Received: 4 September 2020 | Revised: 26 March 2021 | Accepted: 30 March 2021

DOI: 10.1111/jsr.13357

RESEARCH ARTICLE

Journal of Sleep Research

Infant diurnal cortisol predicts sleep

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Funding information
National Institute of Child Health and Human Development, Grant/Award Number: R03HD082550

Abstract

The sleep–wake system is immature at birth and develops in parallel with the hypothalamic–pituitary–adrenal axis, a biological stress system of which the end product is cortisol. Perturbations in one system during infancy can maladaptively influence the maturation of the other system, leading to lasting sleep and cortisol system dysregulation and heightening the risk of enduring health problems. To better understand the early interplay between these systems, we examined whether actigraphy-derived measures of night-time sleep duration and onset were associated with cumulative exposure to cortisol, indexed by hair cortisol concentration, in 12-month-old children. Overall, early sleep onset predicted lower hair cortisol above and beyond sleep duration, family income and chaos experienced at home. Furthermore, both sleep and cortisol levels vary day to day, and temporal dependencies between daily sleep and cortisol regulation are not well understood. Thus, we assessed how the sleep characteristics on a particular evening related to salivary cortisol levels the following day and how daytime and evening cortisol related to the sleep characteristics on the same night. Lower total exposure to cortisol on a particular day was related to longer night-time sleep duration the same night, but not sleep onset. Lower salivary cortisol levels on a given evening related to earlier sleep onset the same night, but not to night-time sleep duration. Sleep duration and onset on a given night were unrelated to total cortisol exposure the following day. Findings suggest that in early development, the day-to-day relation between sleep and cortisol is not bidirectional, but more driven by diurnal cortisol.

KEYWORDS

diurnal salivary cortisol, infancy, physiological stress, sleep duration, sleep onset

1 | INTRODUCTION

Sleep patterns change dramatically over the first year of life. Infants progress from having irregular and fragmented sleep distributed throughout 24 h to the emergence of a circadian rhythm that leads to more consolidated night-time sleep by 12 months of age (Davis, Parker, & Montgomery, 2004; Sheldon, 2002). In parallel, the hypothalamic–pituitary–adrenal (HPA) axis, a biological stress system, also develops throughout infancy along with the establishment of a circadian rhythm (De Weerth, Zijl, & Buitelaar, 2003). At night, sleep plays an important role in the restoration of the body and the brain (Assefa, Diaz-Abad, Wickwire, & Scharf, 2015). During the day, the HPA axis prepares the body to combat daily life stressors by mediating the production of the stress hormone, cortisol (Cone, Low, Elmquist, & Cameron, 2002). It is well established that the regulation of both these systems is closely intertwined in adults (Van Reeth et al., 2000), and their proper functioning is essential for concurrent and lasting positive health outcomes (McEwen, 2006; Palagini,

Drake, Gehrman, Meerlo, & Riemann, 2015). However, the early interplay between sleep and the HPA axis, when both these systems are maturing simultaneously, is not fully understood. The development of these systems during infancy lays the foundation for how they function later in life. It is suggested that early perturbations in one system during such a vulnerable time can maladaptively influence the maturation of the other system (Van Reeth et al., 2000; Palagini et al., 2015). This sets the stage for lasting sleep and HPA axis dysregulation, which ultimately increases an individual's risk of enduring health problems (McEwen, 2006). Thus, there may be an interplay between sleep and the HPA axis during infancy through which early adversities get "under the skin," leading to lasting adverse health outcomes.

Both sleep and the HPA axis follow a circadian rhythm (Borbely, 1982; De Weerth et al., 2003) and get dysregulated due to early life adversities (Flannery et al., 2017; Fisher, Stoolmiller, Gunnar, & Burraston, 2007; Gunnar & Vazquez, 2001; Mrdalj et al., 2013; Palagini et al., 2015; Saridjan et al., 2010; Tiba, Tufik, & Suchecki, 2004). On a daily basis, the HPA axis produces peak levels of cortisol in the morning during the final phases of sleep and minimum levels of cortisol at night during the early phase of night-time sleep (Born & Fehm, 1998). This cyclic change in cortisol levels that is dependent on the circadian rhythm is called the diurnal cortisol rhythm. Newborns lack this adult-like diurnal cortisol rhythm in which mid-afternoon cortisol levels are lower than mid-morning cortisol levels. Instead, newborns exhibit two cortisol peaks that are 12 h apart and unrelated to time of the day. As the HPA axis matures along with the establishment of a circadian rhythm, infants as young as 2 months old begin to exhibit a circadian rhythm for cortisol, which persists and becomes adult like by 8 months of age (De Weerth et al., 2003). Although decline in cortisol from waking to bedtime is normative once the diurnal cortisol rhythm is established, severe early adversity has been associated with slower decline in cortisol, indexing a dysregulated diurnal cortisol rhythm during early and later childhood (Fisher et al., 2007; Flannery et al., 2017; Gunnar & Vazquez, 2001). Early adversity is also related to increased cortisol throughout the day – another marker of dysregulated diurnal cortisol rhythm (Saridjan et al., 2010). In the context of sleep, early stress impacts sleep architecture and consolidation in rodents (Mrdalj et al., 2013; Tiba et al., 2004). In humans, it has been theorized that early adversity disrupts the circadian sleep–wake cycle, which ultimately leads to hyperactivated wake-promoting physiological systems (Palagini et al., 2015). A proposed mechanism is that early adversities lead to higher activation of the HPA axis, which then distorts the sleep–wake cycle.

Prolonged dysregulation of the circadian sleep–wake cycle and diurnal cortisol rhythm has adverse consequences for long-term health. Sleep dysregulation includes sleep deprivation disrupting the circadian rhythm, which is a stressor in itself leading to elevated cortisol levels in young adults (McEwen & Karatsoreos, 2015). This contributes to wear and tear on the body, impairing multiple regulatory systems, a phenomenon known as allostatic load (McEwen, 2006). Likewise, prolonged diurnal cortisol dysregulation contributes to higher cumulative exposure to cortisol over several months (e.g., Flom, St. John, Meyer & Tarullo, 2017). Cumulative exposure to cortisol is assessed from cortisol deposited in the hair shafts (Meyer & Novak, 2012). Increased cumulative exposure to cortisol also adds to the allostatic load and consequently increases the risk of poor health outcomes. Therefore, examining the relation between sleep and cumulative exposure to cortisol during infancy is imperative to understand the emerging pattern of their association.

In infants, sleep deprivation, or poor sleep consolidation, is indexed by shorter night-time sleep duration. Shorter night-time sleep during infancy could also disrupt the circadian rhythm and contribute to elevated cumulative exposure to cortisol, making infants vulnerable to a myriad of health problems, such as mood, cardiovascular and immune-mediated disorders (McEwen, 2006). A recent study found that parent-reported, shorter night-time sleep duration in the first year of life was correlated with increased cumulative exposure to cortisol (Flom et al., 2017). However, parent reports of sleep durations are prone to inaccuracy (Goodwin et al., 2007), and confirming this finding using objective measures of night-time sleep duration is crucial. Falling asleep later at night, or later onset of night-time sleep, is a sleep characteristic associated with shorter night-time sleep duration during infancy (Cheung, Bedford, Saez De Urabain, Karmiloff-Smith, & Smith, 2017). It also disrupts the diurnal cortisol rhythm. Early childhood studies reveal that delay in sleep onset (i.e., time of falling asleep) is related to measures of diurnal cortisol, such as higher cortisol awakening response and lower waking cortisol levels (Gribbin, Watamura, Cairns, Harsh, & LeBourgeois, 2012; Stalder et al., 2013). Thus, it is possible that later sleep onset also relates to cumulative exposure to cortisol during infancy. To our knowledge, this has not been explored. Findings from research on the association of poor sleep with cumulative exposure to cortisol, from as early as infancy, could have implications for improving infant and later health outcomes through early sleep interventions.

In addition to investigating the relations of sleep consolidation and onset with cumulative exposure to cortisol, understanding the interplay between the sleep characteristics and diurnal cortisol function can provide insight on how short-term interplay between these systems could eventually lead to long-term associations. More research has examined the relation of sleep characteristics and diurnal cortisol by averaging the measures across multiple days (e.g., Flom et al., 2017; Gribbin et al., 2012; Stalder et al., 2013). However, both sleep and cortisol levels vary on a daily basis, and it is necessary to disentangle temporal dependencies between daily sleep and diurnal cortisol regulation. Few studies indicate that their association is bidirectional. Induced sleep onset delay in toddlers and preschoolers results in dysregulated cortisol levels the next morning, suggesting that sleep onset delay could influence diurnal cortisol rhythm (Gribbin et al., 2012). However, cortisol dysregulation could also impact sleep. For example, temporal analyses show that adults with elevated cortisol at night had delayed sleep onset (Van Cauter & Spiegel, 1997). Barring these few studies, research examining the relation between sleep and cortisol has not assessed time-based links between daily sleep and diurnal cortisol, especially

in the first year of life. Gaining further insights into the potential bidirectional nature of their association early in development will be important for obtaining a more comprehensive understanding of how sleep and cortisol systems begin to influence each other in their development.

Given that both sleep and cortisol systems develop in parallel and early perturbations have implications for lasting health outcomes, the goal of the current study was to understand how objective measures of sleep were related to cumulative and diurnal cortisol regulation in 12-month-old infants. By this age, both sleep and diurnal cortisol rhythm are relatively established, with consolidated night-time sleep and adult-like diurnal cortisol patterns (Davis et al., 2004; Sheldon, 2002; De Weerth et al., 2003), providing an ideal window to explore the early interplay between the two systems. We compared actigraphy-derived measures of night-time sleep onset and consolidation to cumulative exposure to cortisol, as measured by hair cortisol, and daily cortisol regulation, as measured by salivary cortisol. First, to understand the overall relation between sleep and chronic cortisol function, we assessed whether average measures of sleep characteristics were related to hair cortisol. Based on previous research (Flom et al., 2017), we hypothesized that later night-time sleep onset and shorter night-time sleep duration would relate to higher hair cortisol. Household income, chaotic home environment, breastfeeding, daytime naps and co-sleeping were considered as potential covariates because of their associations with sleep and/or cortisol (Boles et al., 2017; Doom et al., 2018; Flom et al., 2017; Gribbin et al., 2012; Mindell, Sadeh, Kohyama, & How, 2010; Patel, Grandner, Xie, Branas, Gooneratne, 2010; Philbrook & Teti, 2016; Vliegenthart et al., 2016). Additionally, as sleep and cortisol vary daily, to disentangle the temporal relations between daily sleep and diurnal cortisol during infancy, we examined whether daily sleep has time-based associations with diurnal cortisol. Specifically, we assessed how night-time sleep onset and duration on a given night were related to total cortisol exposure over the next day, and how total cortisol exposure over a particular day and bedtime cortisol on a particular night were associated with night-time sleep onset and duration the same night. Informed by previous literature (Flom et al., 2017; Gribbin et al., 2012; Stalder et al., 2013), we hypothesized that later night-time sleep onset and shorter night-time sleep duration on a given night would be related to greater exposure to cortisol the next day, and greater exposure to cortisol over a given day and greater bedtime cortisol on a given night would be related to later night-time sleep onset and shorter night-time sleep duration the same night.

2 | METHODS

2.1 | Participants

We recruited 90 parent–infant dyads from the greater Boston metropolitan area through a departmental database, online advertising, publicly available state birth records and community recruitment events. Four of the infants did not have usable hair or salivary cortisol data and were excluded from the analyses. This resulted in a final sample of 86 healthy, singleton, 1-year-old children (43 female, M_{age} = 12.24 months, standard deviation [*SD*] = 0.82), with no known hearing, visual, neurological or developmental disorders, and their parents (*N* = 86, 80 female). Infants were accompanied by the parent with whom they spent most of their time. All infants were born full term. Infants taking oral or topical steroid medications were ineligible due to potential effects on cortisol levels. Demographic information is provided in Table 1. Descriptive statistics for each variable are presented in Table 2.

TABLE 1 Demographic characteristics of participating families

Variables	
Infant race	
White	62.2%
Black or African American	13.3%
Asian	7.8%
Native American	4.4%
Multiracial	12.2%
Infants breastfed in the 3 months prior to the laboratory visit	59.3%
Infants who engaged in co-sleeping with their parents	48.2%
First-time parents	40.7%
Number of other children in household *M* (*SD*)	0.92 (1.02)
Maternal education (with at least 4-year college degree)	79.9%
Paternal education (with at least 4-year college degree)	67.4%
Maternal occupation prestige (1–5 scale; 1 requiring less to no preparation) *M* (*SD*)	3.52 (1.07)
Paternal occupational prestige (1–5 scale; 1 requiring less to no preparation) *M* (*SD*)	3.41 (1.16)
Economically strained participants (income-to-needs ratio = <3)	42.4%

2.2 | Procedure

This study was approved by Boston University's Institutional Review Board. Parent–infant dyads visited the laboratory for 1.5 h. Following informed parental consent, parents were trained on home salivary sample collection and actigraph recording procedures for their infants. Hair samples were collected from the infants. Parents completed questionnaires on infant sleep environment, home environment, infant hair habits and family demographics. At home, parents completed 3 days of diurnal salivary cortisol collection and actigraph recording from their infants, after which cortisol samples and actigraphs were picked up.

TABLE 2 Descriptive statistics and correlations among variables

Variables	*n*	*M* (*SD*)	1	2	3	4	5	6
Raw cortisol								
1. Hair cortisol concentration (pg/mg)	86	301.16 (1111.25)	-					
2. Average diurnal cortisol exposure across 3 days (μg/dl/h)	70	157.81 (189.33)	0.362**	-				
3. Average bedtime salivary cortisol concentration across 2 days (μg/dl)	76	0.22 (0.47)	0.541**	0.735**	-			
Sleep								
4. Average night-time sleep onset (h:min)	81	21:12 (01:29)	0.484**	0.226	0.246	-		
5. Average night-time sleep duration (h)	81	9.83 (1.16)	−0.334**	−0.216	−0.091	−0.629**	-	
6. Income-to-needs ratio	85	4.09 (2.89)	−0.282*	−0.169	−0.272*	−0.369**	0.238*	-
7. Household chaos	85	2.04 (0.57)	0.236*	0.363**	0.277*	−0.382**	−0.347**	−0.367**

Note: The table includes all the variables that were included in the final analyses.
*$p < .01$.; **$p < .001$.

2.3 | Measures

2.3.1 | Hair cortisol

Hair cortisol measurement procedures followed our validated methods (Meyer, Novak, Hamel, & Rosenberg, 2014). Hair samples were collected from the infants and then assayed to determine hair cortisol concentrations (HCC), indexing cumulative exposure to cortisol. Samples of 3-cm length from the scalp and weighing 15–30 mg were cut from the posterior vertex of the head. Because washing may affect HCC (Hoffman, Karban, Benitez, Goodteacher, & Laudenslager, 2014), parents were asked about how frequently infants got their hair wet. Human scalp hair grows at approximately 1 cm per month (LeBeau, Montgomery, & Brewer, 2011), so the 3-cm sample indexed cortisol accumulated over the past several months prior to the laboratory visit. Hair samples were frozen at −20°C in plastic vials until cortisol analysis. Samples were weighted, washed twice with isopropanol to remove contaminants, dried, and ground into a fine powder. Cortisol was extracted into methanol, which was then evaporated, and the residue was reconstituted in assay buffer. Reconstituted extracts were analysed for cortisol using a sensitive and selective commercially available enzyme immunoassay (Salimetrics, LLC). Assay readout was converted to pg cortisol per mg of dry hair weight. The average intra-assay and inter-essay coefficients of variation were 3.3% and 10.8%, respectively. Raw HCC levels (median [*Mdn*] = 41.10, mean [*M*] = 301.16, *SD* = 1111.25) were natural log-transformed because the data were not normally distributed. Most participants provided useable HCC values (92%). Of those without useable HCC, four infants had biologically implausible values (greater than 1,500 pg/mg), two used topical or oral steroid medication within the 3 months prior to the laboratory visit, and one did not provide a hair sample. HCC was unrelated to frequency of washing, $rs(83) = 0.085$, $p = .451$. Therefore, it was not necessary to correct for variation in frequency of hair washing.

2.3.2 | Diurnal salivary cortisol

Parents were instructed to collect infant saliva samples by placing a synthetic stick in the infant's mouth for a total of 60 s (Salimetrics) immediately upon infants' waking, in the early afternoon (prior to midday feeding or at least an hour past midday feeding) and at bedtime (just before the last feeding). Parents collected saliva across three normal days when they spent most of their day with their infants, and when the infants were not sick. Working parents collected the samples on weekends or on days off from work. Sampling days were prescheduled during the laboratory visit. When infants were sick on prescheduled sampling days, saliva collection was rescheduled to a week after the onset of the sickness. We provided parents with a home kit, including all collection materials, instructions and a home diary to record information about sampling times, bed and wake times, co-sleeping, duration between sampling and last feeding, duration between sampling and last nap, and other factors that can affect cortisol levels. The experimenter was available via text to respond to parents' questions at the time of saliva sample collection. Parents collected saliva samples within 3–87 days ($M = 13$, $SD = 13.69$) after the laboratory visit. The duration between the laboratory visit and saliva collection was long when prescheduled sampling days were postponed by a week or more due to infants falling sick, working parents changed their weekend plans and postponed sample collection to another weekend, and low-socioeconomic status (SES) families forgot sample collection or met with unexpected stressful life events. Collected samples were frozen at −20°C until they were sent to Trier Laboratories in Germany for cortisol assay.

Biologically plausible values for waking, afternoon and bedtime cortisol values were used to calculate area under the curve with respect to ground (AUC_g) from waking to bedtime as an estimate of diurnal cortisol exposure over the day (Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003). We computed summary scores of AUC_g across three days of sampling along with individual scores for each day of sampling. Bedtime salivary cortisol concentration (SCC) for each day of sampling was also recorded.

2.4 | Actigraphy

Sleep onset and offset times were computed based on the absence of movement, as measured by actigraphy. Motion data were recorded to quantify onset and offset of sleep on the three nights preceding the collection of saliva samples. Parents were trained to attach the actigraph (Mini Mitter Actical) to the infant's right ankle before the infant went to sleep. Sleep onset times and durations were calculated from actigraphy data in MATLAB 9.2.0.556344 (MathWorks Inc.) using the algorithms and thresholds put forth by Galland and colleagues to measure sleep–wake states in infants with actigraphy (Galland et al., 2012). These algorithms are reliable in extracting sleep onset and offset times using actigraphy, and are compatible with the actigraph used in this study. The actigraphy-based data for sleep onset and offset times were validated by home diaries completed by parents to ensure that the actigraphy-derived sleep offset occurred before the parent report of infant wake and that the actigraphy-derived sleep onset occurred after the parent report of infant bedtime. There were strong correlations between actigraphy-derived and parent-reported sleep onset and offset times for the data used in the analyses, as correlations ranged from $r(62) = .87$ to $r(61) = .97$ and were significant at $p < .01$. Thus, we used parent-reported sleep onset and offset times obtained from home diaries for participants who were missing objective actigraphy data on all the 3 days ($n = 12$) or just for specific times or days ($n = 10$) instead of excluding these participants from the sample. There were no group differences between participants with full and partial actigraphy data apart from group differences in their family income. Participants who provided complete actigraphy data had higher income-to-needs ratios ($M = 4.79$, $SD = 2.90$) compared to those who provided partial actigraphy data ($M = 3.25$, $SD = 2.47$), $t(65) = 2.16$, $p = .035$. Statistical analyses were considered for both sleep onset and duration across individual days and as average values calculated across all 3 days.

Income-to-needs ratio (ITN) was calculated using household income and family composition based on the federal poverty guidelines of the particular year in which data were collected for each participant (i.e., 2015–2017). For example, an income-to-needs ratio of 2 indicates that the household income is twice the federal poverty line for that household size.

Household chaos was measured using the short version of the Confusion, Hubbub, and Order Scale (CHAOS), a widely used six-item scale ($\alpha = .50$), administered to assess the level of chaos in the home environment (Matheny et al., 1995). Mothers rated the extent to which they agreed with the six statements reflecting a chaotic or calm and organized household environment (1 = definitely true and 5 = definitely untrue). Examples of items from this scale are, "it's a real zoo in our home" and "there is usually a television turned on somewhere in our home."

Co-sleeping was examined by administering an adapted version of the Sleep Practice Questionnaire (SPQ; Goldberg & Keller, 2007) during the laboratory visit. Infants sharing a bed with their parents for at least a part of the night were coded as infants engaging in co-sleeping. Infants who did not share a bed with their parents throughout the night were coded as solitary sleepers. Information on co-sleeping for each saliva sampling day was also collected by having parents fill out this questionnaire as part of the home diary.

Duration of parent-reported daytime sleep was reported in an item of the Brief Infant Sleep Questionnaire (BISQ; Sadeh, 2004).

Breastfeeding history was reported by parents. Infants were classified into whether or not they had been breastfed in the 3 months prior to the laboratory visit. This time window was chosen based on the period indexed by the hair cortisol sample.

2.5 | Analysis plan

Correlation analyses were performed to assess whether average sleep characteristics and HCC were associated. If ITN, household chaos, co-sleeping, parent-reported daytime sleep duration, breastfeeding and age at assessment were significantly related to HCC, they were included as covariates in the subsequent main analysis examining the associations between average sleep characteristics and cumulative exposure to cortisol.

Further, we regressed HCC on average night-time sleep onset and duration. When the potential covariates were significantly related to HCC, we added them as covariates in the next model determining whether both sleep characteristics uniquely predicted HCC after controlling for the covariates.

To understand whether sleep characteristics on a given day contributed to the diurnal cortisol exposure the next day, correlation analyses between sleep characteristics on a given night and AUC_g on the following day were run including data from all the three saliva collection days. Each subject had three measures of AUC_g, and night-time sleep onset and duration. To assess whether sleep characteristics on a given day predicted diurnal cortisol exposure the next day beyond the influences of shared variance due to repeated measures, multilevel regression models clustered by participants were then performed using the software MPlus 7 (Muthén & Muthén, 1998–2012).

To examine whether diurnal cortisol exposure across a particular day predicted sleep characteristics the same night, correlation analyses between AUC_g on a given day and sleep characteristics on the same night were run by including data from the first two saliva collection days. To assess whether cortisol level on a given night predicted sleep characteristics the same night, correlation analyses between bedtime SCC and sleep characteristics on a given

night were run by including data from the first two saliva collection days. Each subject had two measures of AUC_g and bedtime SCC as well as measures of night-time sleep onset and duration. Thus, to examine whether diurnal cortisol exposure across a particular day and evening cortisol on a given night predicted sleep characteristics the same night beyond the influences of the shared variance due to repeated measures, multilevel regression models clustered by participants were again performed. Missing cortisol and sleep values were accounted for by the software using maximum likelihood estimations, and the models were saturated.

Day-to-day age at assessment and co-sleeping were considered as potential covariates and their relations with AUC_g, bedtime SCC and sleep characteristics were examined for each day. If any of the potential covariates were significantly associated with cortisol and sleep characteristics on a particular day, they were considered as covariates in the respective multilevel regression model.

3 | RESULTS

3.1 | Preliminary analyses

Income-to-needs ratio and household chaos significantly correlated with HCC and sleep characteristics. However, parent-reported daytime sleep duration and age at assessment were not significantly correlated with HCC. Independent samples t-tests revealed that co-sleeping and breastfeeding were not significantly related to HCC. Thus, only ITN and household chaos were considered as covariates in the multiple linear regression analysis examining whether average night-time sleep onset and duration each uniquely predicted HCC. Descriptive statistics and correlations between all the variables that were included in the multiple linear regression analysis are provided in Table 2.

For measures collected daily during saliva sampling and sleep assessment days, co-sleeping and age at specific assessment day were not significantly related to AUC_g and night-time sleep onset and duration on any of the days. Thus, they were not considered as covariates in the multilevel regression models assessing the relation between day-to-day sleep and cortisol.

3.2 | Average sleep and infant hair cortisol

As shown in Table 3, later average night-time sleep onset and shorter average night-time sleep duration were associated with greater infant HCC. To determine whether average night-time sleep onset and night-time sleep duration uniquely predicted HCC, we regressed HCC on both sleep characteristics. A linear regression model revealed that average night-time sleep onset uniquely predicted HCC above and beyond the effects of average night-time sleep duration (Table 3).

In the next model, we added ITN and household chaos as covariates. The linear regression analysis with HCC regressed on average night-time sleep onset, average night-time sleep duration, ITN and household chaos revealed that average night-time sleep onset predicted HCC above and beyond average night-time sleep duration even after controlling for ITN and household chaos (Table 3). Thus, infants who went to bed later at night had higher exposure to chronic physiological stress irrespective of how long they slept, their family ITN and the level of chaos at home.

TABLE 3 Linear regression models predicting hair cortisol concentration

	HCC		
		Model 2	
Variable	Model 1 *B*	*B*	95% CI
Constant	−3.380	−1.748	−9.228, 5.733
Average night-time sleep onset	0.364*	0.318*	0.072, 0.562
Average night-time sleep duration	−0.001	−0.002	−0.007, 0.003
Income-to-needs ratio		−0.043	−0.144, 0.57
Household chaos		−0.03	−0.524, 0.464
*R*2	0.235	0.228	
F	11.551***	4.959**	
Changed *R*2		0.007	
Changed *F*		6.592	

Note: In model 1, hair cortisol concentration (HCC) was regressed on average night-time sleep onset and average night-time sleep duration. In model 2, HCC was regressed on average night-time sleep onset, average night-time sleep duration, income-to-needs ratio and household chaos. CI, confidence interval.

*$p < .01$.; **$p < .001$

3.3 | Day-to-day sleep and salivary cortisol

To examine time-based relations between sleep and cortisol, only measures collected on a daily basis were included in the model, such as daily actigraphy and cortisol measures (i.e., AUC_g and bedtime SCC).

3.3.1 | Sleep predicting cortisol

Initial correlation analyses without accounting for repeated measures of cortisol and sleep revealed that later sleep onset, $r(190) = .18$, $p = .016$, and shorter sleep duration, $r(190) = -.19$, $p = .011$, on a given night were associated with higher AUC_g the next day. To account for repeated measures of sleep and cortisol, further multilevel regression analyses clustered by participants were conducted. First AUC_g on a given day was regressed onto sleep onset the night before, clustered by subjects. Then AUC_g on a given day was regressed onto sleep duration the night before, clustered by subjects. Both

these models yielded non-significant associations, indicating that sleep onset and sleep duration on a given night did not significantly predict the level of AUC_g in infants the next day. Although initial analyses revealed that later sleep onset and shorter sleep duration on a given night were associated with higher AUC_g, once we corrected for repeated measures of sleep and cortisol data, the associations were no longer statistically significant.

3.3.2 | Cortisol predicting sleep

Initial correlation analyses without accounting for repeated measures of cortisol and sleep revealed that greater AUC_g on a given day was associated with shorter night-time sleep duration, $r(128) = -.23$, $p = .010$, but not later sleep onset the same night. Higher bedtime SCC on a given night was associated with later sleep onset, $r(139) = .22$, $p = .010$, but not shorter sleep duration on the same night.

Further multilevel regression analysis, regressing sleep duration on a given night onto AUC_g the same day clustered by participants, was performed. The model revealed that greater AUC_g on a given day predicted shorter night-time sleep duration the same night after accounting for repeated measures of AUC_g and sleep duration (Table 4). Thus, there was a temporal relation between sleep and cortisol levels, such that infants who had greater exposure to cortisol across a particular day tended to sleep for a shorter duration the same night.

Further multilevel regression analysis, regressing sleep onset on a given night onto bedtime SCC the same night clustered by participants, was performed. The model revealed that higher bedtime cortisol on a given night predicted later sleep onset the same night after accounting for repeated measures of bedtime SCC (Table 5). Thus, there was a temporal relation between sleep and cortisol levels, such that infants who had higher cortisol levels at bedtime tended to fall asleep later at night.

TABLE 4 Coefficients for the multilevel regression model predicting daily night-time sleep duration

Variable	β	*SE*	β/*SE*	*p*-value
Diurnal cortisol exposure across the day	−0.308	0.110	−2.787	.005

Note: β denotes standardized estimate. *SE*, standard error.

TABLE 5 Coefficients for the multilevel regression model predicting daily night-time sleep onset

Variable	β	*SE*	β/*SE*	*p*-value
Bedtime salivary cortisol concentration	0.26	0.107	2.43	.015

Note: β denotes standardized estimate. *SE*, standard error.

4 | DISCUSSION

We investigated the relation of night-time sleep onset and duration with HCC, an index of cumulative exposure to cortisol, in 12-month-old infants. Further, we explored time-based associations between night-time sleep and salivary cortisol. Specifically, we assessed whether night-time sleep onset and duration on a particular evening predicted diurnal cortisol exposure the next day and whether diurnal cortisol exposure on a particular day and evening salivary cortisol on a particular evening predicted night-time sleep onset and duration the same night. Overall, night-time sleep onset uniquely predicted HCC, suggesting that infants who generally fall asleep earlier at night have lower cumulative exposure to cortisol, regardless of how long they sleep through the night, their economic status and the level of chaos they experience in their homes. Temporally, total cortisol exposure across a given day significantly predicted duration of infant sleep for that night, such that infants who were exposed to greater amounts of cortisol across a particular day slept for a shorter duration that night. Also, salivary cortisol levels in the evening significantly predicted how late infants fell asleep that night, such that infants who had higher evening cortisol levels on a given night fell asleep later the same night. Findings suggest that the directionality of the relation between daily sleep and cortisol is that diurnal cortisol exposure across a given day and evening cortisol levels predict infant sleep the same night, but sleep characteristics over a night do not predict diurnal cortisol exposure in infants the next day.

Prior literature has reported an association between parent-reported infant night-time sleep duration and HCC in 12-month-old children (Flom et al., 2017). Our study bolsters this finding by replicating the results using a relatively objective measure of night-time sleep duration. It expands on previous literature by underscoring the importance of night-time sleep onset for cumulative exposure to cortisol. It is striking that sleep onset uniquely predicted cumulative exposure to cortisol above and beyond sleep duration, ITN and chaos at home. To our knowledge, ours is the first study to demonstrate this by using actigraphy-derived sleep measures. Sleep onset and duration were highly correlated with each other and moderately correlated with HCC in our sample. Thus, it was unlikely that both sleep characteristics would uniquely contribute to HCC due to the high overlapping variance between the sleep characteristics when predicting HCC. Only sleep onset accounted for unique variance, when both the sleep predictors were included in the same model. It seems that going to bed later at night increases the infants' likelihood of having a shorter sleep duration. However, either one of the sleep characteristics is telling of infants' cumulative exposure to cortisol. Although shorter night-time sleep duration could be a stressor in the form of sleep deprivation that contributes to elevated cumulative exposure to cortisol (McEwen, 2006), it is not indicative of infant's cumulative exposure to cortisol over and beyond the effects of sleep onset. Prior research linking sleep duration and cumulative exposure to cortisol might not have assessed how both

these highly intertwined sleep characteristics predicted cumulative exposure to cortisol. Our findings are congruent with prior literature linking other indices of cortisol and sleep onset (Gribbin et al., 2012; Stalder et al., 2013) and further establish that going to bed early for infants is also important to maintain a healthy level of cumulative exposure to biological stress. The current study underscores the value of setting an early bedtime for infants. From an intervention perspective, future studies should explore whether parenting interventions targeted to help infants fall sleep earlier in the night would buffer infants from having chronically heightened levels of cortisol. This could be especially effective for infants who are at risk of higher cumulative exposure to cortisol due to a variety of adversities such as chaotic home environments and poverty.

Another novel finding was that there were temporal associations between diurnal salivary cortisol and sleep characteristics, such that diurnal salivary cortisol predicted daily sleep characteristics in infants as young as 12 months old. First, increased diurnal cortisol exposure across a particular day predicted shorter night-time sleep duration that night. This finding is consistent with the previously mentioned theory that higher activation of the HPA axis disrupts the sleep–wake cycle by promoting wakefulness (Palagini et al., 2015). It is possible that elevated diurnal cortisol levels across the day promoted wakefulness in infants, contributing to shorter night-time sleep duration. Next, we found that lower evening cortisol predicted earlier sleep onset. This finding is congruent with what is known from the adult literature, that diurnal cortisol reaches its minimum level in the earliest phase of sleep (Born & Fehm, 1998; Van Cauter & Spiegel, 1997).

These results show that diurnal cortisol exposure and evening cortisol relate differentially to sleep characteristics that same night. Although diurnal cortisol exposure across a particular day predicted night-time sleep duration that same night, evening cortisol predicted sleep onset the same night. These findings illustrate that night-time sleep onset and duration represent different sleep processes. Although night-time sleep duration is a marker of sleep consolidation reflecting longer periods of night-time sleep, night-time sleep onset indexes sleep initiation, reflecting infants' control over their sleep–wake state.

It is possible that bedtime cortisol is more salient for facilitating night-time sleep onset than diurnal cortisol exposure because night-time sleep onset and production of evening cortisol are two physiologically connected processes. The early phase of night-time sleep is marked by inhibition of cortisol secretion and both these processes are mostly regulated by a common physiological structure, the suprachiasmatic nucleus of the hypothalamus, through different neural pathways (Blumberg, Gall, & Todd, 2014; Morris, Aeschbach, & Scheer, 2012; Saper, Lu, Chou, & Gooley, 2005). Thus, sleep onset could be contingent upon inhibition of evening cortisol secretion, making a drop in evening cortisol a salient antecedent to sleep onset.

Although evening cortisol may be salient for sleep onset, diurnal cortisol exposure could be more closely related to night-time sleep duration. A multitude of common environmental factors could link diurnal cortisol exposure and night-time sleep duration. For example, environmental stressors, such as unpredictable routines, chaotic home environment and lack of sensitive parenting, could have contributed to both increased diurnal cortisol exposure across a given day and shorter sleep duration that same night. Additionally, diurnal cortisol exposure and night-time sleep duration could be closely linked as both follow a diurnal rhythm and represent how an infant's circadian rhythm functions on a particular day and night. It is plausible that a disturbed circadian rhythm on a particular day would impact both exposure to cortisol across that day and how well sleep is consolidated that night.

In our study, night-time sleep onset and duration on a particular evening did not predict diurnal cortisol exposure the following day. Previous literature on toddlers and adults examining temporal associations between sleep and cortisol suggests that sleep onset and duration may lead to dysregulated diurnal cortisol the next day (Bostock & Steptoe, 2013; Gribbin et al., 2012). However, sleep onset delay and short sleep duration were externally manipulated in these studies. Although forced sleep onset delay and shortened sleep duration due to an early-morning work-shift may influence cortisol levels the next day, this may not be the case for our infants, who did not have induced sleep disruptions. Moreover, it is possible that the neural pathways through which the suprachiasmatic nucleus mediates the sleep–wake system and the HPA axis have not completely matured and synchronized at 12 months. Hence, sleep on a given night may not predict cortisol levels the next day at this age. Additionally, salivary AUC_g is a measure of diurnal cortisol exposure throughout the day. Also, however well the infants slept the night before, there may be a number of stressors throughout the day that added to the diurnal cortisol exposure that day.

Although prior literature has implicated a bidirectional association between sleep and cortisol, our findings on diurnal salivary cortisol and daily sleep characteristics suggest that diurnal cortisol is likely to be driving the association early in development. By 12 months, infants have consolidated night-time sleep and a diurnal circadian rhythm similar to that of adults. We speculate that the functioning of the sleep–wake system and the HPA axis begins to synchronize at this age. Limited literature on time-based relations between sleep and cortisol in toddlers (Gribbin et al., 2012) and adults (Van Cauter & Spiegel, 1997) suggests that dysregulation of one system leads to dysregulation of the other system, creating a vicious cycle. Our findings, however, suggest that diurnal cortisol is likely to be driving this cyclical relation early in development. Thus, factors that elevate diurnal cortisol exposure and evening cortisol in infants are unfavourable for their HPA axis functioning. Moreover, it can also adversely impact their sleep–wake system by contributing to poor sleep consolidation and delayed sleep onset. For infants who are at risk of poor sleep consolidation and late sleep onset, interventions (e.g., Fisher et al., 2007) could include parent training on how to eliminate potential stressors from the infants' environment – throughout the day and in the evening. Future studies should also explore whether interventions helping parents develop bedtime routines (e.g., Mindell, Kuhn, Lewin, Meltzer, & Sadeh, 2006) would calm the infants and lower their cortisol levels.

A few limitations must be noted. Infants' experiences throughout the day, such as increased evening activity level and routine disruptions, could impact daytime and evening cortisol levels (Doom et al., 2018; Kertes & Gunnar, 2004). Hence, it is not clear whether diurnal cortisol mediates the impact of daily experiences on sleep characteristics or whether daily experiences influence both diurnal cortisol and sleep characteristics. To answer this question, it is necessary to collect data on these infant experiences that are also variable day to day along with actigraphy and salivary cortisol data. The present study has shown a specific, directional temporal association between diurnal cortisol and sleep characteristics the same night. However, we cannot conclude causality from our findings.

In the day-to-day analyses of sleep and cortisol, although we examined age at assessment and co-sleeping as potential covariates, we did not collect day-to-day information on breastfeeding, which is known to be closely linked with cortisol. In the overall assessment of sleep and cortisol, information on maternal postpartum depression and history of colic was not collected. Maternal postpartum depression is linked to cortisol (see Hostinar & Gunnar, 2013) and history of colic is linked to both sleep and cortisol (e.g., White et al., 2000). Additionally, the association between sleep and cortisol could have differed by infant race. However, the current study did not have enough individuals representing each race to detect significant differences in cumulative exposure to cortisol by race. Follow-up studies should perform a thorough assessment of these environmental and demographic factors.

Although the current study established that, in general, sleep onset is linked to cumulative exposure to cortisol, future studies should recruit a large enough sample to allow for assessment of whether family stressors such as socioeconomic status and household chaos moderate the relation between sleep onset and cumulative exposure to cortisol. In addition, the only measures of sleep we assessed were sleep onset and duration. It is important for future studies to investigate how sleep quality relates to cumulative as well as diurnal indices of cortisol.

Additionally, to examine individual differences in sleep and cortisol we needed a representative infant sample and a high compliance rate. This presented a few limitations. First, when investigating temporal associations, it is ideal to collect data for 7–10 days to better capture the variability in cortisol levels and sleep characteristics. However, acquiring usable salivary cortisol and actigraphy data for so many days would require parents to be extremely dedicated and compliant, and could select for a certain group of parents who can meet such demands. To obtain a representative sample and maintain a high compliance rate, we minimized the data collection burden on families by having them collect data for only three nights and 3 days. Second, although actigraphy is an objective assessment of sleep, polysomnography is considered the gold standard of sleep assessment. During sleep, polysomnography records multiple physiological changes, whereas actigraphy only records motion. However, polysomnography requires complex equipment set-up in a laboratory, posing a barrier to collecting infant sleep data in naturalistic settings (Sadeh, 2015). Thus, we used actigraphy for its feasibility in training parents on accurately placing the actigraphs on their infants at home. Third, we used actigraphs to record only night-time sleep data. As our participants were 12-month-old infants, having infants wear actigraphs throughout the day when they were awake would have yielded low compliance rates. Hence, we did not have actigraphy data on daytime sleep.

In conclusion, this study demonstrates that, on a daily basis, infants' diurnal cortisol predicts sleep and average sleep onset predicts cumulative exposure to cortisol beyond the effects of sleep duration, ITN and chaos at home. Taking measures to maintain healthy cortisol levels throughout the day and in the evening and ensuring earlier sleep onset may, therefore, be important in reducing infants' chronic exposure to cortisol. This, in turn, will decrease infants' allostatic load, ultimately diminishing their risks of long-term health problems.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interests.

AUTHOR CONTRIBUTIONS

CTT: study design, conception, data collection, data analysis and interpretation, and drafting the manuscript. SS: data acquisition and processing, editing and intellectual contributions to the manuscript. ASJ: data acquisition and processing. JSM: data acquisition and methodology. ART: study design and conception, supervision of data analysis and interpretation, and guidance for drafting the manuscript.

DATA AVAILABILITY STATEMENT

The authors elect to not share data.

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How to cite this article: Tuladhar CT, Schwartz S, St. John AM, Meyer JS, Tarullo AR. Infant diurnal cortisol predicts sleep. *J Sleep Res*. 2021;00:e13357. https://doi.org/10.1111/jsr.13357