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S.I. :SLEEP IN AUTISM AND DEVELOPMENTAL DISORDERS

Sleep in Infants with Down Syndrome or Familial Likelihood of Autism in the First Year of Life

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Abstract

Sleep problems have been associated with atypical development, but there is limited understanding of when sleep problems arise and how they differ across clinical populations. We aimed to evaluate sleep characteristics of infants with Down syndrome (DS), higher familial likelihood of autism (HL) and lower familial likelihood of autism (LL) at 6 and 12 months of age. Participants were from two longitudinal, multi-site, studies. Sleep was estimated by parent report on the Brief Infant Sleep Questionnaire at 6 months (59 DS, 173 HL, 54 LL); 12 months (58 DS, 129 HL, 30 LL); and in a longitudinal subset at both 6 and 12 months (100 HL; 23 LL; 33 DS). At 6-months, DS parents reported less concern about infant sleep and less night wakefulness than LL parents; HL parents reported longer sleep onset latency (SOL). At 12 months DS parents reported less night sleep and more night wakefulness; HL parents reported less night sleep, more night wakefulness and longer SOL compared to LL. Night wakefulness increased significantly in the DS and HL groups from 6 to 12 months of age. A higher proportion of DS and HL infants decreased Night Sleep and increased Night Wakefulness compared with the LL group. A higher proportion of DS infants increased SOL compared with the LL group. Sleep alterations are present in the first year of life and may differ in DS and HL infants. The mechanisms behind these sleep alterations may be an important early intervention target.

Keywords Infant · Sleep · Autism · Down syndrome

Sleep is integral to human health and development. It is particularly salient in infancy, a period of dynamic growth and change in sleep patterns and architecture, and brain and behavior development (MacLean et al., 2015). Newborns spend most of each 24-h day asleep. The total amount of sleep declines steadily throughout childhood and consolidates to occur more at night, with decreasing night awakenings (Henderson, et al., 2011; Paruthi, 2016). Sleep in infancy is critical for cognitive and language development, and disturbances can impact performance on motor learning and memory tasks (Berger & Scher, 2017; Hernandez-Reif & Gungordu, 2022; Horger et al., 2023).

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Alterations in sleep and sleep development in infancy are associated with sleep problems later in childhood and can have significant, pervasive negative impacts on child health and well-being (Lam et al., 2003). Although sleep problems are common in children with neurodevelopmental disabilities, little is known about when parent concerns about sleep problems arise, what types of sleep characteristics parents note first, and whether the timing and type of parent-reported sleep problem differs across groups in the first year of life. Increased understanding of parent concerns and perceptions of early sleep characteristics has the potential to improve outcomes through targeted sleep education and intervention and could generate hypotheses for future mechanistic studies (Fauroux et al., 2024).

In Down syndrome (DS) increased rates of obstructive sleep apnea (OSA) are commonly observed by clinicians and researchers (Lee et al., 2018; Rosen et al., 2011). When screened at 6 months of age and treated for OSA if it is identified, infants with DS have improved neurocognitive and adaptive behavior outcomes (Fauroux et al., 2024). Less commonly recognized are problems with decreased sleep duration and sleep efficiency and increased sleep related movement disorders in DS compared with typical development (Esbensen & Schwichtenberg, 2016; Fernandez et al., 2017; Yau et al., 2019). In DS, sleep problems are associated with impaired daytime adaptive function, cognitive functioning, executive function, and compromised cardiovascular health (Chen et al., 2013; Horne et al., 2019; Joyce & Dimitriou, 2017; Nixon et al., 2016). Sleep difficulties in DS often persist throughout adolescence and adulthood (Fleming et al., 2021; Fucà, et al., 2021; Stores, 2019). Parents with a child with DS and sleep problems and clinicians who care for children with DS may have trouble identifying sleep problems and their impact on the child and family (Chawla et al., 2022). Parental observations and concerns about sleep are critical for early identification and treatment of sleep problems. Parent concerns about sleep in the first year of life, and the way in which these concerns map on to early sleep problems in DS have not yet been adequately described.

In autism spectrum disorder (autism; American Psychiatric Association, 2013), insomnia is highly prevalent, with parents reporting longer sleep onset latency, poor sleep maintenance, early morning wakings, and lower overall sleep duration (Estes et al., 2024; Johnson & Zarrinnegar, 2021; Richdale & Schreck, 2009). Over the course of childhood, these sleep problems tend to persist rather than resolve (Verhoeff et al., 2018). Very little is known about the onset and developmental progression of sleep disturbances in infants later diagnosed with autism, in part because autism is not typically diagnosed until an average age of 4 years in the US (Maenner et al., 2021). However, prospective studies of infant siblings of autistic children provide a strategy for studying the developmental characteristics of infants prior to autism diagnosis. This is because infants with a family history of autism have a higher likelihood of developing autism, with a recurrence rate of approximately 20 versus 2% in the general population (Ozonoff et al., 2024). MacDuffie et al., (2020) previously found increased parent-reported sleep onset latency at 6 and 12 months of age in infant siblings later diagnosed with autism. Another recent study using sleep diaries showed that from 0 to 6 months of age, infants later diagnosed with autism slept less than typically developing infants or those with mild, subclinical autism characteristics (Foster et al., 2023). A study of medical records also revealed that night wakings at 12 months were associated with a later autism diagnosis (Nguyen et al., 2018). The increased likelihood of autism in infant siblings is thought to be due to shared genetic variance within families. Consistent with the high heritability of autism, family history of autism is also associated with increased neuropsychiatric symptoms and learning difficulties, even in children who do not meet diagnostic criteria for Autism Spectrum Disorder (Messinger et al., 2013). The role of early emerging sleep alterations in the progression of neurodevelopmental disabilities and associated neuropsychiatric and learning difficulties is not yet established. Parental concerns about sleep in the first year of life can provide a window into early sleep problems and help identify the sleep characteristics that parents observe at this time.

The present study compares parent concerns and parent-reported sleep characteristics in infants with DS, infants with older autistic siblings (high familial likelihood of autism; HL) and infants with no family history of autism (lower familial likelihood of autism; LL). This sample is drawn from two ongoing, multisite, longitudinal cohorts. We evaluated group differences in parent-reported concern about their infant's sleep and sleep characteristics (night sleep, day sleep, night wakefulness, and sleep onset latency) at 6 and 12 months of age. Based on the literature, we expected HL and DS parents would report more concerns than the LL group. Since DS infants have increased rates of OSA, we predicted increased night wakings compared with the LL group. Due to reports of longer SOL in HL infants later diagnosed with autism, we predicted that SOL would be increased in the HL group compared with the LL group. We also investigated change in parent-reported sleep characteristics for the subset of participants who completed the study at both 6 and 12-months of age.

Methods

Participants

The current project draws from two Infant Brain Imaging Study (IBIS) network studies; the IBIS-Down

syndrome (IBIS-DS) study of early brain and behavioral development in infants with DS (DS group) and typical development (LL group) and the IBIS-Early Prediction (IBIS-EP) study of brain and behavioral predictors of autism in HL infants (HL group). IBIS-DS study consists of 4 clinical sites across the United States (University of Washington, University of North Carolina, Children's Hospital of Pennsylvania, and Washington University at St. Louis). The IBIS-EP study consists of 5 clinical sites across the US (University of Washington, University of North Carolina, Children's Hospital of Pennsylvania, Washington University at St. Louis, and University of Minnesota). These are on-going longitudinal studies in which later time points are not yet available. Study procedures for all sites were approved by Washington University in St. Louis single IRB (IBIS-DS and IBIS-EP) single IRB for multi-site research. Informed consent was obtained from each participant's parent or guardian.

Infants with DS were included if their parent reported full Trisomy 21 or translocation DS. Reports of translocation DS were confirmed to involve an unbalanced Robertsian translocation of chromosome 21 through medical records of genetic testing results. LL infants had an older sibling that screened negative via scores below the autism range on the Social Communication Questionnaire (Rutter et al., 2003) or the Modified Checklist for Autism in Toddlers—Revised edition (Robins et al., 2009) according to the child's age. LL infants had no family history of genetic or neurodevelopmental disorders in first- or second-degree relatives. LL infants were enrolled at 6-months of age. DS infants were enrolled from 6–12 months of age. This flexibility was required due to increased medical visits and interventions that occur at high rates in DS in the first year of life. Exclusion criteria for the DS and LL groups included (1) known genetic conditions or syndromes (other than DS); (2) significant medical conditions affecting growth, development, cognition or sensory impairments (in the DS group this was defined as only medical conditions unrelated to DS); (3) birth weight < 2500 g or gestational age < 34 weeks (DS infants) or < 36 weeks (LL infants), significant perinatal adversity, in-utero neurotoxin exposure or maternal gestational diabetes; (4) contraindication for MRI due to the brain imaging component of the study; (5) English not predominant home language; (6) family history of a first-degree relative with psychosis or bipolar disorder. The DS and EP studies were separate studies but were designed to facilitate later data harmonization. The gestational ages of the LL group and the HL group were the same, but the criteria for DS infants was broader to facilitate recruitment. Thus, the DS and LL groups had somewhat different exclusion criteria with regard to gestational age.

HL participants, enrolled at 6-months of age, were included if they had an older sibling who scored in the autism range on the Social Communication Questionnaire (Rutter et al., 2003) and met criteria for autism using the Autism Diagnostic Interview—Revised edition (Rutter et al., 2003). Exclusion criteria for the HL group included: (1) birth weight < 2000 g or gestational age < 36 weeks or significant perinatal adversity and/or exposure in utero to neurotoxins; (2) medical/neurological conditions affecting growth, development, or cognition (e.g., seizure disorder) or significant sensory impairments (e.g., vision or hearing loss); (3) known genetic conditions or syndromes; (4) twins; (5) first-degree relative with psychosis, schizophrenia, or bipolar disorder; (6) contraindication for MRI and; (7) predominant home language other than English.

The total sample consisted of 286 participants with completed sleep questionnaires at 6-months (173 HL; 54 LL; and 59 DS) and 217 participants with completed sleep questionnaires at 12-months (129 HL; 30 LL; 58 DS). 156 of the participants had data at both ages (100 HL; 23 LL; 33 DS). Participant demographics are shown in Table 1. The LL group differed in terms of maternal education and race, but due to the high proportion of non-responses to these questions it is difficult to interpret these differences. At 6 months, 12 parents (4 HL; 0 LL; 8 DS) reported concern about sleep apnea or sleep disordered breathing on a telephone screening interview. At 12 months, 4 parents (1 HL; 0 LL; 3 DS) reported concern about sleep apnea or sleep disordered breathing on a follow-up telephone interview. As part of the larger IBIS-DS and IBIS-EP studies, behavioral and developmental measures were collected at 6 and 12 months of age (see Estes, et al., 2015 for description of procedures). Questionnaires were completed in-person on paper or via the internet. The behavioral testing battery was administered by licensed clinicians or trained and reliable research staff

Table 1 Participant Characteristics by Group

Group	n 6 m (female)	Mean Age 6 m	n 12 m (female)	Mean Age 12 m	Cognitive[a] (6 m/12 m)	% Maternal Ed (some college or higher/high school/not provided)	% Non-White
DS	59 (32)	6.60	58(33)	12.77	82.24/71.45	82.1/4.8/13.1	27.3
HL	173 (86)	6.59	129(68)	12.67	105.49/97.43	89.6/6.0/4.5	22.6
LL	54 (23)	6.51	30(12)	12.67	107.35/101.35	68.9/1.6/29.5	49.2

[a]Developmental Quotient, Bayley Scales of Infant Development, Standard Score

when infants were 6 and 12 months of age with caregivers present. This included the Bayley Scales of Infant and Toddler Development- 4th edition (Bayley & Aylward, 2019), reported in Table 1. No diagnostic outcomes or longitudinal sleep data at 24 months of age were available because IBIS-DS and IBIS-EP studies are still in progress.

Measures

Sleep

The Brief Infant Sleep Questionnaire (BISQ; Sadeh, 2004) is a parent-report questionnaire on sleep in infants from birth to 29-months of age. The BISQ provides a validated measure of quantitative sleep characteristics and qualitative descriptions of the sleep environment. Norm-referenced scoring was not available for the version of the BISQ used in this study. This measure was collected concurrently with each age point in these longitudinal studies. We compared the scores of the LL group to the scores reported in the original BISQ (i.e., Sadeh, 2004) and found they did not differ significantly (data available by request to AE, JM). Parent concern about child sleep (Parent Concern) was categorized on a three-point scale as "Not at Problem at all", "A Small Problem" or "A Very Serious Problem". The duration in hours of Night Sleep, Day Sleep, Wakefulness (at night), Sleep Onset Latency (SOL) were used in this study. We categorized longitudinal participants as Increased, Same, or Decreased Day Sleep, Night Sleep, Night Wakefulness or SOL based on change in scores from 6 to 12 months of age.

Analysis Plan

Differences between diagnostic groups in parent-reported sleep concerns was explored via Fisher-exact test, which allows for an exact computation of the probability of observing the given distribution pattern from the hypergeometric distribution of all possible alternatives. Group differences in the primary BISQ outcome measures (day sleep hours, night sleep hours, night wakefulness hours, and sleep onset latency) were analyzed with a linear model with explicit contrasts for comparing the HL and DS groups with the LL group as the reference (lm command from the R stats package, R Core Team, 2024). Linear mixed-effects models (lmer command from R lme4 package, Bates et. al., 2015) were used to examine longitudinal change in BISQ outcome measures, with fixed effects for group and time and their interaction and a random intercept term for each participant. In the linear and mixed models results, unadjusted p-values are reported. We conducted the Benjamini–Hochberg procedure to adjust for multiple comparisons and indicate the parameters whose adjusted p-value fall above the 0.05 threshhold.

Results

Parental Concern About Sleep

Cross Sectional

At *6-months of age* there was an overall group difference in parent concern about child sleep (See Fig. 1; Parent Concern; Fisher Exact Test, $p = 0.006$). The proportion of 6-month Parent Concern scores by group was as follows: "not a problem at all" (DS 91.5%; HL 72.5%; LL 73.5%), "a small problem" (DS 8.5%; HL 25%; HL 24.5%), or "a very serious problem (DS 0%; HL 2.3%; LL 1.9%). We combined the "very serious problem" group with the "a small

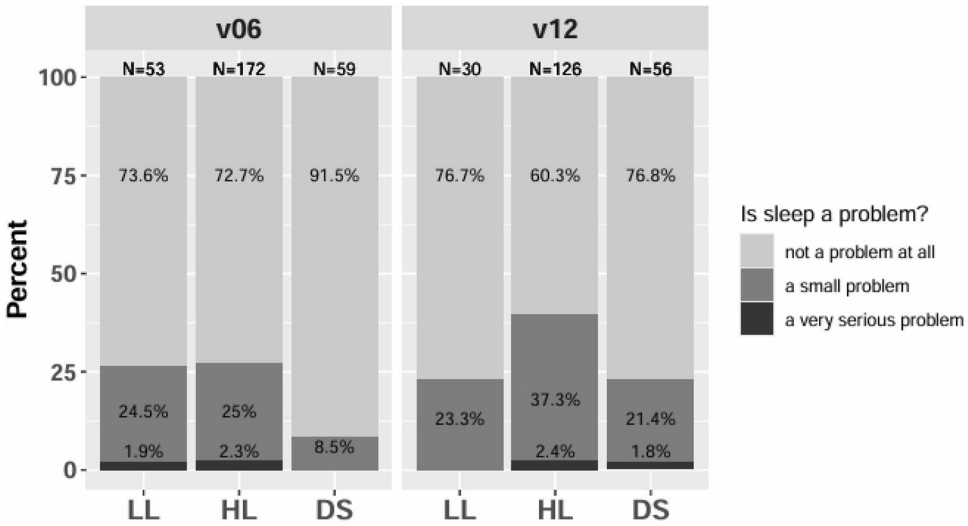

Fig. 1 Parent concern about infant sleep by group and age: Full sample

problem" group due to the small numbers in each. Pairwise comparisons using Fisher's exact tests revealed DS parents were less likely to report concerns at 6 months than LL (p = 0.021) and HL (p = 0.002). There was not a significant difference between the HL vs LL group (p = 1.0).

At *12-months of age* there was no overall group difference in parent concern about child sleep (See Fig. 1; Parent Concern; Fisher Exact Test; p = 0.051). The proportion of 12-month Parent Concern scores by group was as follows: "not a problem at all" (DS 76.8%; HL 60.3%; LL 76.7%), "a small problem" (DS 21.4%; HL 37.3%; LL 23.3%), or "a very serious problem (DS 1.8%; HL 2.4%; LL 0%). Pairwise comparisons revealed no significant differences between the DS and LL or HL and LL groups. The DS group parents reported fewer concerns than the HL group (Fisher's exact, p = 0.042).

Longitudinal

Of the LL with longitudinal data (n = 22) 86.4% reported no change in concern (no problem 68.2%, small/serious problem 18.2%), whereas 13.6% changed (no problem to small/serious problem 4.6%, small/serious problem to no problem, 9.1%). Of the HL with longitudinal data (n = 98) 69.4% reported no change in concern (no problem 51.0%, small/serious problem 18.4%), whereas 30.6% changed (no problem to small/serious problem 19.4%, small/serious problem to no problem,11.2%). Of the DS with longitudinal data (n = 33) 76.6% reported no change in concern (no problem 69.7%, small/serious problem 6.1%), whereas 24.3% changed (no problem to small/serious problem 18.2%, small/serious problem to no problem, 6.1%). The smaller n's with longitudinal data in the LL and DS groups, coupled with only about 25% of parents reporting problems, resulted in observed counts of less than five in the majority of the cells in the contingency tables for the LL and DS groups. Thus, statistical tests between groups were not performed.

Infant Sleep Characteristics

Cross Sectional

We examined mean differences between diagnostic groups using univariate linear models with the LL group set as the reference group (R Core Team, 2024, package: stats). These results are reported in Table 2. At 6-months, the DS group had significantly fewer hours of Night Wakefulness than the LL group (coeff = − 0.36, p = 0.019), 22 min less than the LL average of 44 min, coeff = 0.73). The HL group had longer SOL (8 min more, coeff = 0.14, p = 0.029) than the LL group (average 24 min, coeff = 0.4). No other sleep characteristics were significantly different. At 12-months, the DS group had fewer hours of Night Sleep (coeff = − 0.57, p = 0.038) and

Table 2 Sleep Characteristics by Group at 6 and 12 Months of Age: Cross sectional

Age 6 Months															
	Day Sleep hours				Night Sleep hours				Night Wakefulness				SOL h			
Predictors	*Coeff*	*SE*	*t*	*p*	*Coeff*	*SE*	*t*	*p*	*Coeff*	*SE*	*t*	*p*	*Coeff*	*SE*	*t*	*p*
Intercpt [LL]	3.54	0.21	16.73	< 0.001	10.22	0.20	50.88	< 0.001	0.73	0.11	6.68	< 0.001	0.40	0.05	7.42	< 0.001
grp [HL]	0.32	0.24	1.33	0.185	− 0.44	0.23	− 1.92	0.055	0.02	0.13	0.15	0.879	0.14	0.06	2.19	**0.029**[a]
grp [DS]	− 0.09	0.29	− 0.31	0.753	− 0.27	0.28	− 0.99	0.323	− 0.36	0.15	− 2.36	**0.019**	− 0.00	0.08	− 0.03	0.977
Obs	284				283				277				281			
R2 / R2 adj	0.014 / 0.007				0.013 / 0.006				0.035 / 0.028				0.028 / 0.021			
Age 12 Months																
Predictors	*Coeff*	*SE*	*t*	*p*	*Coeff*	*SE*	*t*	*p*	*Coeff*	*SE*	*t*	*p*	*Coeff*	*SE*	*t*	*p*
Intercpt [LL]	2.81	0.17	16.77	< 0.001	10.82	0.22	48.65	< 0.001	0.17	0.11	1.53	0.127	0.28	0.06	5.00	< 0.001
grp [HL]	− 0.07	0.19	− 0.40	0.687	− 0.58	0.25	− 2.35	**0.020**	0.26	0.12	2.07	**0.040**[a]	0.15	0.06	2.42	**0.016**
grp [DS]	0.04	0.21	0.19	0.849	− 0.57	0.27	− 2.08	**0.038**[a]	0.30	0.14	2.21	**0.028**[a]	0.12	0.07	1.81	0.072
Obs	217				217				209				216			
R2 / R2 adj	0.003 / -0.006				0.026 / 0.017				0.025 / 0.016				0.027 / 0.018			

[a]denotes parameters in which adjusted p-values are no longer significant (exceed 0.05) using the Benjamini–Hochberg procedure

more hours of Night Wakefulness (coeff = 0.30, p = 0.028) than the LL group. The HL group had fewer hours of Night Sleep (coeff = − 0.58, p = 0.02), more hours of Night Wakefulness (coeff = 0.26, p = 0.04), and longer SOL (coeff = 0.15, p = 0.016) than the LL group. No other sleep characteristics were significantly different.

Longitudinal

Mixed effects models examining change from 6 to 12 months show a similar pattern of results for Day sleep hours and SOL hours, in which the parents in the LL group reported less Day sleep hours (30 min less, coeff = − 0.54, see Table 3) and shorter SOL (10 min less, coeff = − 0.18) however these did not reach statistical significance. There were no significant HL or DS group effects or group by time interaction effects in Day sleep hours or SOL hours. In contrast, for Night sleep hours parents in the LL group report a significant increase of roughly 45 min (coeff = 0.74). Here again, the HL and DS groups did not differ significantly from the LL group suggesting that overall the HL and DS also report more Night sleep at 12 months. Finally, LL parents report a significant decrease in Night Wakefulness of roughly 50 min (coeff = − 0.84). The significant group by time interactions show that neither the HL nor the DS groups show a similar decrease as HL parents report an average decrease of only about 12 min (coeff = 0.63, that is 0.63 h more than average LL decrease of 50 min) and DS parents an average increase in Night Wakefulness of about 10 min (coeff = 1.02, that is 1.02 h more than the average LL decrease of 50 min.).

These results reflect group patterns in longitudinal change, but not all parents within these groups report these same patterns. As an illustration of the heterogeneity that exists within these groups we categorized the Night sleep hours and Night Wakefulness hours from 6 to 12 months with a simple framework of whether parents reported an increase, the same, or a decrease in Night sleep and Night Wakefulness time. This is illustrated in Fig. 2, where the vast majority of LL parents report an increase in Night sleep (78.3%) and decrease in Night Wakefulness (89.5%). In contrast, parents of HL and DS infants are less likely to report this typical developmental pattern over the 6 to 12-month time frame.

Discussion

This study found evidence of differences in parent concerns about sleep in infants with Down syndrome and infants with elevated likelihood of autism compared with infants at low likelihood of autism in the first year of life. DS parents had significantly lower overall levels of sleep concerns for their infant at 6 months of age compared with HL and LL parents

Table 3 Change in Sleep from 6 to 12 Months: Longitudinal subgroup

	Day Sleep h				Night Sleep h				Night Wakefulness				SOL h			
Predictors	*Coeff*	*SE*	*t*	*p*	*Coeff*	*SE*	*t*	*p*	*Coeff*	*SE*	*t*	*p*	*Coeff*	*SE*	*t*	*p*
(Intercept—[LL]	3.46	0.26	13.34	**< 0.001**	10.02	0.26	38.44	**< 0.001**	1.03	0.14	7.13	**< 0.001**	0.45	0.07	6.54	**< 0.001**
grp [HL]	0.26	0.29	0.90	0.368	− 0.11	0.29	− 0.37	0.711	− 0.40	0.16	− 2.50	**0.013**	0.06	0.08	0.76	0.445
grp [DS]	0.09	0.34	0.26	0.798	0.17	0.34	0.49	0.622	− 0.60	0.19	− 3.25	**0.001**	− 0.04	0.09	− 0.49	0.622
12mo—[LL]	− 0.54	0.28	− 1.95	0.052	0.74	0.30	2.51	**0.013**	− 0.84	0.18	− 4.55	**< 0.001**	− 0.16	0.09	− 1.82	0.070
grp [HL] × [12mo]	− 0.38	0.31	− 1.23	0.218	− 0.40	0.33	− 1.21	0.227	0.63	0.20	3.10	**0.002**	0.06	0.10	0.65	0.513
grp [DS] × [12mo]	− 0.16	0.36	− 0.45	0.654	− 0.64	0.39	− 1.65	0.100	1.02	0.23	4.36	**< 0.001**	0.20	0.11	1.77	0.077
Random Effects																
σ^2	0.88				1.01				0.35				0.08			
τ_{00}	0.67 $_{id}$				0.55 $_{id}$				0.11 $_{id}$				0.02 $_{id}$			
ICC	0.43				0.35				0.24				0.22			
N	156 $_{id}$				156 $_{id}$				156 $_{id}$				156 $_{id}$			
Observations	312				311				305				309			
Marginal R^2 / Conditional R^2	0.101 / 0.488				0.033 / 0.375				0.070 / 0.296				0.031 / 0.247			

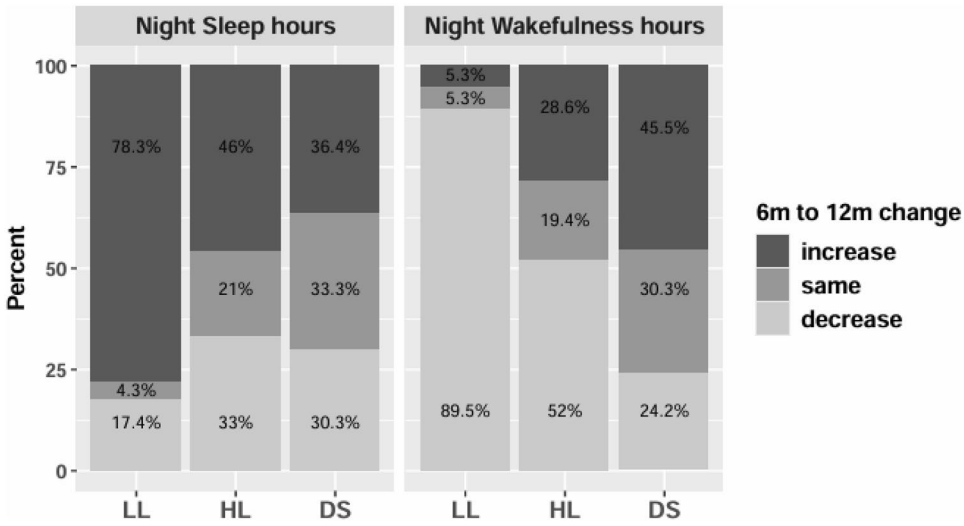

Fig. 2 Longitudinal change in sleep characteristics by group

Parent report of infant sleep characteristics were similar across groups at 6 months with the exception of longer HL SOL and less DS night wakefulness. At 12 months, the DS and HL groups had less night sleep and more night wakefulness than the LL group. The HL group continued to have longer SOL compared with the LL group. This suggests the need to better understand early parent sleep concerns and whether parent insights can help characterize disorder-specific sleep profiles that could be important targets for treatment and support.

It was unexpected that DS group parents reported less concern about their infant's sleep and less night wakefulness than LL parents at 6 months of age given previous reports of sleep disorders, particularly OSA, in children with DS. However, a recent study of parent experiences of having a child with DS and sleep problems suggests that parents and clinicians may tend to normalize or minimize sleep problems and their impact (Chawla et al., 2022). This study found that although sleep problems have a negative impact on parents and children, it is difficult for parents to identify sleep problems in children with DS. Parental understanding of sleep in children with DS may be made more difficult by experiences with healthcare providers who minimize or negate parent-reported child sleep problems in this population (Chawla et al., 2022). Recent evidence also demonstrates that 6-month OSA screening and treatment of infants with DS results in improved neurocognitive and adaptive functioning at 36 months of age and points to the importance of parental and clinician recognition of OSA in this population (Bull, 2011; Fauroux et al., 2024). In the first year of life, parental concern about sleep in DS may be overshadowed by other medical comorbidities such as heart conditions requiring surgery and gastrointestinal conditions (Hickey, et al., 2012). Parents may modify expectations for sleep milestones or attribute sleep challenges to external factors such as the developmental delays demonstrated by most infants with DS, reducing concerns about sleep problems in the first year of life (Harrison & Sofronof, 2002; Larkin, et al., 2020). Alternatively, it is possible that motor delays (Malak et al., 2015) may make it difficult for DS infants to wake their parents at night, reducing parental awareness of sleep issues. OSA is highly prevalent in DS, but in this sample, parent reported medical diagnosis of OSA was relatively low compared with a prospectively screened sample of DS infants at 6 months (Fauroux et al., 2024). It is possible that increased night wakings in the DS infants reflects OSA that has not yet been identified. OSA and other sleep problems might become evident to parents later in development in DS, emphasizing the role of medical providers in screening for OSA in infancy. This hypothesis is consistent with reports of increased severity and types of sleep problems in DS from toddler-age (under 4 years) to school age (Carter, et al, 2009). Notably, our findings of increased night awakenings and less night sleep at 12 months in the DS group are consistent with studies of young children with DS (up to 36 months of age) that report lower sleep duration (Yau, et al., 2019) and decreased sleep efficiency (Fernandez et al., 2017).

Increased sleep onset latency at 6 and 12 months in the HL group replicates previous findings (MacDuffie et al., 2020) in a new cohort and extends these findings by using a validated infant sleep measure (BISQ), rather than relying on a scale derived from an infant temperament measure. Sleep alterations occurring before the diagnostic features of ASD that have emerged sufficiently to allow for diagnosis could be related to later diagnosis or could be an endophenotype related to the common genetic background for autism. High familial likelihood infants are an important population to study because if sleep problems are increased in relatives, this may indicate a shared genetic liability that could shed light on the pathogenesis of both autism and sleep problems.

The HL group also has a household environment in common, which can contribute to sleep patterns. If the older autistic sibling has trouble sleeping, this may lead the younger sibling to have sleep problems due to noise or altered parental availability at bedtime. One way to begin sorting this out is through examining sleep in animal models of autism. Taking longer to fall asleep, now found in two cohorts of HL infants at 6 and 12 months of age, has also been reported in a Shank3 mouse model of autism (Ingiosi et al., 2019). Typically, it takes control mice less time to fall asleep after sleep loss, but this homeostatic response is absent in mice with the Shank3 mutation (Medina et al., 2022). This mechanism is a potential contributor to the sleep challenges so commonly observed in autism. Additionally, the HL group reported less night sleep and more night wakefulness at 12 months than the LL group. These findings of lower sleep duration in infancy are consistent with both animal studies of Shank3 mice (Medina et al., 2022) and human studies of HL infants who go on to develop autism (Foster et al., 2023). This is an example of how it may be possible to identify mechanisms for sleep alterations that can lead to innovations in sleep intervention. Novel interventions may help reduce the impact of sleep problems on brain and behavioral development in infants with or at elevated likelihood of neurodevelopmental disabilities.

This is the first study of which we are aware to report longitudinal changes in sleep in the first year of life in DS infants, and one of the few to do so in HL infants. In a longitudinal model, night wakefulness changed significantly from 6 to 12 months in both DS and HL infants. Night wakefulness is an interesting feature because going back to sleep quickly after waking up at night is potentially reliant on many of the same mechanisms as going to sleep in a timely way at bedtime (sleep onset latency). Thus, it is possible that problems with the sleep homeostat contributes to both the SOL and Night Wakefulness alterations observed in this study. A difference in the longitudinal pattern of sleep alterations reported in the DS versus HL groups is that longer SOL was initially reported at 6 months of age in the HL group but at 12 months in the DS group. Additionally, the DS parents had a later onset of concerns about sleep, significantly increasing between 6 and 12 months. It is unclear what mechanisms may underlie these parent reports, but this suggests there may be differences in early sleep development in DS vs HL infants. Future studies are needed to investigate whether infants who show signs of altered sleep patterns from 6 to 12 months of age represent a clinically relevant subgroup. Over half of the HL and DS group reported decreased night sleep at 12 months, compared with only a fifth of the LL group. Similarly, the HL and DS groups have a sizeable proportion of infants who had more night wakefulness and longer sleep onset latency at 12 months compared with the LL group. These longitudinal findings point to the importance of tracking early developmental changes in sleep characteristics, rather than relying on cross sectional snapshots of group differences in sleep characteristics. Sleep is tightly linked to brain and behavioral development, and understanding early sleep development has significant implications for improving outcomes for children with developmental disabilities (Girault & Piven, 2020; Piven et al., 2017).

The current study was limited by not having developmental outcome data at 24 months of age. Both the DS and HL groups have an increased likelihood of ASD. But until diagnostic outcome data is available, it will be unclear whether the current findings are due to a disorder-specific effect in which the infants who develop ASD have increased sleep problems (HL-ASD > HL-nonASD = LL), follow a familial pattern (HL-ASD = HL-nonASD > LL), or an endophenotypic pattern (HL-ASD > HL-nonASD > LL). The measurement of sleep in this project was limited to parent-report on a previously validated infant sleep questionnaire. Studies using objective sleep measures such as actigraphy or coded video are needed to shed additional light on sleep in the home environment. Sleeping EEG studies are also needed to understand developmental alterations in sleep architecture. Active (REM) and quiet (NREM) sleep may be drivers of group differences in sleep characteristics and could relate to later developmental changes associated with sleep architecture. Extending evidence based on parent-report to objective, in-home and lab-based sleep studies is needed to reveal issues that may be outside of parental awareness. Also notable is that the BISQ version used in this study is not compatible with a later version that yields norm-referenced scores. To mitigate this limitation, we compared the scores of the LL group to the scores reported in the original BISQ and found they did not differ significantly (Sadeh, 2004; data available by request to AE, JM). Nonetheless, our findings should be interpreted with caution, especially when comparing this study to studies using the newer version of the BISQ (Mindell, et al., 2019).

It is important to note that the families in this study were predominantly white, highly educated, and from English speaking communities in the US. There was geographic diversity in this multisite study that sampled from across the US. However, participating in the larger study required parents of infants who were willing to complete in-person testing batteries, multiple questionnaires, and infant brain imaging while asleep. The consecutive sampling approach used in this study was the only practical approach for recruiting these difficult to obtain participants. Although taking all eligible subjects reduces selection bias, this group was not randomly selected from the entire population, resulting in a larger proportion of higher resource families than the general population. Thus, these results should be interpreted as preliminary and needing replication and extension

in families with less formal education, minoritized communities, and non-English speaking countries. Parents with infants with sleep problems may be underrepresented in this study because participating in research can be more difficult for parents who are caring for children with increased sleep needs.

Future studies are needed to evaluate whether the differences observed in this study persist later in development and whether they predict later sleep problems and developmental outcomes. We are in the process of evaluating this cohort of HL and LL infants at 24 months of age including direct assessment of cognitive ability and diagnostic outcomes. This will allow us to see whether the early sleep alterations observed here are related to later autism diagnosis (in the case of the HL group), as previous studies have reported (MacDuffie et al., 2020; Nguyen et al., 2018), or other aspects of developmental functioning. We are also conducting in-home evaluation of sleep using subjective parent-report questionnaires and objective actimetry. Future research is needed to expand these findings using EEG to evaluate naturalistic sleep patterns and sleep architecture, which are not currently well understood in this population. Child sleep problems are known to have an effect on caregiver sleep. Future studies are needed to evaluate caregiver stress around sleep problems in children with DS or a family history of autism. The perspective of parents with a child with DS warrants further investigation to better understand the lower level of parent concern at 6 months. Longitudinal research will help determine whether sleep alterations in the first year of life in children with DS or family history of autism are associated with brain growth trajectories and later developmental and neuropsychiatric outcomes.

The current study provides a new window into parent concerns about sleep in DS and HL infants in the first year of life. Getting adequate, high-quality sleep in infancy is associated with improved health, attention, behavior, and learning throughout childhood (e.g., Berger & Sher, 2017; Hernandez-Reif & Gungordu, 2022; Lam et al., 2003). These are critical considerations for children with developmental disabilities such as DS and children with a higher likelihood of autism, both groups who are at a higher risk of developing sleep disorders. Parent reports of infant sleep in clinical populations are important because parents serve as advocates for their infants' healthcare and are the first-line reporters of infant sleep problems. Parent reports of early sleep characteristics suggest the need for future studies using objective sleep measures and studies aimed at understanding mechanisms. Variations in early developmental features of sleep may have longer term impact on development. There are now two studies showing an association between sleep alterations in the first year of life and later autism diagnosis (MacDuffie et al., 2020; Nguyen et al., 2018). If this association continues to be replicated, and is extended to DS, or if sleep in the first year of life is found to be associated with other developmental outcomes (e.g., cognitive and adaptive functioning, psychiatric symptoms), early sleep may be an important target for early intervention in DS and HL infants. Improving sleep in these infants could have important positive effects on quality of life for children and their caregivers.

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