	3.32	2.38	6.24	26.15	11.03	5.30
Q2, 46.93 to 61.72 min/day	80	0.57	1.38	2.82	1.50	6.22	12.38	10.19	3.63
Q3, 61.72 to 78.64 min/day	79	0.94	1.40	3.41	2.01	5.89	30.29	11.12	4.76
Q4, 78.64 to 131.83 min/day	79	0.72	1.47	3.15	2.21	5.99	15.96	10.53	4.32
P value		0.51		0.09		0.92		0.30	
Consumed alcohol in the past year									
No	269	0.78	1.60	3.22	1.84	6.32	24.61	10.65	4.17
Yes	41	0.62	0.89	3.27	1.65	5.65	22.38	10.86	4.39
P value		0.23		0.66		0.86		0.77	
Ever smoked cigarettes									
No	152	0.78	1.73	3.12	1.83	5.58	14.56	11.02	4.16
Yes	193	0.71	1.39	3.29	2.07	7.60	27.06	10.36	4.43
P value		0.12		0.27		0.09		0.07	

[a] Sample sizes vary slightly according to demographic information examined.
[b] P values were obtained from Kruskal-Wallis test.
[c] From the WHO reference.

Similar findings have been reported in Korean adults, such that longer weekend catch-up sleep was associated with lower hs-CRP (IL-6 was not examined) [41].

Overall, the fact that there were many more associations at the mid-to-late pubertal visit than the late-to-post pubertal visit may suggest that the mid-to-late pubertal period is a sensitive period for the sleep and inflammation relationship. The first visit occurred towards the middle and end of puberty for most participants in the sample while many participants in the second visit were past puberty and could be classified as entering young adulthood (almost one-third of the sample was between 17 and 21 years old). Of note, sleep timing continues to get later as puberty progresses but then typically begins to shift back to earlier bedtimes in early adulthood (i.e., age 21 or 22) [42]. Other physiological changes occur during

Table 3
Adjusted association between sleep duration, variability, midpoint, and inflammation biomarkers among adolescents at the mid-to-late pubertal visit.

	log hs-CRP		log IL-1β		log IL-6		log TNF-α	
	Adjusted Beta (95% CI)	p value	Adjusted Beta (95% CI)	p value	Adjusted Beta (95% CI)	p value	Adjusted Beta (95% CI)	p value
Sleep duration during weekday, adjusted model[a]								
Q1, 308.4 to 465.4 min	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Q2, 465.4 to 515.8 min	−0.22 (−0.58, 0.14)	0.23	0.04 (−0.08, 0.15)	0.55	−0.02 (−0.41, 0.38)	0.94	0.05 (−0.07, 0.17)	0.39
Q3, 515.8 to 565.8 min	−0.03 (−0.41, 0.35)	0.89	0.05 (−0.08, 0.17)	0.47	0.04 (−0.38, 0.46)	0.86	0.08 (−0.05, 0.20)	0.24
Q4, 565.8 to 709 min	−0.41 (−0.81, −0.01)	0.046	0.06 (−0.07, 0.19)	0.38	0.23 (−0.21, 0.67)	0.31	0.03 (−0.10, 0.17)	0.65
Sleep duration during weekend[b]								
Q1, 232 to 502.5 min	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Q2, 502.5 to 553 min	0.18 (−0.19, 0.55)	0.35	0.02 (−0.10, 0.14)	0.78	−0.03 (−0.44, 0.38)	0.89	0.06 (−0.06, 0.18)	0.35
Q3, 553 to 596 min	0.01 (−0.37, 0.38)	0.97	−0.06 (−0.18, 0.06)	0.31	−0.04 (−0.45, 0.36)	0.83	−0.01 (−0.13, 0.12)	0.91
Q4, 596 to 763 min	0.04 (−0.33, 0.41)	0.83	0.03 (−0.09, 0.15)	0.65	−0.16 (−0.57, 0.25)	0.44	−0.03 (−0.15, 0.10)	0.66
Sleep variability[c]								
Q1, 16.33 to 56.15 min	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Q2, 56.15 to 82.41 min	0.26 (−0.11, 0.62)	0.16	0.08 (−0.04, 0.19)	0.20	−0.04 (−0.44, 0.36)	0.84	0.04 (−0.09, 0.16)	0.57
Q3, 82.41 to 109.57 min	−0.05 (−0.42, 0.32)	0.78	0.14 (0.02, 0.26)	0.02	0.25 (−0.16, 0.65)	0.23	−0.004 (−0.13, 0.12)	0.95
Q4, 109.57 to 217.55 min	−0.14 (−0.52, 0.24)	0.46	0.02 (−0.10, 0.14)	0.72	0.03 (−0.38, 0.44)	0.90	−0.06 (−0.19, 0.06)	0.31
Sleep midpoint during weekday[d]								
Q1, 0:56 to 2:38	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Q2, 2:38 to 3:27	0.18 (−0.18, 0.54)	0.33	−0.03 (−0.14, 0.09)	0.64	0.32 (−0.08, 0.72)	0.11	0.02 (−0.10, 0.15)	0.69
Q3, 3:27 to 4:48	0.37 (−0.01, 0.76)	0.06	−0.01 (−0.13, 0.11)	0.87	0.21 (−0.21, 0.64)	0.32	0.03 (−0.10, 0.16)	0.63
Q4, 4:48 to 7:59	0.55 (0.13, 0.97)	0.01	−0.03 (−0.17, 0.10)	0.63	0.08 (−0.37, 0.54)	0.71	0.01 (−0.12, 0.15)	0.85
Sleep midpoint during weekend[e]								
Q1, 1:54 to 3:45	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Q2, 3:45 to 4:33	0.38 (0.02, 0.75)	0.04	0.06 (−0.06, 0.18)	0.33	−0.29 (−0.69, 0.10)	0.15	0.03 (−0.09, 0.15)	0.62
Q3, 4:33 to 5:27	0.04 (−0.32, 0.41)	0.82	−0.01 (−0.13, 0.11)	0.85	−0.16 (−0.56, 0.24)	0.42	0.05 (−0.07, 0.17)	0.43
Q4, 5:27 to 9:30	0.10 (−0.28, 0.48)	0.61	−0.004 (−0.12, 0.12)	0.99	0.003 (−0.42, 0.42)	0.99	0.01 (−0.12, 0.13)	0.91
Midpoint difference between weekday and weekend[f]								
Less than 1 h	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
1 to 2 h	0.07 (−0.24, 0.38)	0.67	0.05 (−0.05, 0.15)	0.33	0.15 (−0.19, 0.49)	0.39	−0.08 (−0.18, 0.03)	0.15
2 to 3 h	−0.15 (−0.55, 0.25)	0.47	0.15 (0.02, 0.28)	0.02	0.30 (−0.14, 0.74)	0.18	−0.02 (−0.15, 0.11)	0.77
More than 3 h	−0.68 (−1.41, 0.05)	0.07	−0.04 (−0.27, 0.20)	0.76	−0.13 (−0.93, 0.67)	0.75	−0.01 (−0.26, 0.23)	0.91

[a] Adjusted model for weekday sleep duration included sex, age, smoking status, month of measurement, and weekday sleep midpoint.
[b] Adjusted model for weekend sleep duration included sex, age, smoking status, month of measurement, and weekend sleep midpoint.
[c] Adjusted model for sleep variability included sex, age and smoking status, and month of measurement.
[d] Adjusted model for weekday sleep midpoint included sex, age, smoking status, month of measurement, and weekday sleep duration.
[e] Adjusted model for weekend sleep midpoint included sex, age, smoking status, month of measurement, and weekend sleep duration.
[f] Adjusted model for midpoint difference between weekday and weekend included sex, age, smoking status, month of measurement, weekdays and weekend sleep duration.

Table 4
Adjusted association between sleep duration, variability, midpoint, and inflammation biomarkers among adolescents at the late-to-post pubertal visit.

	log hs-CRP		log IL-1β		log IL-6		log TNF-α	
	Adjusted Beta (95% CI)	p value	Adjusted Beta (95% CI)	p value	Adjusted Beta (95% CI)	p value	Adjusted Beta (95% CI)	p value
Sleep duration during weekdays[a]								
Q1, 166 to 452.8 min	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Q2, 452.8 to 519.8 min	0.33 (−0.04, 0.71)	0.08	0.02 (−0.13, 0.17)	0.81	0.11 (−0.46, 0.69)	0.70	0.11 (−0.46, 0.69)	0.70
Q3, 519.8 to 565 min	0.27 (−0.13, 0.67)	0.18	0.05 (−0.11, 0.21)	0.58	0.36 (−0.26, 0.97)	0.26	0.36 (−0.26, 0.97)	0.26
Q4, 565 to 752.4 min	0.26 (−0.15, 0.67)	0.22	−0.03 (−0.20, 0.14)	0.72	0.09 (−0.55, 0.73)	0.78	0.09 (−0.55, 0.73)	0.78
Sleep duration during weekend[b]								
Q1, 307.5 to 479.1 min	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Q2, 479.1 to 544 min	0.17 (−0.20, 0.55)	0.36	0.05 (−0.10, 0.20)	0.54	−0.02 (−0.59, 0.56)	0.95	−0.02 (−0.59, 0.56)	0.95
Q3, 544 to 594.1 min	0.03 (−0.35, 0.41)	0.87	−0.06 (−0.22, 0.09)	0.41	0.14 (−0.45, 0.73)	0.63	0.14 (−0.45, 0.73)	0.63
Q4, 594.1 to 789 min	0.21 (−0.17, 0.60)	0.27	−0.13 (−0.29, 0.02)	0.09	−0.05 (−0.64, 0.55)	0.88	−0.05 (−0.64, 0.55)	0.88
Sleep variability[c]								
Q1, 14.85 to 66.37 min	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Q2, 66.37 to 86.15 min	0.15 (−0.22, 0.52)	0.42	0.00 (−0.15, 0.15)	0.98	0.00 (−0.57, 0.57)	0.99	0.03 (−0.06, 0.12)	0.47
Q3, 86.15 to 117.84 min	0.00 (−0.37, 0.37)	0.99	−0.05 (−0.20, 0.10)	0.53	−0.37 (−0.94, 0.20)	0.21	0.01 (−0.08, 0.10)	0.82
Q4, 117.84 to 228.63 min	0.34 (−0.03, 0.71)	0.07	0.05 (−0.10, 0.20)	0.52	−0.09 (−0.67, 0.48)	0.75	−0.02 (−0.11, 0.07)	0.67
Sleep midpoint during weekdays[d]								
Q1, 0:32 to 3:02	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Q2, 3:02 to 4:06	0.03 (−0.35, 0.41)	0.87	−0.01 (−0.16, 0.14)	0.93	0.09 (−0.48, 0.67)	0.75	0.00 (−0.09, 0.09)	1.00
Q3, 4:06 to 5:12	−0.10 (−0.51, 0.32)	0.67	0.07 (−0.09, 0.24)	0.39	0.34 (−0.30, 0.98)	0.30	0.00 (−0.10, 0.09)	0.94
Q4, 5:12 to 10:18	−0.02 (−0.45, 0.40)	0.93	−0.03 (−0.20, 0.14)	0.70	−0.36 (−1.01, 0.29)	0.28	0.03 (−0.07, 0.13)	0.55
Sleep midpoint during weekend[e]								
Q1, 0:37 to 4:01	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Q2, 4:01 to 4:47	−0.07 (−0.44, 0.30)	0.72	0.14 (−0.01, 0.29)	0.07	0.48 (−0.10, 1.05)	0.11	0.02 (−0.07, 0.11)	0.69
Q3, 4:47 to 5:40	0.12 (−0.26, 0.50)	0.53	0.05 (−0.11, 0.20)	0.49	0.21 (−0.37, 0.80)	0.48	0.07 (−0.02, 0.16)	0.11
Q4, 5:40 to 11:36	0.32 (−0.05, 0.70)	0.09	0.03 (−0.13, 0.18)	0.74	0.17 (−0.41, 0.76)	0.56	0.00 (−0.09, 0.09)	0.96
Midpoint difference between weekdays and weekend[f]								
Less than 1 h	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
1 to 2 h	0.15 (−0.17, 0.47)	0.36	0.02 (−0.11, 0.15)	0.74	0.03 (−0.46, 0.53)	0.89	−0.03 (−0.10, 0.05)	0.51
2 to 3 h	0.63 (0.21, 1.06)	<0.001	−0.10 (−0.27, 0.07)	0.26	−0.15 (−0.81, 0.52)	0.66	−0.04 (−0.14, 0.06)	0.47
More than 3 h	0.39 (−0.41, 1.20)	0.33	0.08 (−0.24, 0.41)	0.62	0.69 (−0.56, 1.95)	0.28	0.05 (−0.14, 0.24)	0.60

[a] Adjusted model for weekday sleep duration included sex, age, smoking status, month of measurement, and weekday sleep midpoint.
[b] Adjusted model for weekend sleep duration included sex, age, smoking status, month of measurement, and weekend sleep midpoint.
[c] Adjusted model for sleep variability included sex, age and smoking status, and month of measurement.
[d] Adjusted model for weekday sleep midpoint included sex, age, smoking status, month of measurement, and weekday sleep duration.
[e] Adjusted model for weekend sleep midpoint included sex, age, smoking status, month of measurement, and weekend sleep duration.
[f] Adjusted model for midpoint difference between weekday and weekend included sex, age, smoking status, month of measurement, weekdays and weekend sleep duration.

this time period as well, including a rise in insulin resistance during late puberty that normalizes upon full sexual maturation [43]. Another possible explanation for differences in the sleep and inflammation relationship across late adolescence to early adulthood is that relationships depend on overall levels of systemic inflammation. Notably, the inflammatory biomarkers were considerably higher in the late-to-post pubertal visit than the earlier visit. This increase with age has also been noted in other studies; for example, Park et al. found a 0.67 mg/L increase in CRP over a 4-year span in a US study [18]. Similarly, Park et al. found that age modified the association between weekend sleep duration and CRP, such that there was an inverse association between ages 14 to 17, no association from age 18–21, and a positive association at age 22. We also found several inverse associations between sleep duration and inflammatory biomarkers at the mid-to-late pubertal visit, but a positive association between sleep duration and hs-CRP among boys in the late-to-post pubertal visit.

This study had some strengths, including objective sleep measurements and the ability to account for multiple confounders, as well as to carry out sex-stratified analyses. There were also limitations. Because sleep and inflammatory markers were measured within the span of one week, we cannot preclude the possibility that higher inflammation caused worse sleep patterns rather than vice versa. Although outside the scope of the present aims, whether inflammatory markers at age 14 predict sleep patterns at age 16 would be worth pursuing to consider the bidirectional nature of sleep and inflammation. We assessed a limited number of cytokines, which may not provide a complete picture of the sleep-inflammation relationships present. Nonetheless, overall there were a large number of statistical tests run, which could increase the likelihood of type 1 errors. Finally, our sample population included Mexico City adolescents and thus may not be generalizable to other populations.

In summary, in a group of Mexico City adolescents, we report multiple associations between sleep characteristics and inflammatory biomarkers during a mid-to-late pubertal visit but not at a follow-up visit that occurred 2 years later. Specifically, at the mid-to-late pubertal visit we found that shorter sleep duration and delayed sleep timing were related to increased hs-CRP. Markers of short sleep duration and inconsistent duration and timing were also related to individual inflammatory cytokines in a sex-specific manners. At the late-to-post pubertal visit, there was a positive association between sleep duration and hs-CRP among boys and a positive association between social jetlag and hs-CRP among girls. Altogether, findings point to highly sex and age-specific associations between sleep and inflammation during the transition from puberty to young adulthood.

Funding

This work was supported by the US Environmental Protection Agency grant RD 83543601; National Institute of Environmental Health Sciences grants: P01 ES02284401, P30 ES017885, R24 ES028502, and T32 ES007062; National Heart, Lung, Blood Institute

grant K01 HL151673. This study was also supported and partially funded by the National Institute of Public Health/Ministry of Health of Mexico. The funding sources had no involvement in the study design, collection, analysis, or interpretation of the data, the writing of the report, and the decision to submit the article for publication.

CRediT authorship contribution statement

Kelvin Pengyuan Zhang: Formal analysis, Writing – original draft. **Miatta Buxton:** Writing – review & editing. **Yanelli Rodríguez-Carmona:** Writing – review & editing. **Karen E. Peterson:** Funding acquisition, Writing – review & editing. **Yun Liu:** Writing – review & editing. **Helen J. Burgess:** Writing – review & editing. **Alejandra Cantoral:** Writing – review & editing. **Martha María Tellez-Rojo:** Supervision, Writing – review & editing. **Libni A. Torres-Olascoaga:** Project administration, Writing – review & editing. **Laura Arboleda-Merino:** Data curation, Writing – review & editing. **Erica C. Jansen:** Conceptualization, Supervision, Writing – original draft, Writing – review & editing.

Acknowledgements

We gratefully acknowledge the American British Cowdray Hospital for use of their research facilities, and we are extremely grateful to the research staff and participants for their commitment to the project.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sleep.2022.08.007.

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