



Review article

Are sleep time and quality associated with inflammation in children and adolescents? A systematic review

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ABSTRACT

Sleep restriction in children can trigger the development of problems such as impaired cognition, behavioral problems, cardiovascular problems, and obesity. In addition, the inflammatory profile of children can also be influenced by sleep restriction. The aimed to review and analyze the association between time and sleep quality with inflammatory biomarkers in children and adolescents. Three electronic databases (MEDLINE, Web of Science and Scopus) were searched from August 30, 2022. The search strategy used the following descriptors: children and adolescents; sleep, and inflammatory profile. This review protocol is registered in the PROSPERO database (CRD42020188969). We obtained 2.724 results of articles with potentially relevant titles. Sixteen percent of the articles were excluded because they were duplicates, 84.3% were excluded after reading the title, and 0.9% were studied from systematic reviews or textbooks (0.9%). Accelerometers are the most commonly used method for the objective measurement of sleep time, while the PSQI questionnaire is the most commonly used subjective method to measure sleep quality. The results indicated an inconsistent association between sleep time and CRP in the literature. Sixty percent of studies used the Pittsburgh Sleep Quality Index (PSQI) for subjective assessment of sleep quality and possible sleep disorders. However, only one retrieved study showed significant association between sleep quality and CRP. Thus, sleep time does not present significant association with inflammatory biomarkers; whereas, poor sleep quality shows positive association with CRP with a lower magnitude.

1. Introduction

The National Sleep Foundation provides clear guidelines on the amount of sleep children should be getting per day. For children aged between 3 and 5 years, they recommend 10–13 h of sleep each day, while children in the age bracket of 6 to 10 years should get 9–11 h of sleep daily (Ohayon et al., 2017). The literature presents evidence that has shown a significant correlation between irregular sleep patterns in children and adolescents and numerous health complications. These health issues include cognitive impairments (Astill et al., 2012; Kassim et al., 2016; Kelly et al., 2013; Kopasz et al., 2010), emotional regulation

difficulties, and aggressive behavior (Kopasz et al., 2010), a decline in academic performance (Hill et al., 2007) an increased risk of obesity (Nielsen et al., 2011) and poor cardiometabolic health (LaVoy et al., 2020; Quist et al., 2016).

The underlying biological rationale for the impact of sleep time can be traced back to the sleep-wake cycle's role in regulating the production and activation of immunity-regulating cells. Research reveals that the levels of immune system cells in the blood are at their highest in the early evening and drop to their lowest point in the morning (Besedovsky et al., 2012; Rico-Rosillo and Vega-Robledo, 2012). While the precise physiological mechanism that leads to these diurnal variations remains

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elusive, it has been demonstrated that any disruption in the normal sleep-wake cycle - like sleep deprivation - can have a profound effect on the functionality of the immune system (Mortensen, 2001). This reduction in sleep duration and quality triggers a surge in inflammatory markers such as C-reactive protein (CRP) (Mortensen, 2001), which is the body's response to the aforementioned changes. Therefore, it is reasonable to hypothesize that inadequate sleep duration and poor sleep quality could be linked to an increase in inflammatory biomarkers in children and adolescents.

Despite the mounting evidence, no systematic review has been carried out to establish the connection between sleep duration and quality and inflammatory biomarkers in children and adolescents. Hence, the objective of this study is to fill this gap by reviewing and analyzing the association between sleep duration and quality and inflammatory biomarkers in this population.

2. Methods

2.1. Search strategy

This systematic review was conducted and prepared following the PECO structure (Population of interest, Exposure, Comparator, Outcome) (Table 1), and we used the PRISMA checklist to report the results found (Page et al., 2021). We performed electronic searches on MEDLINE (PubMed), Web of Science, and SCOPUS databases for records from their inception up until the most recently published articles in August 30, 2022. After that, we reviewed the articles found in these databases; finally, we contacted the corresponding authors to identify other relevant studies, critical articles, and previous reviews. This article does not contain any studies with human participants or animals performed by any of the authors. However, the review protocol was approved by PROSPERO under protocol number (CRD42020188969).

2.2. Ethics approval and consent to participate

Institutional Review Board approval was not required because it was a Systematic Review only and did not include any human participants or animals performed by any of the authors or require access to any confidential information. Written informed consent was not required for this study because it was a Systematic Review and did not involve any participants.

We used MeSH descriptors for searches and adjusted them for each

database. We divided the descriptors into two independent lists, one for children (A) and the other for adolescents (B):

List A: child OR children OR childhood OR school OR preschool OR preschoolers AND short sleep duration OR long sleep duration OR sleep OR sleep time OR sleep duration AND inflammatory profile OR inflammation OR inflammatory biomarker OR C-reactive protein OR CRP OR interleukin 6 OR IL-6 OR adiponectin OR TNF alpha OR TNF- α AND cross-sectional studies OR case-control OR prospective cohort study, OR prevalence studies OR survey.

List B: adolescent OR adolescents OR adolescence OR teen OR teenager OR youth AND short sleep duration OR long sleep duration OR sleep OR sleep time OR sleep duration AND inflammatory profile OR inflammation OR inflammatory biomarker OR C-reactive protein OR CRP OR interleukin 6 OR IL-6 OR adiponectin OR TNF alpha OR TNF- α AND cross-sectional studies OR case-control OR prospective cohort study, OR prevalence studies OR survey.

2.3. Eligibility criteria

The inclusion criteria were i) a study population composed of children and/or adolescents according to the World Health Organization classification (2 to 19 years old); ii) observational epidemiological studies and original research; iii) studies that involved sleep time or sleep quality; and iv) studies that reported inflammatory biomarkers (IL-6, TNF α , CRP) (Table 1). We defined these criteria to increase comparability between studies. In addition, studies were excluded if they met one or more of the following criteria: (1) review articles or books and studies, (2) studies that do not describe sleep time with inflammation associations; or (3) included specific populations with medical conditions, such as diabetes, obesity, and hypertension, or individuals who were using medication for CVD.

2.4. Data selection and extraction protocol

We reviewed articles according to the following steps: (1) articles published in English, Spanish, and Portuguese; (2) screening of titles; (3) abstracts; and (4) full texts. Two authors (Medeiros de Oliveira and Vianna, R) performed literature screenings independently using the criteria described above and a data extraction form, after which the results were compared. If there was any disagreement, the article was evaluated by a third researcher, De Moraes AC, to decide whether the article would be included in this review.

Table 1
Description of studies included.

Reference	Survey year	Country	Study/Article title	Mean age (years)	Sample size		Study type
					Total (n)	Girls (%)	
El-Sheikh et al. (2007)	NI	Southeastern USA	The association between children's sleep disruption and salivary interleukin-6	8.74	64	NI	Cross-sectional study
Adolescent							
Chiang et al. (2019)	NI	Los Angeles, CA	Daily interpersonal stress, sleep duration, and gene regulation during late adolescents	18.37	91	56.18	Longitudinal Study
Park et al. (2016)	2011–2012	Los Angeles, CA	Sleep and Inflammation During Adolescence	16.39	315	57	Longitudinal Study (1 year follow-up)
Park et al. (2020)	2013–2014	Los Angeles, CA	Sleep and Inflammation During Adolescents' Transition to Young Adulthood	16.40	350	57	Longitudinal Study (1 year follow-up)
Hall et al. (2015)	2008–2011	Pittsburgh, PA	Sleep duration during the school week is associated with C-reactive protein Risk Groups in healthy adolescents	15.71	244	52.5	Longitudinal Study (3 years follow-up)
Children and Adolescent							
LaVoy et al. (2020)	NI	Houston, TX	Bidirectional relationships between sleep and biomarkers of stress and immunity in youth.	12.20	55	53	Cross-sectional study

NI: Not Informed

The data extraction form had information about the characteristics of each study: first author, year, place of publication, sample size, age group, type of exposure (sleep time and sleep quality), measurement of exposures (accelerometer and questionnaires), and measurement of adjusted inflammatory biomarkers and confounders.

2.5. Evaluation and analysis of associations

We extracted the β coefficients and their respective 95% confidence intervals from the studies that estimated the association between exposures and inflammatory biomarkers (Chiang et al., 2019; El-Sheikh et al., 2007; Hall et al., 2015; LaVoy et al., 2020). In some cases, we reported results only by subgroups and not by the entire study sample; in these cases, we did not include these studies in the meta-analysis. In this study, associations between exposures and outcomes, regardless of statistical significance, are reported; however, the different definitions and measures used in the studies prevented the comparison of results. As a result, performing a meta-analysis was impossible (Chiang et al., 2019; El-Sheikh et al., 2007; Hall et al., 2015; LaVoy et al., 2020).

3. Results

The systematic literature review included articles published up until August 30, 2022, yielding 2,724 potentially relevant articles (Fig. 1). Sixteen percent of these articles were duplicates and subsequently excluded. After reviewing the titles, 84.3% of the articles were eliminated. A further 0.9% were removed as they were from systematic reviews or textbooks (Fig. 1). Six studies met the systematic review eligibility criteria, encompassing a total of 1,119 children and adolescents aged 3 to 19 years. Notably, all studies were conducted in the United States. Of these, only one article addressed children (El-Sheikh et al., 2007) (Table 1). We did not identify studies assessing the

association between sleep time and quality with inflammatory biomarkers in lower-middle-income countries (WB., 2018).

Table 2 provides details of the association between sleep time, quality, and inflammatory biomarkers. In all the studies included, sleep time was assessed using accelerometers attached to the nondominant wrist at bedtime for a minimum of seven consecutive nights. The average sleep time over these days was then computed. The inflammatory biomarkers, including CRP, were assessed via serum blood collection in these studies (Hall et al., 2015; Park et al., 2020; Park et al., 2016), nuclear factor kappa B (NF- κ B) (Chiang et al., 2019), and interferon response factors (IRF) (Chiang et al., 2019). Interleukin 6 (IL-6) was measured by salivary samples in two articles (El-Sheikh et al., 2007; LaVoy et al., 2020).

Two articles employed IL-6 and TNF α to investigate the association between sleep and inflammation, although one article (LaVoy et al., 2020) did not report the beta coefficient for sleep time and quality, adjusted for inflammation. Among the three articles evaluating this relationship using CRP (Hall et al., 2015; Park et al., 2020; Park et al., 2016), one did not describe in detail the method for exposure measurement (Hall et al., 2015). Two articles from the same research group carried out studies in the same population at different times (Park et al., 2020; Park et al., 2016), revealing an inconsistent association between sleep time (measured by accelerometer) and CRP in the literature. The Pittsburgh Sleep Quality Index (PSQI) was used for subjective sleep quality and potential sleep disorder assessment in sixty percent of the studies (Chiang et al., 2019; Park et al., 2020; Park et al., 2016). The findings varied, with only one study showing a significant association between sleep quality and CRP (Table 3).

4. Discussion

We performed a comprehensive systematic review of studies that

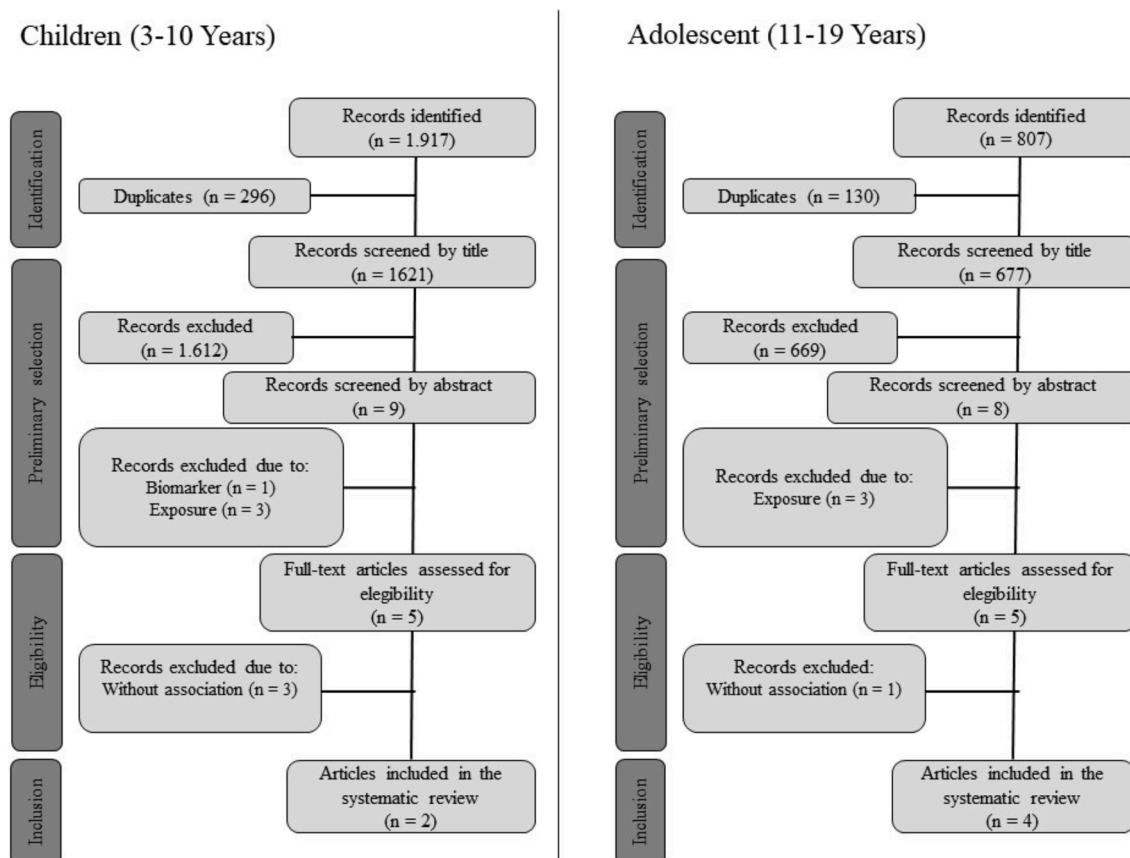


Fig. 1. PRISMA flow diagram of the literature search.

Table 2
Summary information of the studies that used sleep assessment method and inflammatory biomarkers as an outcome.

Reference	Sleep assessment method	Biomarkers	Outcome	b-adjusted	Covariates in fully adjusted model
El-Sheikh et al. (2007)	Actigraph accelerometer wear in the non-dominant wrist at bedtime for 7 consecutive nights; SSSH scales; The Morning/Eveningness Scale and CSHQ	Salivary IL-6 and IL-6 reactivity	IL-6: Pre-laboratory challenge = 3.23 pg/mL IL-6: Post-laboratory challenge = 2.98 pg/mL	0.27	Age, gender, ethnicity, BMI, sleepiness, morning/evening, sleepiness-parent, sleep disordered, breathing-parent, total sleep, sleep efficiency, min awake, activity index, IL-6 baseline, IL-6 reactivity
Chiang et al. (2019)	Actigraph accelerometer in the non-dominant wrist at bedtime for 8 consecutive nights and PSQI	NF-κB, IRF	NF-κB and sleep duration and sleep efficiency: log 0,596 ± 0,187 IRF and sleep duration and sleep efficiency: log -1,249 ± 0,368	NFκb: 0.23 IRF: -0.69	Gender, age, ethnicity, parental education), body mass index (BMI), smoking behavior, and alcohol consumption
Hall et al. (2015)	Actigraphy Actiwatch-16 wear in the wrist for a 7 consecutive days	CRP	CRP: > 3 mg/L Risk Group.	-0.04	Sex, race, highest parental education and, BMI
Park et al. (2016)	Actigraphy watch MicroMotionlogger wear in the non-dominant wrist at bedtime for 8 consecutive nights and PSQI	CRP	CPR: 1–3 mg/l Low-risk, CPR: > 3 mg/l High risk CRP: above 10 mg/l	-0.01	Sex, ethnicity, parental education, perceived stress, and BMI percentile
Park et al. (2020)	Actigraphy watch MicroMotionlogger wear in the non-dominant wrist at bedtime for 8 consecutive nights and PSQI	CRP	Wave 1: 0.69 mg/l Wave 2: 0.89 mg/l Wave 3: 1.36 mg/l	-0.04	Age, sex, waist circumference, depressive symptoms, and substance use
LaVoy et al. (2020)	Motionlogger Micro wristwatch wrist for 7 days and SSSH scales	sAA, cortisol, IL-6, and IL-1β	sAA: 42.81U/mL Cortisol: 9.36 nmol/L IL-6: 24.95 pg/mL IL-1β: 713.70 pg/mL	NI	Age, sex, zBMI, and study characteristics (collection time and season)

SSHS: School Sleep Habits Survey; CSHQ: Children s Sleep Habits Questionnaire, PSQI: Pittsburgh Sleep Quality Index, CPR: C-Reactive Protein, sAA: α-amylase; IL-6: interleukin 6; IL-1β: interleukin 1 beta; BMI: Body Mass Index; IRF: Interferon Response Factors; NI: Not Informed.

Table 3
Description of studies on sleep quality and sleep time and inflammation in children and adolescents.

Reference	Sleep assessment method	Biomarkers	Outcome	Magnitude of Association	Covariates in fully adjusted model
El-Sheikh et al. (2007)	Actigraph accelerometer wear in the non-dominant wrist at bedtime for 7 consecutive nights; SSSH scales; The Morning/Eveningness Scale and CSHQ	Salivary IL-6 and IL-6 reactivity	IL-6 Salivary = 3.23 pg/mL IL-6 reactivity = 2.98 pg/mL	Sleep time β = 0.27	Age, gender, ethnicity, BMI, sleepiness, morning/evening, sleepiness-parent, sleep disordered, breathing-parent, total sleep, sleep efficiency, min awake, activity index, IL-6 baseline, IL-6 reactivity
Chiang et al. (2019)	Actigraph accelerometer in the non-dominant wrist at bedtime for 8 consecutive nights and PSQI	NF-κB, IRF	NF-κB = 0,596 IRF = -1,249	Sleep time NI Sleep quality NFκb β = 0.23 IRF β = -0.69	Gender, age, ethnicity, parental education), body mass index (BMI), smoking behavior, and alcohol consumption
Hall et al. (2015)	Actigraphy Actiwatch-16 wear in the wrist for 7 consecutive days	CRP	CRP = 1.71 (mg/L).	Sleep time OR = 0.62 (95 %CI = 0.36–1.06)	Sex, race, highest parental education and BMI
Park et al. (2016)	MicroMotionlogger watch wear in the non-dominant wrist at bedtime for 8 consecutive nights and PSQI	CRP	NI	Sleep time β = -0.01 Sleep quality β = 0.01	Sex, ethnicity, parental education, perceived stress, and BMI percentile
Park et al. (2020)	MicroMotionlogger watch wear in the non-dominant wrist at bedtime for 8 consecutive nights and PSQI	CRP	Wave 1: 0.69 mg/L Wave 2: 0.89 mg/L Wave 3: 1.36 mg/L	Sleep time β = -0.04 Sleep quality β = 0.07	Age, sex, waist circumference, depressive symptoms, and substance use
LaVoy et al. (2020)	Motionlogger Micro wristwatch wrist for 7 days and SSSH scales	sAA, cortisol, IL-6, and IL-1β	sAA: 42.81U/mL Cortisol: 9.36 nmol/L IL-6: 24.95 pg/mL IL-1β: 713.70 pg/mL	NI	Age, sex, zBMI, and study characteristics (collection time and season)

SSHS: School Sleep Habits Survey; CSHQ: Children s Sleep Habits Questionnaire, PSQI: Pittsburgh Sleep Quality Index, CPR: C-Reactive Protein, sAA: α-amylase; IL-6: interleukin 6; IL-1β: interleukin 1 beta; OR = Odds Ratio, 95 %CI = confidence interval 95%, BMI: Body Mass Index; IRF: Interferon Response Factors; NI: Not Informed. **Significant associations (p < 0.05) highlighted in bold.**

addressed the association between sleep time and quality with inflammatory biomarkers in children and adolescents (3 to 19 years old). Whereas, poor sleep quality shows positive association with CRP with a lower magnitude. No clear evidence of an association between sleep quality (assessed subjectively) and inflammatory biomarkers. We did not find any studies conducted in lower-middle-income countries in our

searches (WB., 2018); the high costs of accelerometers, exams, and biochemical analyses can be a limiting factor in measuring these indicators in countries with these income characteristics.

Two studies involving children (El-Sheikh et al., 2007; LaVoy et al., 2020) evaluated the association between sleep time and quality with inflammatory biomarkers measured by salivary samples. According to

the literature, in adults, increased salivary IL-6 is a valid method for this estimation because it is associated with interruptions in the quantity and quality of sleep (Reinhardt et al., 2016; Reinhardt et al., 2019). After all, cytokines are one of the primary mediators that stimulate the hypothalamic–pituitary–adrenal axis during inflammatory stress generated by sleep deprivation (Papanicolaou and Vgontzas, 2000).

The results of the studies indicate that sleep time does not have a significant association with CRP or weak associations moderated by demographic factors (gender and age). This finding may offer some insight into the inconsistency in the literature about the role of sleep duration in inflammation. Research in adult populations has led to the understanding that the association between sleep duration and inflammation is inconsistent because there are variations in sleep assessment methods, as well as follow-up time in cohort studies (Irwin, 2015; Taheri et al., 2007; van den Berg et al., 2008), and this is probably also the case in our review with the association between sleep time and inflammation. Inflammation can be related to the follow-up time of the studies, in which the adolescents were followed for only one year, and this period is not sufficient to observe the negative effect of sleep restriction on the inflammatory system in this age group (Park et al., 2020; Park et al., 2016).

On the other hand, we found inconsistent associations between PSQI questionnaire scores for sleep quality, a valid method used for this population (de la Vega et al., 2015), and serum levels of CRP (Park et al., 2020; Park et al., 2016). This inconsistency in the results indicated by the comparison of the studies can be explained because disturbances in sleep quality have a chronic effect on the inflammatory system (Irwin, 2015) and also partially due to the inability of PCR to quantify chronic inflammation (Sproston and Ashworth, 2018). Therefore, we suggest that future studies analyze a set of inflammatory markers (adiponectin, IL-1, IL-6, TNF α , in addition to CRP) that are more sensitive for measuring associations between sleep and inflammation. Therefore, future longitudinal studies with high methodological quality are needed to identify temporal relationships between exposures and outcomes.

4.1. Limitations

The primary studies included in this review may have methodological limitations; that is, the methods of measuring sleep time and quality and inflammatory biomarkers may be different, and there is no consensus on which inflammatory biomarker should be used in research involving pediatric populations. Four of the six eligible articles were cross-sectional studies. Cross-sectional studies have many limitations, particularly the inability to identify temporal relationships between exposures and outcomes; this limitation may partially explain the low number of associations found in the studies (Carlson and Morrison, 2009). These are essential issues to consider, particularly when studying pediatric health, and form a complex system of interactions that may be difficult to assess with a linear drug trial approach, such as that used in clinical trials (Carlson and Morrison, 2009). However, when cross-sectional studies are inconsistent and if financial resources are available, well-conducted prospective cohort studies that monitor children and adolescents over follow-up periods should be performed to infer causality with a greater degree of certainty (Tylavsky et al., 2020).

5. Conclusion

No clear evidence of association between sleep time and quality with inflammatory biomarkers is available in the literature. Accelerometers and the PSQI questionnaire serve as key measures for sleep duration and quality, respectively. Sleep duration, primarily measured using accelerometers, shows no significant association with inflammatory biomarkers. However, poor sleep quality, as assessed via the PSQI questionnaire, demonstrates a modest positive correlation with CRP in one study. The association between sleep parameters and inflammatory biomarkers in lower-middle-income countries remains unexplored.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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