NEW RESEARCH

JCSM
Journal of Clinical Sleep Medicine

http://dx.doi.org/10.5664/jcsm.3618

High Prevalence of Sleep Disorders and Associated Comorbidities in a Community Sample of Children with Down Syndrome

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SCIENTIFIC INVESTIGATIONS

Study Objectives: Down syndrome (DS) is a neurodevelopmental disorder characterized by multiple comorbidities. Sleep disorders are common among children with DS and can cause significant distress for families. However, research is limited describing sleep problems and correlates in large population-based samples. Accordingly, we aimed to describe sleep behavior among children with DS and its relationship with medical conditions in this population.

Methods: We conducted a population-based, cross-sectional study (2009-2011) of sleep disturbances in children and adolescents with DS 7 to 17 years of age (N = 107). We assessed sleep problems using caregiver report on two validated screening tools: the Childhood Sleep Habits Questionnaire (CSHQ) and the Pediatric Sleep Questionnaire (PSQ). The prevalence of sleep problems was compared in children with and without important comorbidities using modified Poisson regression with robust standard errors.

Results: 65% of children screened positive on the CSHQ for significant sleep problems in the past month, but their parents often did not report sleeping difficulties in their children. On the PSQ, 46% screened positive for sleep related breathing problems and 21% screened positive for sleep related movement disorders. Children with asthma, autism, and a history of enlarged adenoids and tonsils had more current sleep problems than children without these comorbidities.

Conclusions: Our findings suggest that sleep problems may be an important but under-recognized problem in children with DS. Sleep problems appear to be correlated with prevalent comorbidities, which may provide guidance to augment current practice guidelines to evaluate sleep problems in this population.

Keywords: Down syndrome, sleep disorders, sleep apnea syndromes, pediatrics

Citation: Hoffmire CA; Magyar CI; Connolly HV; Fernandez ID; van Wijngaarden E. High prevalence of sleep disorders and associated comorbidities in a community sample of children with down syndrome. *J Clin Sleep Med* 2014;10(4):411-419.

Every year, approximately 5,400 infants are born with Down syndrome (DS) in the United States, making it one of the most common birth defects and the leading genetic cause of intellectual disability in the country.[1] Multiple comorbidities can compromise quality of life for individuals with DS. Prevalent conditions in children with DS include dysmorphic features of the head and neck, congenital heart defects, gastrointestinal defects, celiac disease, seizures, hematologic disorders, thyroid disease, intellectual disability, emotional and behavioral disorders (EBD), and autism.[2-4]

Sleep problems are also a considerable concern in children with DS. Sleep patterns, also referred to as sleep architecture, have been shown to differ between children with and without DS beginning in infancy and continue throughout childhood, adolescence, and early adulthood.[5] For example, most studies show that individuals with DS experience considerable abnormalities in the REM sleep phase, including a decreased percentage of time spent in REM, a decrease in REM activity, and an increase in time to initiation of REM sleep.[6-9] Individuals with DS have also been shown to experience greater sleep fragmentation, night wakings, and undifferentiated sleep, as well as lower sleep efficiency (% of time in bed spent asleep) than typically developing individuals.[6-8,10,11]

BRIEF SUMMARY

Current Knowledge/Study Rationale: Children with Down syndrome are believed to experience significant sleep problems, especially obstructive sleep apnea syndrome. Further research is needed, however, to examine a broader range of sleep problems in population-based samples of children with DS and to determine if sleep problems vary by the pattern of comorbidities a child with DS experiences.

Study Impact: This study suggests that sleep problems beyond obstructive sleep apnea, such as behavioral and sleep related movement problems greatly impact children with DS. Optimal physician monitoring of individuals with DS could benefit from more comprehensive evaluations of sleep in this population across childhood and adolescence

Less is known regarding how these observed differences in sleep structure translate to notable sleep problems and/or clinically relevant sleep disorders in children with DS. Obstructive sleep apnea syndrome (OSAS) has been shown to be considerably more prevalent among children with DS than in the general pediatric population.[12-15] Prevalence estimates for OSAS in children with DS range from 24% to 79% in population-based samples and up to 97% in children referred to a sleep clinic with a history of snoring.[16-20] There is a relative paucity of research addressing other problematic sleep behaviors in this population,

and non-standardized measures of childhood sleep problems and disorders in previous research hinder the comparison and summary of the limited findings to date. Nevertheless, a small number of studies do suggest that bedtime resistance, restless sleep, nocturnal enuresis, nighttime awakenings, sleep talking, and daytime sleepiness may all be common in children with DS, warranting future research to confirm and expand upon these findings.[13-15,21] These findings suggest that current practice guidelines,[2] which focus on OSAS, may not fully inform optimal physician monitoring and assessment activities to evaluate sleep problems within the DS population.

The literature on pediatric sleep disturbances in the general population indicates that sleep problems, even when transient, are not benign. There appears to be a complex, bidirectional relationship between pediatric sleep disturbances and health: sleep problems have been associated with obesity and cardiovascular disease, epilepsy, autism spectrum disorders, attention deficit hyperactivity disorder, mood and anxiety disorders, and a wide range of neurocognitive problems.[22-30] The relationship between OSAS and cognitive and behavioral problems has been particularly well documented.[29] Understanding health concerns related to sleep becomes even more pertinent among children and adolescents with certain medical, psychiatric, and developmental disorders, such as DS. These special populations have preexisting medical, cognitive, emotional, and behavioral deficits, and may therefore suffer more profound impacts from sleep disturbances. For example, children with DS exhibit greater cardiovascular compromise than typically developing children following an obstructive respiratory event during sleep, and it has therefore been hypothesized that OSAS in this population may be more strongly related to cardiovascular complications such as pulmonary hypertension.[31] Furthermore, prevalent comorbidities among children with DS (seizures, obesity, enlarged adenoids and tonsils, and autism), which are associated with sleep disturbances in otherwise healthy children, may alter the pattern of sleep problems within the DS population and/or result in more severe sleep problems.[32]

Despite the potential impact of sleep problems on the well-being of children with DS, research describing sleep disturbances in large population-based samples of children with DS is lacking. Furthermore, very few studies have investigated the degree to which the variability of sleep problems in these children is related to specific comorbidities. Such information may help practitioners identify children with DS whose pattern of comorbidities suggest that they have a higher likelihood of experiencing sleep problems and can guide more thorough assessment protocols. Accordingly, this study aimed to address these important research gaps in a large population-based sample of children with DS, 7 to 17 years of age, by describing the prevalence and types of sleep disturbances encountered and examining the relationships between common comorbidities and sleep disturbances.

METHODS

Sampling Frame and Recruitment Methods

We conducted a cross-sectional survey from 2009 to 2011, drawing our sample from responders to a previous population-based, cross-sectional study conducted through the University of Rochester between 2006 and 2008 to investigate medical and behavioral characteristics in children with DS. The original study identified children with DS 3 to 13 years of age living in New York State outside of New York City through the New York State Congenital Malformations Registry (NYCMR) to estimate the prevalence of Autism Spectrum Disorders in children with DS. A total of 1,453 children were identified from the NYCMR, and 457 (31.5%) families participated in this study and completed multiple autism screening questionnaires. During a second level of assessment, parents of 217 children completed the Autism Diagnostic Interview-Revised (ADI-R)[33] via a telephone interview.

Sleep disorders and potentially relevant covariates were not fully examined in the previous study; therefore, participants were re-contacted for the current study. The sampling frame included the 217 participants who completed the ADI-R to ensure the availability of information on autism comorbidity for the current study. Participants who completed the ADI-R included a subsample of study participants screening both negative and positive on initial autism screening tools; 42% of children screened positive for autism on the ADI-R.

At the time of initiation of this study, participant ages ranged from 7 to 18 years. Between 2 and 4 years had passed since the last known study contact with these participants, and an average of 3.2 years elapsed from the time of ADI-R completion to this study's questionnaire completion. Among the 217 participants, we aimed to recruit parents of all subjects < 18 years of age who agreed to be contacted regarding future studies (N = 146). Two of the children were 18 at the time they were contacted for the current study and were therefore not eligible for inclusion. After contacting the families of 144 eligible children, surveys were returned from 116 (80.6% of eligible and 53% of the original sampling frame). Complete data for all variables of interest were available for 107 subjects. Thus, 49% of participants who completed the ADI-R assessment in the original study were included in this analysis.

Recruitment materials were designed to present a study evaluating a broad array of medical and behavioral comorbidities in children with DS and did not highlight sleep disturbances or autism in particular. This was done to minimize the likelihood that parents of children with DS and sleep difficulties or comorbid autism were more likely to participate than parents of children with DS without these additional problems. This study was approved by the University of Rochester Institutional Research Subjects Review Board.

Measurement of Sleep Behaviors and Disturbances

Two validated and widely used questionnaires, the Childhood Sleep Habits Questionnaire (CSHQ)[34] and the Pediatric Sleep Questionnaire (PSQ)[35-37] were chosen for this study to enable clear interpretation of findings within the broader context of past and future pediatric sleep research. The CSHQ was developed for use with school-aged children 4 to 10 years of age; it is a parent-report screening survey which addresses sleep problems based on symptoms used to assess sleep disorders according to the second edition of the International Classification of Sleep Disorders (ICSD-2).[34] Thirty-three of the questions on the CSHQ are combined to generate a "Total Sleep Disturbance Scale." The total scale is made up

of 8 subscales: (1) Bedtime Resistance, (2) Sleep Onset Delay, (3) Sleep Duration, (4) Sleep Anxiety, (5) Night Wakings, (6) Parasomnias, (7) Sleep Disordered Breathing, and (8) Daytime Sleepiness. The CSHQ total score has been shown to have good reliability and validity in general pediatric populations,[34] and the CSHQ has been successfully applied, but not specifically validated, in special pediatric populations relevant to the current study.[13,15] Although 3 questions on the sleep disordered breathing subscale and one additional CSHQ question regarding restlessness during sleep aim to address more physiological sleep problems, the CSHQ is primarily focused on symptoms relating to behavioral insomnia of childhood; parasomnias such as sleep walking, sleep talking, night terrors, and nightmares; and daytime sleepiness. A CSHQ total score > 41 has been shown to reliably identify children with clinically meaningful sleep problems.[34]

The PSQ is also a standardized parent-report questionnaire used to assess childhood sleep disorder symptoms. Two PSQ subscales were used: sleep related breathing disorders (SRBD),[35,37] and periodic limb movement syndrome/restless legs syndrome (PLMS/RLS).[36] These scales have been validated in children 2-18 years of age without severe medical or mental impairments. For both scales, a score > 0.33 has been shown to reliably identify children with these specific sleep problems.

Finally, parents were asked directly if they felt their child had trouble sleeping and if their child had ever been diagnosed with specific sleep disorders. Because there are no validated cutoffs for clinically meaningful sleep problems using the CSHQ subscales, the CSHQ total score was used as an indicator of behavioral sleep problems in this study and the PSQ was used to address the more physiologic sleep problems of PLMS/RLS and OSAS.

Assessment of Comorbidities

Comorbidities of interest were assessed in a questionnaire which asked parents to report on their child's medical and psychiatric history by answering whether their child had ever been diagnosed and/or received treatment for a given health condition. Health conditions of interest due to their suspected or known relationships with sleep included cardiovascular disease (congenital heart disease, systemic hypertension, pulmonary hypertension), overweight and obesity, seizures, autism, asthma and reactive airway disease, vision problems, thyroid disease, celiac disease, and adenotonsillar hypertrophy.[22-26] Obesity and overweight were assessed using the body mass index (BMI) based on parental report of their child's last measured height and weight. BMI was compared to the gender-specific Centers for Disease Control (CDC) BMI-for-age growth charts to obtain a percentile ranking.[38] We categorized BMI percentiles based on the CDC-recommended cutoffs. A BMI percentile between the 85th and 95th percentile is considered overweight and ≥ 95th percentile is considered obese.[38] Autism comorbidity was determined using the ADI-R assessment conducted in the original NYS study. The ADI-R is a clinical diagnostic measure for autistic disorder that can be used in children and adults with a mental age > 2 years.[39] The ADI-R was administered to a parent or caretaker over the telephone by a trained clinical interviewer. The ADI-R can be scored with 2 algorithms, diagnostic and current. The diagnostic algorithm, which is based on developmental history,[39] was chosen for 2 reasons. First, it was not feasible to re-administer the ADI-R for the current study, and the current algorithm from 2-4 years ago may not have been an accurate assessment of autistic symptoms the time of this study. Second, current behavior may reflect improvements due to treatment or aging alone and therefore may result in a higher false negative rate and/or may capture fewer children with less severe symptoms.

Assessment of Demographic Characteristics

Age, gender, race, parental education level, parental occupation, and medication usage were considered as covariates because these variables may be associated with pediatric sleep problems.[40-44] Parental education and occupation were included as indicators of socioeconomic status. All demographic variables were collected via parental report. The age groups chosen (7-11 years, 12-17 years) correspond to a split between childhood and adolescence, as sleep problems can vary considerably during these time periods.[40] Primary medications of interest included antidepressants, antipsychotics, antihypertensive agents, antiepileptic drugs, hypnotics, and melatonin as these have been shown to negatively affect sleep and/or are used to treat sleep disturbances.[44] On the medical history questionnaire, parents were asked to list all medications (prescription and over-the-counter) that their child took on a regular basis (≥ 3 days/week) at the time of the survey. An exhaustive list of all current medication from both questionnaires was compiled and reviewed to determine and classify known sleep effects of each medication: (1) a primary sleep effect (sleep aid, etc.) or significant sleep side effect (promoting or disrupting), or (2) no/minimal sleep effects.

Statistical Analysis

Univariate analyses described the study respondents in terms of the frequency of parental-reported demographic factors, medical conditions, and autism comorbidity. Bivariate analyses were conducted to identify demographic covariates that had the potential to affect (or "confound") the relationship between sleep and our medical comorbidities of interest. Covariates found to be associated with one or more of the sleep problem scales (χ^2 p-value ≤ 0.10) were included in multivariable analyses.

To describe sleep behaviors and disturbances in this sample based on CSHQ and PSQ findings, the prevalence of total sleep problems (i.e., CHSQ score > 41), sleep related breathing disorders and PLMS/RLS (i.e., PSQ domain-specific scores > 0.33) was computed for all children with DS and among demographically defined subgroups. To evaluate the relationships between sleep and medical comorbidities, the prevalence of overall and specific sleep problems was compared between children with and without parentally reported medical conditions and autism. Crude and adjusted prevalence ratios and 95% confidence intervals were computed. Prevalence ratios for rare medical or behavioral conditions (n < 10: cancer, systemic hypertension, pulmonary hypertension) could not be accurately estimated and are therefore not reported. Prevalence ratios adjusted for covariates significantly associated with CSHQ and PSQ scores in bivariate analyses were computed using modified Poisson

Table 1—Relationships between demographic characteristics, medication usage, and current sleep problems in children with Down syndrome

		CSHQ		PSQ SRBD		PSQ PLMD/RLS	
Covariate	N	Total Sleep Problem Prevalence (%)	Prevalence Ratio (95% CI)	Sleep Problem Prevalence (%)	Prevalence Ratio (95% CI)	Sleep Problem Prevalence (%)	Prevalence Ratio (95% CI)
Total	107	65	–	46	–	21	–
Age							
7-11 years	55	60		40		16	
12-17 years	52	71	1.2 (0.9, 1.6)	52	1.3 (0.9, 2.0)	27	1.6 (0.8, 3.5)
Gender							
Female	50	50		34		12	
Male	57	79	1.6 (1.2, 2.1)*	56	1.7 (1.1, 2.6)*	30	2.5 (1.1, 5.8)*
Race							
White	101	66		47		0	
Other	6	50	0.8 (0.3, 1.7)	33	0.7 (0.2, 2.3)	23	NA
Highest Parental Education Level							
< College Degree	18	78		50		33	
≥ College Degree	89	63	0.8 (0.6, 1.1)	45	0.9 (0.5, 1.5)	19	0.6 (0.3, 1.3)
Highest Parental Occupation Level							
Unemployed, semi-skilled, skilled workers	11	91		91		45	
Semi/minor professionals, small owners	53	72	0.8 (0.6, 1.0)*	45	0.5 (0.4, 0.7)*	23	0.5 (0.2, 1.1)*
Professionals, larger owners	43	51	0.6 (0.4, 0.8)*	35	0.4 (0.2, 0.6)*	14	0.3 (0.1, 0.8)*
Medication Sleep Effects							
None	30	58		39		19	
Any	77	83	1.4 (1.1, 1.8)*	63	1.6 (1.1, 2.4)*	27	1.4 (0.6, 2.9)*

CSHQ, Childhood Sleep Habits Questionnaire; PSQ, Pediatric Sleep Questionnaire; PLMD, periodic limb movement disorder; RLS, restless legs syndrome; CI, confidence interval. *p-values reported from χ^2 tests < 0.1.

regression with robust standard errors. Modified Poisson regression is less prone to overestimating prevalence or risk ratios than logistic regression when used for analysis of cross-sectional data with binary outcomes, especially when the outcome is common.[45]

RESULTS

Geographically, the sample was widely distributed throughout New York State (outside of New York City); participants represented 35 of the 55 counties in the sampling region. The sample was equally distributed between the younger (7-11 years) and older (12-17 years) age groups, and children were predominately of white race and had well-educated parents. Nearly 72% of children were regularly taking one or more medications known to affect sleep. Gender, parental occupation, and medication usage were found to be related to all sleep problems of interest (**Table 1**) and were therefore included as covariates in multivariable analyses. The most commonly reported medical comorbidities in this sample included congenital heart defects (66%), vision problems (68%), enlarged adenoids and/or tonsils (66%), and overweight and obesity (for a combined 54%). More than 85% of the children whose parents reported a history of enlarged adenoids and/or tonsils had undergone removal surgery.

Approximately 65% of children 7 to 17 years of age experienced clinically meaningful behavioral sleep problems within the past month, as defined by the CSHQ. Additionally, 46% screened positive for sleep related breathing problems and 21% screened positive for a sleep movement disorder on the PSQ. When asked directly, however, 66% of the parents of children classified by validated questionnaires as having sleep problems did not perceive that their child had trouble sleeping. Fewer parents reported their child had a diagnosed sleep disorder: 30% (n = 32) reported a diagnosis of OSAS, 2% (n = 2) reported a diagnosis of RLS, 2% reported a diagnosis of behavioral insomnia, 2% (n = 2) reported a diagnosis of sleep terrors, and 1% (n = 1) reported a diagnosis of sleepwalking.

Compared to the literature on sleep disturbances among typically developing children,[41,46-53] the prevalence of sleep problems in this sample does appear to be elevated (**Table 2**). In particular, while 65% of this sample screened positive on the CSHQ, only 23% of a sample of 469 elementary school children screened positive on the same questionnaire.[41] In addition to looking at the CSHQ total problem score, mean CSHQ domain scores for this sample were compared to those from a community sample of school-age children.[41] Significantly elevated problem scores were observed in this DS population for bedtime resistance, sleep duration, sleep anxiety, night

Table 2—Comparison of sleep problem prevalence reported by parents of children with DS to previous estimates for typically developing school-aged children

	Literature Review	Current Sample	
Sleep Problem	**Typically Developing Children[a]**	**Parentally Reported Diagnoses**	**Questionnaire Estimates**
Overall problem			
Parent Report of sleep problem symptoms or trouble sleeping	21% - 62%[46-49]	–	39%
Child Sleep Habits Questionnaire	23%[41]	–	65%
Behavioral Insomnia	15% 22%[49,53]	2%	–
Parasomnias	12% - 15%[49,50]	3%[2]	–
Movement Disorders			
Restless Legs Syndrome	15% - 18%[51]	2%	21%
Obstructive Sleep Apnea	1% - 10%[52]	30%	46%

[a]The literature review for typically developing children includes sleep problem prevalence estimates from parental questionnaires. Children in these studies ranges from 2-18 years, but most were limited to school-age children. [2]One parent reported their child had been diagnosed with sleepwalking, and two parents reported diagnosed sleep terrors.

Table 3—Crude and adjusted[a] sleep problem prevalence ratios for children with DS and multiple comorbidities

		CSHQ-Defined Overall Sleep Problem (n = 70)		PSQ-Defined Sleep-Related Breathing Problem (n = 49)		PSQ-Defined Sleep-Related Movement Problem (n = 23)	
Comorbidity	**n**	**Crude PR (95% CI)**	**Adjusted PR (95% CI)**	**Crude PR (95% CI)**	**Adjusted PR (95% CI)**	**Crude PR (95% CI)**	**Adjusted PR (95% CI)**
Congenital Heart Defect	71	0.9 (0.7, 1.1)	0.9 (0.7, 1.2)	0.8 (0.5, 1.2)	0.8 (0.6, 1.3)	1.0 (0.4, 2.0)	1.1 (0.5, 2.4)
Hearing Problem	47	1.1 (0.9, 1.5)	1.1 (0.9, 1.5)	1.2 (0.8, 1.8)	1.2 (0.8, 1.8)	0.8 (0.4, 1.7)	0.9 (0.4, 1.8)
Vision Problem	73	0.8 (0.6, 1.1)	0.9 (0.7, 1.1)	1.6 (0.9, 2.7)	1.7 (1.0, 2.7)	0.9 (0.4, 1.9)	0.9 (0.4, 2.0)
Enlarged Adenoids or Tonsils	71	1.4 (1.0, 1.9)	1.3 (0.9, 1.3)	2.0 (1.1, 3.5)	2.0 (1.1, 3.4)	1.8 (0.7, 4.5)	1.8 (0.7, 4.6)
Thyroid Disease	44	1.0 (0.7, 1.3)	0.9 (0.7, 1.2)	1.3 (0.8, 1.9)	1.3 (0.8, 1.9)	1.3 (0.6, 2.7)	1.4 (0.6, 3.1)
Celiac Disease	10	0.9 (0.5, 1.5)	0.8 (0.5, 1.3)	1.1 (0.6, 2.1)	1.0 (0.6, 1.7)	1.5 (0.5, 4.1)	1.3 (0.5, 3.1)
Seizure(s)	10	1.1 (0.7, 1.7)	1.1 (0.8, 1.5)	0.9 (0.4, 1.9)	0.9 (0.4, 1.9)	0.4 (0.1, 2.9)	0.4 (0.1, 2.3)
Dx or Tx for Asthma or RAD	38	1.3 (1.0, 1.7)	1.1 (0.9, 1.4)	1.9 (1.3, 2.8)	1.7(1.1, 2.5)	1.2 (0.6, 2.4)	0.9 (0.5, 1.9)
BMI							
Overweight	26	0.7 (0.5, 1.1)	0.8 (0.5, 1.2)	0.8 (0.4, 1.5)	1.0 (0.5, 1.7)	0.7 (0.2, 1.9)	0.8 (0.3, 2.4)
Obese	32	1.0 (0.8, 1.4)	1.1 (0.8, 1.4)	1.4 (0.9, 2.1)	1.6 (1.0, 2.4)	1.1 (0.5, 2.5)	1.1 (0.5, 2.4)
Autism (ADI-R Positive)	45	1.5 (1.1, 1.9)	1.3 (1.0, 1.7)	1.1 (0.7, 1.7)	0.9 (0.6, 1.3)	2.6 (1.2, 5.6)	2.1 (0.9, 4.7)

Prevalence ratios are computed using modified Poisson regression with robust standard errors. [a]Adjusted models include the comorbidity of interest, gender, parental occupation, and medication usage

waking, parasomnias, daytime sleepiness, and sleep disordered breathing. These results should be interpreted with caution, however; although evaluating and comparing mean CSHQ subscale scores does provide some additional information on specific sleep concerns, many of the subscales have very narrow ranges and thus are not truly continuous.

Table 3 presents observed prevalence ratios for the relationships between medical comorbidities and clinically meaningful sleep problems. In crude analyses, a history of enlarged adenoids or tonsils, asthma or reactive airway disease, and an ADI-R based autism diagnosis were related to overall behavioral sleep problems identified on the CSHQ. In addition, autism was related to PLMD/RLS, while enlarged adenoids and tonsils and asthma were related to SRBD. Specifically, children with a history of enlarged adenoids or tonsils were 1.4 times more likely to exhibit current CSHQ-defined behavioral sleep problems and twice as likely to screen positive for SRBD on the PSQ. These significant relationships were observed despite the fact that most children had already been treated with surgical adenotonsillectomy. Very similar findings were observed for a diagnosis of asthma or RAD in the crude analysis; children with DS and an ADI-R-based autism diagnosis were 1.5 times more likely to demonstrate overall sleep problems and 2.6 times more likely to screen positive for PLMD/RLS.

After adjusting for medication usage and demographic correlates, a history of enlarged adenoids or tonsils (PR = 2.0; CI = 1.1, 3.4) and asthma or reactive airway disease (PR = 1.7; CI = 1.1, 2.5) were independently related to SRBD, but not total sleep problems or PLMD/RLS. A model including both enlarged adenoids/tonsils and asthma/RAD did not meaningfully alter these findings (data not shown). Although the magnitude of the relationship between autism and sleep remained much higher for PLMD/RLS, after adjusting for demographic covariates and medication usage, autism comorbidity only remained independently and significantly related to CSHQ-defined, primarily behavioral, sleep problems (PR = 1.5; CI = 1.1, 1.9).

DISCUSSION

Both behavioral and physiologic sleep problems were common in this sample of children with DS. However, 66% of the parents of children classified by validated questionnaires as having sleep problems did not perceive that their child had trouble sleeping when asked directly, and even fewer reported diagnosed sleep disorders. Together these findings suggest that sleep problems may be an important, but under-recognized problem in this population by both parents and treating physicians. Furthermore, common comorbidities among children with DS including a history of enlarged adenoids or tonsils, a diagnosis of asthma or reactive airway disease, and an ADI-R-based autism diagnosis were found to be positively associated with one of more of the sleep domains evaluated.

The authors believe that these findings are of both clinical and public health significance. From a clinical practice standpoint, findings from this study should increase physician awareness regarding the importance of sleep problems among children with DS and encourage physicians to address these issues with their patients in an attempt to provide comprehensive care and improve health and quality of life. Similarly, but from a more public health standpoint, the findings from this study can help to support the supplementation and/or revision of existing health care guidelines for children with DS by providing a more comprehensive picture of the prevalence and nature of sleep problems in this population. Consideration of sleep disturbances other than obstructive sleep apnea may improve the clinical care of children with DS. Broader screening for both respiratory and non-respiratory sleep disturbances could be clinically useful in decreasing the impact of sleep disturbances on this population. However, this study was not designed to validate parental questionnaire responses with objective testing like polysomnography. Thus, because these scales have not been specifically validated in this special pediatric population, further research is warranted to determine their true utility for children with DS. Furthermore, consideration of correlates, such as autism and a history of enlarged adenoids and/or tonsils could help identify children who may benefit from more comprehensive screening, such as an overnight sleep study. Finally, close follow-up for children identified with sleep concerns appears to be an important component of clinical care for children with DS, as some treatments (such as adenotonsillectomy for obstructive sleep apnea) may not be curative.

Although this study is more comprehensive than previous research on sleep in children with DS, it is not the first to evaluate and identify the importance of sleep disturbances in this special pediatric population. The vast majority of previous sleep studies in children with DS focused on obstructive sleep apnea; however, and the findings presented here suggest that sleep problems in this population are not limited to OSAS. Behavioral and sleep related movement problems appear to be significant problems as well. Given the known abnormalities in sleep architecture among children with DS, this is not unexpected. For example, increased sleep fragmentation is often associated with OSAS, but can and has been shown in children with DS to be associated with sleep movements as well.[54] Furthermore, regardless of whether sleep fragmentation and night wakings originate from respiratory or movement events, they create the opportunity for behavioral problems related to both sleep initiation and maintenance.

Two previous studies that used the CSHQ to screen children with DS provide a basis of comparison for the findings presented here. Carter et al.[13] and Breslin et al.[15] reported CSHQ total scores for 40 children 4-18 years old and 35 children 7-18 years old, respectively. Compared to the estimated sleep problem prevalence of 65% presented here, 100% of Carter's sample, and 86% of Breslin's sample scored in the clinical range on the CSHQ. The higher prevalence observed in these two samples could be explained by a lack of statistical precision due to smaller sample sizes. The higher mean CSHQ score in Carter's sample could also be due, in part, to age differences, as Carter's study included children below 7 years of age though the percentage of children in this age range was not reported. Neither the current sample nor Breslin's included children between 4 and 7 years of age. Age differences in the mean CSHQ total score between the young (7-11) and old (12-17) age groups were not observed in this study, but CSHQ scores could be higher in children with DS under 7 years of age, perhaps considerably so because of their lower developmental age. The CSHQ total score is observed to be elevated among children in first and second grade (approximately 5-8 years) compared to those in third and fourth grade (approximately 6-11 years) in the general population,[41] and toddlers and preschoolers appear to score even higher.[55] Thus, the findings presented here are consistent with previous research on sleep in children with DS.

As discussed, current recommendations for the routine care and health supervision of children with DS only identify OSAS as a specific sleep concern.[2] Prior research using polysomnography as the gold standard suggests that OSAS is prevalent in 24% to 79% of children with DS.[16,19] Forty-five percent of this sample screened positive for sleep related breathing disorders, a midrange estimate compared to previous findings. Because snoring may not be as good a predictor of OSAS in children with DS as it is in the general pediatric population,[16] the PSQ, or any screening tool addressing observed breathing events, may result in lower than optimal sensitivity. Children with DS are affected by many other craniofacial abnormalities including mid-face hypoplasia and glossomegaly as well as adenotonsillar hypertrophy and truncal obesity, all of which increase the propensity for sleep related upper airway obstruction and therefore may affect sleep. Additionally, because of global hypotonia, children with DS may be at increased risk of sleep related airway closure, yet not generate sufficient airflow rates to result in palatal vibration necessary to produce the sound of snoring. Nonetheless, the PSQ was the best standardized instrument to assess OSAS in this sample for three reasons: (1) there is a validated cutoff for the SRBD subscale with good sensitivity (85%) and specificity (87%) to identify children in the general population at high risk for OSAS[28]; (2) it includes questions addressing important OSAS symptoms beyond observable breathing difficulties such as daytime sleepiness and daytime behavior; and (3) it is widely used in research to describe pediatric sleep problems and to assess treatments for OSAS facilitating comparisons across

studies. In the absence of polysomnography it is not possible to accurately ascertain the true prevalence of SRBD in this population. Such studies are sorely needed in the published literature.

The relationship observed between adenotonsillar hypertrophy and OSAS among children with DS has been previously documented in at least one study.[18] Of note, however, is the fact that most (87%) of the children screening positive for SRBD in this sample had their adenoids and/or tonsils removed, yet the observed association was still significant. This suggests that treatment for OSAS in the DS population is not entirely effective. Although important, this is not completely unexpected. Treatment studies have shown that even when improvements are made after surgical treatments in children with DS, many children will continue to suffer from clinically significant sleep disordered breathing.[56] The complicated craniofacial anatomy in this population, generalized muscular hypotonia and CNS suppression, higher rates of pharyngeal and lingual collapse compared to typically developing children, and the possibility for adenotonsillar regrowth are all factors which may limit treatment success in this population.[2,57-59] It is likely that symptoms improve and the severity of OSAS decreases with surgical treatment even in those who still experience problems, but these children may remain at risk for the cognitive, behavioral, and medical consequences of incompletely treated obstructive sleep apnea. Clearly, continued follow-up with a pediatric sleep specialist is very important for all children and adolescents with DS and OSAS.

Finally, sleep related movement disorders were identified in almost a quarter of this sample, with a two-fold increased prevalence of sleep related movement problems among children with autism comorbidity. Conversely, only 2% of parents reported a diagnosis of restless legs syndrome or periodic limb movement disorder for their children, indicating that such problems may be under-diagnosed in this population. However, although the sensitivity of the PSQ movement scale is quite good (79%), the specificity is not ideal (56%) and could therefore result in an increased false positive rate. This study is not the first to recognize the importance of sleep movement problems in DS. One polysomnographic study found that arousals and awakenings in children with DS were more often associated with sleep movements (45%) than with respiratory events (9%).[54]

As is true for most epidemiologic studies, this study is vulnerable to limitations, but it is balanced by much strength. It is the largest population-based study to date to investigate sleep in children with DS; it is one of the most comprehensive in terms of the sleep problems addressed; and it is the first to carefully evaluate the interrelationships between common comorbidities and sleep disturbances in children with DS. Furthermore, the population-based sampling frame improves the external validity of study findings considerably compared to DS sleep studies conducted within a clinical setting. Participants were drawn from across New York State and included children living in rural and metropolitan regions.

The authors recognize that all variables in this study are based on subjective parental or caregiver report, not objective measurement, and that the accuracy of parental report is likely to depend on many factors. For example, the types of questions being asked and the way they are asked (i.e., standardization of instruments), who is responding (mother vs. father), the child's age, and the seriousness of the event being recalled have been associated with accuracy of parental report for children's health variables.[60] Despite these limitations, parental report was chosen for multiple reasons. With a population of children and adolescents with DS, it would have been far less accurate, and often infeasible to solicit direct self-report. It was also infeasible to use objective sleep measures such as actigraphy or polysomnography due to cost, time, and geographic constraints inherent to the population-based design. Furthermore, although polysomnography is the diagnostic gold standard for sleep disorders, it may not provide the best information regarding usual sleep behaviors, as children are removed from their normal environment and are only observed for one or two nights. Additionally, although we relied on parental report, one of the strengths of this study compared to the existing literature was the use of standardized instruments to assess sleep (CSHQ, PSQ) as well as autism (ADI-R). The measures used have all been validated in their target populations, although much less information on validity is available for their use in children with DS specifically.

Finally, although this is the largest population-based study of sleep in children with DS to date, we were only able to recruit approximately 53% of the subjects in our sampling frame and included 49% in this analysis. This is not an unusually low success rate for mail-based survey studies,[61] but does increase the concern for non-response bias. Non-response may result in a non-representative sample, biasing findings and/or limiting external validity, particularly if responders and non-responders differ in regards to characteristics related to the study variables of interest.[62] Race, ethnicity, and parental education levels were found to be different in the sampling frame as compared to the New York State population of families of children with DS, with a higher percentage of whites, lower percentage of Hispanics, and a high percentage of parents with at least college education. In the current study, parental education levels appear to be even higher. Children living in families from lower socioeconomic strata have been shown to have later and more irregular bedtimes compared to their more socially advantaged peers.[63] Thus, the current study may underestimate the true prevalence of sleep problems among children with DS in New York State.

In summary, findings from this study suggest that sleep problems in children with DS go beyond obstructive sleep apnea, and such problems may be more common in children with certain comorbidities. Sleep problems are an important problem in children with DS; these children are burdened by many comorbidities, which can negatively affect health and quality of life both independently and through their relationships with sleep problems. Additionally, sleep problems are a significant source of distress for families.[64] Thus, these findings can help guide clinical practice aiming to improve the health and well-being for children and their families. Although future research is warranted prior to recommending specific screening schedules, increasing physician awareness of the breadth of sleep problems that affect this population and providing insight into which children with DS may be more likely to experience sleep concerns, such as those

with enlarged adenoids and tonsils or comorbid autism, is an important first step.

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SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication June, 2013
Submitted in final revised form December, 2013
Accepted for publication December, 2013

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DISCLOSURE STATEMENT

This was not an industry supported study. Financial Support was from the National Heart, Lung and Blood Institute Research Training Fellowship in Preventive Cardiology (grant # 5 T32 HL07937 – 9). The authors have indicated no financial conflicts of interest. All work for this study was conducted at the University of Rochester School of Medicine and Dentistry, Department of Public Health Sciences, Rochester, NY.