NEW RESEARCH

JCSM
Journal of Clinical Sleep Medicine

http://dx.doi.org/10.5664/jcsm.3368

Effect of Body Position and Sleep State on Obstructive Sleep Apnea Severity in Children with Down Syndrome

Lauren C. Nisbet, Ph.D.[1]; Nicole N. Phillips, M.D.[2]; Timothy F. Hoban, M.D., F.A.A.S.M.[3]; Louise M. O'Brien, Ph.D., M.S.[3,4]

[1]The Ritchie Centre, Monash Institute of Medical Research, Monash University, Melbourne, Victoria, Australia; [2]Comprehensive Sleep Network Inc., Seattle, WA; [3]Department of Neurology, University of Michigan Sleep Disorders Centre, Ann Arbor, MI; [4]Department of Oral and Maxillofacial Surgery, University of Michigan Sleep Disorders Center, Ann Arbor, MI

SCIENTIFIC INVESTIGATIONS

Study Objectives: To investigate the influence of sleep position and sleep state on obstructive sleep apnea (OSA) severity in in children with Down syndrome (DS).

Design: Retrospective review.

Setting: Sleep disorders laboratory of a tertiary medical center.

Participants: Children with Down syndrome and typically developing children matched for age, gender, apnea-hypopnea index (AHI), and year of polysomnogram.

Measurements and Results: Sleep variables from baseline polysomnography. Sensor-recorded position (supine, prone, lateral) was expressed as the percentage of total sleep time. The AHI was calculated in each sleep state (NREM, REM), position, and position-sleep state combination. Of 76 DS subjects (55% male) the median age and AHI were 4.6 years (range 0.2-17.8 years) and 7.4 events/h (range 0-133). In all subjects, AHI was higher in REM than NREM ($p < 0.05$); however, the NREM AHI was higher in DS subjects than controls ($p < 0.05$). Compared to controls, the percentage of prone sleep was greater in DS subjects ($p < 0.05$), but the percentage of supine or non-supine (prone plus lateral) sleep was no different. For DS subjects alone, NREM AHI was higher in supine than non-supine sleep ($p < 0.05$).

Conclusion: In DS and non-DS children alike, respiratory events are predominantly REM related. However, when matched for OSA severity, children with DS have a higher NREM AHI, which is worse in the supine position, perhaps indicating a positional effect compounded by underlying hypotonia inherent to DS. These findings illustrate the clinical importance of NREM respiratory events in the DS population and implications for treatment options.

Keywords: Down syndrome, sleep position

Citation: Nisbet LC; Phillips NN; Hoban TF; O'Brien LM. Effect of body position and sleep state on obstructive sleep apnea severity in children with Down syndrome. *J Clin Sleep Med* 2014;10(1):81-88.

Down syndrome (DS), or Trisomy 21, is the most common chromosomal disorder and is associated with multiple coexisting medical conditions affecting the cardiovascular, respiratory, neurological, gastrointestinal, and hormonal systems. One such disorder is obstructive sleep apnea (OSA), which has a reported prevalence of 45% to 79% in children with DS.[1-6] In striking contrast, OSA has a prevalence of 1% to 5% in the general pediatric population.[7,8] Several clinical characteristics present in DS heighten the risk of OSA and additional sleep disturbance, including hypotonia, overweight, an underdeveloped midface and narrow nasopharynx, occurring in conjunction with relative macroglossia as a function of a normal sized tongue within a small pharynx.[9,10] In addition, the pharynx is frequently crowded by both lymphoid hyperplasia and a more posterior location of the tongue, further compounded by a reduction in pharyngeal muscle tone.[9,10]

OSA is the more severe form of a spectrum of disorders known as sleep disordered breathing (SDB), the hallmark of which is snoring. OSA in children is characterized by frequent prolonged partial obstruction or intermittent complete collapse of the upper airway.[11] The pediatric ramifications of OSA are vast, including adverse cardiovascular outcomes such as elevated blood pressure,[12] autonomic dysfunction,[13,14] and neurocognitive and behavioral deficits.[15-19] The gold-standard method to diagnose OSA is overnight polysomnography (PSG), from which OSA severity is typically defined using the apnea-hypopnea index (AHI)—the total number of respiratory events per hour of sleep.[20]

It has long been known in adults that both body position during sleep and sleep state can affect OSA severity, such that AHI is typically reported to be higher in supine sleep,[21-28] and to a lesser extent, during REM sleep.[21] In fact, the respiratory disturbance index has been reported to be 40% to 50% lower when adult patients with OSA sleep in the lateral position

BRIEF SUMMARY

Current Knowledge/Study Rationale: It has long been known that body position and sleep state can affect OSA severity in adults although findings conflict in the pediatric literature. Although highly prevalent in children with Down syndrome, the effects of body position and sleep state on OSA severity have received little attention despite that consideration of both may impact interpretation of polysomnography and subsequent treatment modality.

Study Impact: When matched for severity of OSA, children with Down syndrome have worse OSA in NREM sleep compared to typically developing children. While the effect of sleep position on OSA severity was similar in both groups of children, those with Down syndrome had worse NREM OSA severity in the supine position. For the clinician, these findings highlight the importance of NREM sleep contribution to OSA severity in children with Down syndrome.

compared to supine position.[23,25,28,29] More recently, a significant effect of body position on OSA severity has emerged in pediatric studies, although findings are conflicting; some studies observed an improvement in OSA severity in the supine position[30]; others reported a worsening when supine[31,32]; and some found no positional difference.[33-35] Furthermore, the long-held conviction that pediatric OSA is a REM-related disorder[11,35,36] has also been challenged; while the majority of children do exhibit a higher AHI in REM sleep[37,38] a considerable minority of children (30% in one study),[38] were found to have predominantly NREM-related OSA.

Despite the astoundingly high prevalence of OSA in children with DS,[1-6] the effects of body position and sleep state on OSA severity in the DS population have received little attention. Knowing the effects of these factors on OSA severity is important, as previously the validity of a diagnosis or classification of OSA severity based on PSG has been questioned in those who had inadequate supine and/or REM sleep, as these factors may result in an underestimation of severity.[32] There are multiple reasons why the effects of body position and sleep state on OSA severity may be different in the DS population compared to patterns reported in typically developing children or adults with OSA. Positional effects may differ as a function of the etiology of OSA, considering the physical characteristics of DS (relative macroglossia, posterior tongue position, etc.); sleep state effects may also vary as a result of the generalized hypotonia commonly associated with DS and also due to alterations in sleep architecture, notably decreased amounts of REM sleep.[39] We therefore aimed to investigate the effects of body position and sleep state on OSA severity, as measured by AHI, in children with DS in comparison to typically developing children matched for age, gender, OSA severity (total AHI), and year of PSG. We hypothesized that, in general, the influence of position and sleep state on OSA severity would differ between DS and non-DS subjects. Specifically, we hypothesized that compared to controls, changes in position would have less effect on OSA severity in DS subjects, such that AHI in the non-supine position would be higher in DS subjects than controls. We also hypothesized that while overall OSA would still be predominantly REM related in DS subjects, it would be to a lesser extent compared to controls, such that the NREM AHI would be higher in DS subjects than in controls.

METHODS

Subjects and Study Protocol

Ethics approval for this retrospective case-control chart review was granted by the University of Michigan Health System Institutional Review Board. Subjects were children aged 0 to < 18 years, with or without SDB, who were referred to the University of Michigan Pediatric Sleep Disorders Clinic or Pediatric Multidisciplinary Behavioral Sleep Clinic for suspected SDB. All subjects subsequently underwent baseline polysomnography (PSG) between August 2008 and January 2013. Index cases were identified as children with a diagnosis of "Down Syndrome," "Down's Syndrome," or "Trisomy 21." Children with DS were excluded if their baseline PSG was conducted as a split-night PSG involving a period of continuous positive airway pressure (CPAP) titration. Cases were then matched for age, gender, AHI, and year of PSG with control subjects who did not have DS or other major medical conditions (including craniofacial abnormalities). Subjects with adenotonsillectomy (AT) or other upper airway surgery prior to baseline PSG were not excluded, as this is a common clinical SDB treatment pathway for children both with and without DS.

All subjects (cases and controls) underwent standard clinical overnight PSG using a commercially available PSG system. This included 6-channel electroencephalograms (F3-A2, F4-A1, C3-A2, C4-A1, O1-A2, O2-A1 of the 10-20 international system for electrode placement), electro-oculogram (right and left outer canthi), submental and bilateral anterior tibialis surface electromyograms, 3-lead electrocardiogram, thoracic and abdominal excursion (piezoelectric strain gauges), oronasal airflow (thermocouples and nasal pressure), and finger oximetry. As this was a retrospective study, body position during sleep was entirely up to the individual. Position was identified by a calibrated position sensor, located midline on the anterior aspect of the thoracic belt of each subject. Body posture during sleep was recorded as supine, prone, left lateral, and right lateral positions based on the truncal position as detected by the position sensor. Head and neck positions were not recorded.

Data Analysis

Demographic variables were reported alongside standard sleep and respiratory PSG parameters for each subject. Height and weight measured on the night of PSG were used to calculate body mass index (BMI) in subjects ≥ 2 years, which was converted to a BMI z-score according to age and gender.[40] Sleep staging was performed in 30-s epochs and followed standard criteria.[20] The percentage of total sleep time (TST) spent in each sleep state (NREM and REM) was calculated in each subject, along with the percentage of TST spent in each body position (supine, prone, right lateral, left lateral). Durations of sleep in the prone, right lateral, and left lateral positions were combined and termed non-supine sleep, and similarly expressed as a percentage of TST in each subject. Additionally, the percentages of TST spent in both supine and non-supine positions in NREM and REM sleep were calculated separately.

Respiratory events ≥ 2 respiratory cycles in duration were scored as obstructive apneas, hypopneas, RERAs, or central apneas according to pediatric criteria recommended by the American Academy of Sleep Medicine (AASM) in 2007.[20] Obstructive apnea was defined as cessation of thermocouple-derived airflow, or decrement > 90% from previous baseline, with continued chest and abdominal movement. Hypopnea was defined as a decrease in oronasal airflow, thoracic, or abdominal excursion ≥ 50% when followed by a decrease in oxyhemoglobin saturation ≥ 4% or an EEG arousal ≥ 3 seconds. The AASM-2007 apnea-hypopnea index was calculated as the number of apneas and hypopneas per hour of sleep, and the AASM-2007 respiratory disturbance index (RDI) was calculated similarly, with the addition of RERAs.[20] The mean oxygen saturation (SpO_2) during sleep was reported for each subject alongside the SpO_2 nadir. Sleep efficiency was calculated as the percentage of time asleep following lights out. The arousal index was calculated as the number of arousals per hour of TST, the periodic leg movement index (PLMI) as the number of periodic

leg movements per hour of TST, and the periodic leg movement with arousal index as the number of periodic leg movements per hour of TST that were associated with an arousal.

In addition to the total AHI, the AHI was calculated separately in NREM sleep, REM sleep, and again in each body position (supine, prone, right lateral, left lateral, collective non-supine). Finally, the AHI in supine and non-supine NREM and REM sleep was calculated. There exists no accepted description of positional sleep apnea in children; therefore, 2 methods were used to describe the effect of body position. Firstly, "positional patients" were defined as those in whom the AHI was at least twice as high in one body position as another. For example, "supine positional" meant that the AHI in the supine position was at least twice that of the non-supine position. This description is similar to that used previously in adults[23,41] and children,[33] although we used non-supine instead of lateral to incorporate the prone position. Secondly, positional patients were identified simply by the absolute numeric majority of AHI for either supine or non-supine sleep in each child.[33]

Medical records were reviewed, and the number of subjects who underwent a successful CPAP titration study following the baseline PSG were recorded. The difference in total AHI, NREM AHI, and REM AHI from baseline to titration was expressed as a percentage of the relevant baseline AHI.

Statistical Analysis

Statistical analysis was performed using SPSS (Version 20, IBM SPSS, Armonk, NY, USA). Data were first tested for normality and equal variance. Normality could not be achieved through log transformation; hence, demographic and sleep characteristics were compared between DS and control subjects using the Wilcoxon-signed rank test. The predominance of respiratory events in REM sleep (termed REM predominance index, REM PI) was calculated to reflect the ratio of REM to NREM events, using an adjustment factor (0.5) added to the AHI values to allow inclusion of zero values in analysis.[38] The equation used was REM PI = log(REM AHI + 0.5) – log(NREM AHI + 0.5), equivalent to log(REM AHI + 0.5 / NREM AHI + 0.5). The REM PI was subsequently compared with a value of 0 (no difference between REM and NREM AHI) using the Wilcoxon-signed rank test. Within DS subjects as a whole and again within control subjects, the Wilcoxon-signed rank test was used to compare the effects of sleep state (NREM, REM) on AHI, of body position (supine, non-supine) on total AHI, and of body position (supine, non-supine) on NREM AHI as well as REM AHI. As infancy and/or puberty may influence the effects of body position and/or sleep state on AHI, analyses were repeated in a subsample of subjects aged ≥ 2 years and < 13 years. The proportion of subjects in each of the DS and control groups with a REM PI < 0 was compared using χ^2 analysis, as were the proportion of positional patients (supine positional, non-supine positional, non-positional), for both methods of categorization of "positional patients." Statistical significance was taken at $p < 0.05$, and data were expressed as the median and interquartile range.

RESULTS

A total of 76 children with DS were compared with 76 control subjects matched for age, sex, total AHI, and year of PSG.

Table 1—Demographic and basic polysomnographic characteristics of DS and control subjects

	DS	Control	p value
N	76	76	–
Male n (%)	42 (55%)	42 (55%)	–
Age, years	4.6 (2, 8.4)	5.1 (1.9, 8.8)	NS
BMI z-score†	1.32 (0.44, 1.91)	1.36 (0.19, 1.96)	NS
TST, min	430 (391, 468.5)	442.5 (406, 474)	0.03
NREM sleep, %TST	83.7 (78.5, 90.4)	82.3 (77, 86.2)	NS
REM sleep, %TST	16.3 (9.6, 21.8)	17.7 (13.7, 23)	NS
Total AHI, events/hour	7.4 (4.1, 14.9)	7.5 (3.5, 14.7)	< 0.001
Sleep efficiency, %	83 (73.8, 88.4)	87.7 (79.7, 91.7)	0.002
Mean SpO_2, %	96 (95, 97)	97 (96, 98)	< 0.001
SpO_2 nadir, %	86 (83, 90)	88 (84, 91)	0.05
Arousal index, events/hour	11.3 (7.4, 15.3)	12.2 (8.3, 20.1)	NS
PLMI, events/hour	0.3 (0, 2.1)	1.1 (0, 5.8)	0.04
PLM arousal index, events/hour	0 (0, 1.1)	0.1 (0, 0.7)	NS
NREM AHI, events/hour	5.6 (2.5, 12.4)	5.3 (2.3, 11.4)	0.03
REM AHI, events/hour	13.6 (5, 33.6)*	12.6 (5.4, 21.3)*	NS
REM PI	0.56 (-0.05, 1.33)	0.69 (0.11, 1.3)	NS

†n = 57 case-control pairs. *p < 0.05 compared to NREM AHI of the same group. Data presented as median (25th percentile, 75th percentile). DS, Down syndrome; BMI, body mass index; TST, total sleep time; NREM, non-rapid eye movement; REM, rapid eye movement; AHI, apnea-hypopnea index; SpO_2, oxygen saturation; PLMI, periodic leg movement index; PLM, periodic leg movement; NS, not significant; REM PI, REM predominance index.

Subject Demographics and Basic Polysomnographic Parameters

Demographic and basic polysomnographic variables for DS and control subjects are shown in **Table 1**. Forty-two case-control pairs (55%) were male. The median age was subjects was 4.6 years (range 0.2-17.8 years) in DS subjects and 5.1 years (range 0.3-17.7 years) in control subjects. There were no differences between DS and control subjects in age or BMI z-score. Compared to controls, TST was reduced in DS subjects ($p < 0.05$), but there were no differences in the percentage of TST spent in either NREM or REM sleep. Despite matching for severity of SDB, the total AHI was significantly higher in DS subjects than control counterparts ($p < 0.05$). Sleep efficiency, mean oxygen saturation, and the oxygen saturation nadir were significantly lower in DS subjects than controls ($p < 0.05$ for all). There was no difference in arousal index or PLM arousal index between DS and control subjects, although subjects with DS had a lower PLMI than controls ($p < 0.05$).

Effect of Sleep State on Apnea-Hypopnea Index

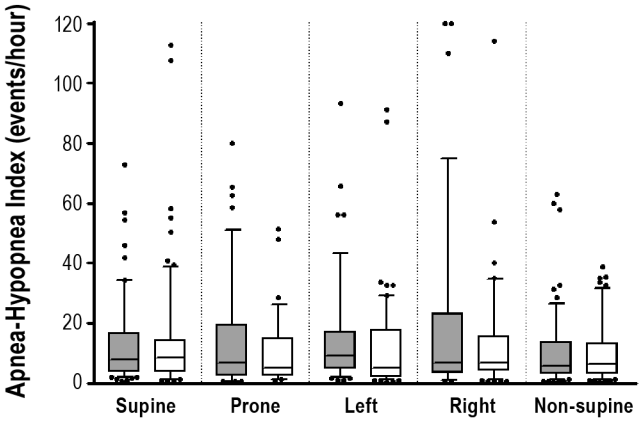
The NREM AHI was significantly higher in DS subjects than control counterparts ($p < 0.05$ for both), although the REM AHI was not different (**Table 1**). In both DS and control subjects,

Table 2—Body position as a percentage of TST in DS and control subjects

	DS	Control	p value
Prone, %TST	12.6 (0, 41.9)	3.9 (0, 22)	0.02
Supine, %TST	36.6 (10, 72.8)	44.7 (25.2, 72.5)	NS
Left lateral, %TST	9.8 (0, 31.4)	16.2 (3.6, 29.6)	NS
Right lateral, %TST	7.2 (0.3, 21.8)	15.7 (3.2, 28.7)	0.04
Non-supine, %TST	62.3 (22.7, 86)	52.7 (26.1, 74.1)	NS

Values are presented as median (25th percentile, 75th percentile). DS, Down syndrome; TST, total sleep time; NS, not significant.

Figure 1—Comparison of the apnea-hypopnea index in Down syndrome (gray) and control subjects (white) in each sleep position



The box represents the 25th percentile, median, and 75th percentile. The whiskers represent the 10th and 90th percentiles, and outliers are represented by circles.

the REM AHI was significantly higher than the NREM AHI ($p < 0.001$ for both). The REM PI was significantly greater than 0 in both DS and control groups ($p < 0.001$ for both), further indicating an overall predominance of events in REM sleep. However, the REM PI was not different between DS and control subjects. A REM PI < 0 was seen in 28% of DS subjects, indicating a predominance of NREM events in these subjects, in comparison to 20% of control subjects, although the proportion of subjects with an REM PI < 0 was not different between groups ($p = 0.22$).

Body Position during Sleep

The percentage of TST spent in each body position (supine, prone, right lateral, left lateral, and total non-supine) in both DS and control subjects is shown in **Table 2**. Compared to controls, DS subjects spent a significantly larger percentage of sleep in the prone position and a smaller percentage of time in the right lateral position ($p < 0.05$ for both). However, overall there were no differences between DS and control subjects in the percentage of time spent asleep in the non-supine position, or in the supine position.

Effect of Body Position on Apnea-Hypopnea Index

Figure 1 compares the AHI in DS and control subjects for each position of sleep. There were no significant differences in AHI between DS and control subjects for supine or any non-supine sleep position. In DS subjects overall, and similarly in control subjects as a whole, the AHI was not significantly different in the supine compared to the non-supine position, although numerically the AHI appeared to be higher during supine sleep.

Table 3—The proportion of positional patients in DS and control groups, categorized according to the AHI "twice as high" rule

	DS	Control
Positional patients (supine)	19 (33%)	22 (31%)
Positional patients (non-supine)	9 (15%)	15 (21%)
Non-positional patients	30 (52%)	34 (48%)
Total	58 (100%)	71 (100%)

Data presented as n (% of subjects within that group). 18 DS subjects and 5 control subjects could not be included in this analysis as AHI could not be calculated in both supine and non-supine positions.

Table 4—The proportion of positional patients in DS and control groups, categorized according to the "absolute majority AHI" rule

	DS	Control
Higher supine AHI	31 (53%)	38 (54%)
Higher non-supine AHI	24 (42%)	30 (42%)
Supine AHI = Non-supine AHI	3 (5%)	3 (4%)
Total	58 (100%)	71 (100%)

Data presented as n (% of subjects within that group). 18 DS subjects and 5 control subjects could not be included in this analysis as AHI could not be calculated in both supine and non-supine positions.

DS and control subjects were categorized as "positional patients" using the "twice as high" rule, as shown in **Table 3**. Categorization was not possible in 18 DS subjects and 5 control subjects, as they had not slept in either the supine or non-supine position, precluding calculation of an AHI in both positions. Of the DS subjects, 48% were found to be "positional patients"; 33% of subjects had an AHI twice as high in the supine position, and 15% of subjects had an AHI twice as high in the non-supine position. The proportion of positional patients was not significantly different between the DS and control groups.

According to absolute numerical majority, there were no differences between the DS and control groups in the proportion of subjects with either a higher supine AHI or a higher non-supine AHI (**Table 4**). In DS subjects, AHI was higher in the supine position in 53%, in the non-supine position in 42%, and was equal in supine and non-supine positions in 5% of subjects.

Effect of Body Position on Apnea-Hypopnea Index in Each Sleep State

The percentage of TST spent in the supine or non-supine position in both NREM and REM sleep is shown in **Table 5**. There were no differences between DS and control subjects in the percentage of non-supine NREM sleep, supine NREM sleep, non-supine REM sleep, or supine REM sleep. The AHIs in each of the respective body position and sleep state combinations

were not different between control and DS subjects. In DS subjects as a whole, the AHI of NREM sleep was significantly higher in the supine than the non-supine position ($p < 0.05$); however, in control subjects this positional difference was not observed. The AHI of REM sleep was not significantly different in the supine and non-supine position in either the DS or control group separately.

Effect of Age on the Sleep State and Positional Influences on Apnea-Hypopnea Index

As the subject age range was wide, analyses were repeated in a subsample of children aged ≥ 2 and < 13 years to exclude the possible effects of infancy and puberty. A total of 51 subjects with DS with a median age of 6.0 years and AHI of 7.5 events/h (range 0-61.3) were compared with 51 matched controls. Results of the effects of sleep state, body position, and the combination of sleep state and body position on AHI were similar to findings with children of all ages (data not shown).

Changes in Apnea-Hypopnea Index with Continuous Positive Airway Pressure

In order to determine the distribution of respiratory events in NREM and REM sleep, we reviewed charts of a subsample of DS subjects who underwent successful CPAP titration (n = 10). Four subjects had a greater percentage improvement in NREM AHI than in REM AHI. Although not statistically significant, a greater improvement in total AHI was observed in those with a greater improvement in NREM AHI than those who had a greater improvement in REM AHI (median change in total AHI 87% [interquartile range 74% to 96%] compared to 76% [37% to 87%]; data not shown).

Table 5—Percentage of TST spent supine and non-supine in NREM and REM sleep and associated AHI in DS and control subjects

	DS	Control	p value
NREM			
Supine, %TST	32.2 (10.3, 61.2)	39.3 (19.9, 60.3)	NS
Non-supine, %TST	47.3 (20.4, 69.9)	41.7 (20.1, 58.4)	NS
AHI supine, events/hour	5.3 (2.8, 12.5)	5 (2.4, 12.6)	NS
AHI non-supine, events/hour	3.8 (1.6, 8.8)*	4.6 (1.5, 9.8)	NS
REM			
Supine, %TST	3.2 (0, 9.5)	7.6 (1.6, 11.5)	NS
Non-supine, %TST	8.1 (3.4, 17.5)	9.9 (2.9, 14.3)	NS
AHI supine, events/hour	17.8 (4.6, 49.2)	13 (3.6, 26.6)	NS
AHI non-supine, events/hour	10.7 (1.4, 19.7)	8.3 (3.7, 24.4)	NS

*$p < 0.05$ compared to NREM AHI in the supine position in DS subjects. Values are presented as median (25^{th}, 75^{th} percentile). TST, total sleep time; DS, Down syndrome; NS, not significant; AHI, apnea-hypopnea index; NREM, non-rapid eye movement.

DISCUSSION

The present study is the first to investigate both the effects of sleep state and body position on OSA severity in children with DS. Previous studies have assessed these factors, often as a secondary aim, in only a small number of children with DS and have not always included a comparison group of children.[5,42,43] The main findings of this study were that, in comparison to typically developing children with OSA of a similar severity, children with DS similarly exhibited a REM predominance of respiratory events, with a minority of individuals demonstrating a preponderance of NREM-related events; and the DS children had a higher NREM AHI, despite being matched for total AHI and having a similar percentage of sleep time in NREM. Notably, children with DS exhibited a higher NREM AHI in the supine position compared to the non-supine position—a finding not observed in the control children or during REM sleep in either group. While the children with DS spent a greater amount of time sleeping prone, overall the amount of non-supine sleep (prone plus lateral) was not different.

In children with and without DS alike, we found respiratory events to be predominantly, although not exclusively, present in REM sleep. This pattern is not surprising and has been reported previously in typically developing children with OSA.[37,38] Verginis and colleagues found that a significant subset of children (30%) exhibit a NREM predominance of obstructive events.[38] In our DS population, we similarly found 28% of children to have NREM-predominant OSA, illustrating that consideration of sleep state distribution is just as important in individuals with DS. While numerous studies have investigated the prevalence of OSA in children with DS, few have assessed the effects of either sleep state or body position on OSA severity. Two studies provided in-depth descriptions of respiratory events in children with DS but did not report positional or sleep state-specific AHI.[2,44] Another study, of 33 children with DS aged 0-19 years, found the REM AHI to be three times higher than the NREM AHI and to be associated with the lowest oxygen saturation recorded.[5] The present study introduced another element by comparing AHI with typically developing children. Interestingly, we found that in children of similar overall OSA severity, the NREM AHI was significantly higher in children with DS. Together, these findings suggest a heightened importance of the NREM sleep contribution to OSA in DS subjects, even in the context of REM-predominant OSA.

We observed an increased proportion of sleep time in the prone position in children with DS compared to controls, although when grouped into supine or non-supine sleep, the two groups of children were similar. A previous study of 17 children with DS, aged 2-18 years, found a tendency for an increased proportion of supine sleep compared to controls of similar age, gender and AHI, but no difference in the amount of prone sleep.[42] Aside from differences in sample size, findings may differ from the present study due to a lower OSA severity (median total AHI of 4.3 events/h compared to present study AHI of 7.4 events/h). Other studies in children with DS have reported a higher number of changes in position during sleep[42,45] and an increased amount of sleep time in the "leaning forward" position[42] in comparison to controls; however, we did not measure either of these variables. Our findings suggest

that children with DS and moderately-severe OSA generally exhibit positional preferences during sleep similar to those of typically developing children of similar OSA severity. Interestingly, studies of small cohorts of children with OSA have found that the supine position is highly prevalent throughout the night,[32,33,46] such that the sleeping positions of children are altered by the presence of OSA. A larger study determined that when compared to children without OSA, children with OSA spent more time in the supine position and less time in the lateral position, while obese children with OSA were more likely to sleep prone.[34] The adoption of the prone position in the presence of obesity suggests that the supine or lateral positions may increase the risk for more severe respiratory disturbance when OSA and obesity coexist. It is likely that a similar pattern exists in DS, which could be further augmented not just by the presence of obesity but by other physical characteristics which may act to increase the risk of respiratory difficulty in certain positions. The contention that OSA affects positional sleeping preferences is further supported by the findings of increased supine time, reduced lateral time, and reduced prone time in a relatively overweight group of children with OSA following adenotonsillectomy.[46] The positional preferences of children with DS but without OSA are yet to be elucidated.

We observed no difference between DS and non-DS children in relation to the positional effects of OSA severity over the night as a whole. In each position, the AHI was similar in DS and control children despite possible differences in OSA etiology, including contributions of physical characteristics. The only previous study to measure positional AHI in children with DS similarly reported no difference between DS and control groups in the various positions.[42] We did not detect a difference in AHI between the supine and non-supine positions in either DS or control children, although OSA severity appeared to be increased in supine sleep. In typically developing children, OSA severity is reportedly worsened when supine or not affected by position, depending on the study.[31-35] In our cohort of DS subjects, 53% had a numerically higher supine AHI than non-supine AHI, and 33% of subjects had an AHI twice as high in the supine position. The proportion of subjects in these "positional" categories was not different from proportions seen in our typically developing control children. Supine positional OSA is more common in adults with OSA, accounting for 50% to 60% of individuals.[22,25-27] Our findings suggest a heterogeneous effect of position on overall OSA severity in children with DS.

We subsequently examined the effect of supine and non-supine sleep on OSA severity specific to each sleep state and found that children with DS were different from controls in one aspect alone; during NREM sleep the AHI was significantly higher in the supine position compared to the non-supine position. This difference was not found in the control children or in either group during REM sleep, suggesting that the effects of position are more overt in NREM sleep in those with DS. In view of the hypotonia inherent to DS, we contend that the gravitational effect on airway patency associated with supine sleep is possibly augmented by increased pharyngeal muscle hypotonia, which would not normally be seen during NREM sleep in typically developing children. It fits that during REM sleep, a degree of hypotonia occurs regardless of position in children with and without DS alike, hence reducing the positional difference on OSA severity in this state. Therefore, the combination of sleep state and position merits consideration when both interpreting PSG and guiding treatment choices for children with DS.

In typically developing children, the effect of position on OSA severity can vary not only with obesity but also with age[32,35]; however, we did not find this to be the case in children with DS. Our findings were similar both when all subjects were included, aged from 2 months to less than 18 years, and when restricted to those aged 2 years to less than 13 years. While we could not characterize the positional and sleep state effects during infancy or puberty due to small numbers of subjects of these ages, for the majority of pre-pubescent children with DS, to the best of our knowledge it appears that the positional effects remain the same in children with DS irrespective of age.

Knowledge of the positional and sleep state effects on OSA severity may be important for optimizing treatment in children with DS as a whole, but also on an individual level. We demonstrated in a small subsample of children that improvement in total AHI was greater in children who had a larger change in NREM AHI than in REM AHI. This occurred in spite of a REM predominance of respiratory events. Thus consideration of the sleep state distribution of respiratory events should be an important factor when interpreting PSGs and formulating management plans in children with DS. As recently reported by Eiseman[47] in adults with OSA, it is important to consider "conditional" AHI values when position and/or sleep state dependent OSA is evident on PSG, as there is a clear risk for potential misclassification of disease presence or severity. As suggested in both that study and by our findings, routine PSG interpretation should include the frequency of respiratory events by both sleep state and body position, values that may have particular importance for the DS population.

On an individual level, consideration of therapies which treat OSA preferentially in one sleep state or which make a bigger improvement in a certain position may prove helpful. For example, a study in adults with non-positional OSA found uvulopalatopharyngoplasty to produce a much greater decrease in the lateral RDI than in supine RDI.[48] Indeed, knowledge of the positional and sleep state distribution of events would allow clinicians to estimate the range of OSA severity that could occur, for example, from presumably the most severe in cases where a child has the majority of sleep in the supine position, to the least severe where the child is mostly in the lateral/prone positions. One night in the sleep laboratory may not be representative of the child's typical sleep in his/her own environment, particularly in regard to position and sleep state distribution, and so the ability to extrapolate data as described is likely to result in improved individual treatment recommendations. It follows that consideration of the OSA pattern may prove beneficial in OSA patients, DS and non-DS alike.

This study is not without limitations. Despite matching, total AHI was statistically higher in children with DS than controls. However, this statistical difference is unlikely to be clinically significant, as paired values were consistently of the same OSA severity grouping as defined clinically; moreover, median total AHI values of each group differed by only 0.1 events per hour. It is possible that the difference in NREM AHI between groups is a result of the statistical difference in total AHI between

groups; however, as the median, 25th and 75th percentile values of NREM AHI were all consistently higher in the DS group, this effect is less likely. As this was a retrospective review of the positional effects of OSA, we did not control sleeping positions, and thus not all subjects slept in all positions. However, in doing so, it permitted us to compare the preference for sleep positions in our subjects, albeit in a clinical laboratory setting. For analysis of AHI according to each sleep state-position combination, prone and lateral sleep durations were grouped together as non-supine sleep in order to maximize the number of subjects contributing to the findings. Furthermore, we do not have record of head or neck flexion or rotation during sleep, or of upper airway examination in our subjects. Children in the prone or lateral position can have flexion of their neck, which may lead to increased upper airway collapsibility.[49-51] Using rigid video endoscopy, a study of typically developing children with OSA determined that the positional effects varied as a function of the type of upper airway narrowing; the supine position was preferable to lateral in those with only adenoidal hypertrophy; however, in the case of hypertrophic tonsils and adenoids, breathing was worse in the supine position.[33] Their findings support a gravitational component of OSA in children, even if the level of obstruction is typically at the adenoids or soft palate[52] rather than the tongue as seen in adults, in whom gravity is a key contributor to OSA. As the etiology of OSA in DS is arguably more multifactorial, the delineation of positional effects according to adenoidal or tonsillar hypertrophy may not be possible, although is a potential area for future research. Despite these limitations, the present study has nonetheless provided important insights into factors which affect OSA severity in DS, highlighting areas for future focus and for clinical consideration.

CONCLUSION

The present study found that in DS and typically developing children of similar age and OSA severity, respiratory events are predominantly REM related but can be related to NREM sleep or the supine position in significant subset of individuals. When matched for total AHI, children with DS have a higher NREM AHI. The effect of position on total AHI is similar in DS and control children, however in children with DS, NREM AHI worsened in the supine position, perhaps indicating a positional effect compounded by underlying hypotonia inherent to DS. These findings illustrate the importance of the NREM sleep contribution to OSA severity in the DS population. Consideration of both sleep state and position warrant attention when interpreting OSA severity and choosing treatment modalities.

REFERENCES

1. Dyken ME, Lin-Dyken DC, Poulton S, Zimmerman MB, Sedars E. Prospective polysomnographic analysis of obstructive sleep apnea in Down syndrome. *Arch Pediatr Adolesc Med* 2003;157:655-60.
2. de Miguel-Diez J, Villa-Asensi JR, Alvarez-Sala JL. Prevalence of sleep-disordered breathing in children with Down syndrome: Polygraphic findings in 108 children. *Sleep* 2003;26:1006-9.
3. Shott SR, Amin R, Chini B, Heubi C, Hotze S, Akers R. Obstructive sleep apnea: Should all children with down syndrome be tested? *Arch Otolaryngol Head Neck Surg* 2006;132:432-6.
4. Ng DK, Hui HN, Chan CH, et al. Obstructive sleep apnoea in children with Down syndrome. *Singapore Med J* 2006;47:774-9.
5. Fitzgerald DA, Paul A, Richmond C. Severity of obstructive apnoea in children with Down syndrome who snore. *Arch Dis Child* 2007;92:423-5.
6. Marcus CL, Keens TG, Bautista DB, von Pechmann WS, Ward SL. Obstructive sleep apnea in children with Down syndrome. *Pediatrics* 1991;88:132-9.
7. Lumeng JC, Chervin RD. Epidemiology of pediatric obstructive sleep apnea. *Proc Am Thorac Soc* 2008;5:242-52.
8. Marcus CL, Brooks LJ, Draper KA, et al. Diagnosis and management of childhood obstructive sleep apnea syndrome. *Pediatrics* 2012;130:e714-55.
9. Allanson JE, O'Hara P, Farkas LG, Nair RC. Anthropometric craniofacial pattern profiles in Down syndrome. *Am J Med Genet* 1993;47:748-52.
10. Silverman M. Airway obstruction and sleep disruption in Down's syndrome. *BMJ (Clin Res Ed)* 1988;296:1618-9.
11. Marcus CL. Sleep-disordered breathing in children. *Am J Respir Crit Care Med* 2001;164:16-30.
12. Horne RS, Yang JS, Walter LM, et al. Elevated blood pressure during sleep and wake in children with sleep-disordered breathing. *Pediatrics* 2011;128:e85-92.
13. O'Brien LM, Gozal D. Autonomic dysfunction in children with sleep-disordered breathing. *Sleep* 2005;28:747-52.
14. Walter LM, Nixon GM, Davey MJ, Anderson V, Walker AM, Horne RS. Autonomic dysfunction in children with sleep disordered breathing. *Sleep Breath* 2013;17:605-13.
15. O'Brien LM. The neurocognitive effects of sleep disruption in children and adolescents. *Child Adolesc Psychiatr Clin N Am* 2009;18:813-23.
16. Bourke R, Anderson V, Yang JS, et al. Cognitive and academic functions are impaired in children with all severities of sleep-disordered breathing. *Sleep Med* 2011;12:489-96.
17. Jackman AR, Biggs SN, Walter LM, et al. Sleep-disordered breathing in preschool children is associated with behavioral, but not cognitive, impairments. *Sleep Med* 2012;13:621-31.
18. Bourke RS, Anderson V, Yang JS, et al. Neurobehavioral function is impaired in children with all severities of sleep disordered breathing. *Sleep Med* 2011;12:222-9.
19. O'Brien LM, Mervis CB, Holbrook CR, et al. Neurobehavioral correlates of sleep-disordered breathing in children. *J Sleep Res* 2004;13:165-72.
20. Iber C, Ancoli-Israel S, Chesson A, Quan SF. The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications. Westchester, IL: American Academy of Sleep Medicine, 2007.
21. Gillman A, Roebuck T, Ho S, van Braak E, Naughton MT. Comparison of supine-only and rem-only obstructive sleep apnoea. *Sleep Med* 2012;13:875-878.
22. McEvoy RD, Sharp DJ, Thornton AT. The effects of posture on obstructive sleep apnea. *Am Rev Respir Dis* 1986;133:662-6.
23. Cartwright RD. Effect of sleep position on sleep apnea severity. *Sleep* 1984;7:110-4.
24. Cartwright RD, Diaz F, Lloyd S. The effects of sleep posture and sleep stage on apnea frequency. *Sleep* 1991;14:351-3.
25. Phillips BA, Okeson J, Paesani D, Gilmore R. Effect of sleep position on sleep apnea and parafunctional activity. *Chest* 1986;90:424-9.
26. George CF, Millar TW, Kryger MH. Sleep apnea and body position during sleep. *Sleep* 1988;11:90-9.
27. Oksenberg A, Silverberg DS, Arons E, Radwan H. Positional vs nonpositional obstructive sleep apnea patients: Anthropomorphic, nocturnal polysomnographic, and multiple sleep latency test data. *Chest* 1997;112:629-39.
28. Penzel T, Moller M, Becker HF, Knaack L, Peter JH. Effect of sleep position and sleep stage on the collapsibility of the upper airways in patients with sleep apnea. *Sleep* 2001;24:90-5.
29. Oksenberg A, Silverberg DS. The effect of body posture on sleep-related breathing disorders: Facts and therapeutic implications. *Sleep Med Rev* 1998;2:139-62.
30. Fernandes do Prado LB, Li X, Thompson R, Marcus CL. Body position and obstructive sleep apnea in children. *Sleep* 2002;25:66-71.
31. Zhang XW, Li Y, Zhou F, Guo CK, Huang ZT. Association of body position with sleep architecture and respiratory disturbances in children with obstructive sleep apnea. *Acta Otolaryngol* 2007;127:1321-6.
32. Pereira KD, Roebuck JC, Howell L. The effect of body position on sleep apnea in children younger than 3 years. *Arch Otolaryngol Head Neck Surg* 2005;131:1014-6.
33. Cuhadaroglu C, Keles N, Erdamar B, et al. Body position and obstructive sleep apnea syndrome. *Pediatr Pulmonol* 2003;36:335-8.
34. Dayyat E, Maarafeya MM, Capdevila OS, Kheirandish-Gozal L, Montgomery-Downs HE, Gozal D. Nocturnal body position in sleeping children with and without obstructive sleep apnea. *Pediatr Pulmonol* 2007;42:374-9.

35. Pereira KD, Rathi NK, Fatakia A, Haque SA, Castriotta RJ. Body position and obstructive sleep apnea in 8-12-month-old infants. *Int J Pediatr Otorhinolaryngol* 2008;72:897-900.
36. Goh DY, Galster P, Marcus CL. Sleep architecture and respiratory disturbances in children with obstructive sleep apnea. *Am J Respir Crit Care Med* 2000;162:682-6.
37. Spruyt K, Gozal D. REM and NREM sleep-state distribution of respiratory events in habitually snoring school-aged community children. *Sleep Med* 2012;13:178-84.
38. Verginis N, Jolley D, Horne RS, Davey MJ, Nixon GM. Sleep state distribution of obstructive events in children: Is obstructive sleep apnoea really a rapid eye movement sleep-related condition? *J Sleep Res* 2009;18:411-4.
39. Miano S, Bruni O, Elia M, et al. Sleep phenotypes of intellectual disability: A polysomnographic evaluation in subjects with Down syndrome and Fragile-X syndrome. *Clin Neurophysiol* 2008;119:1242-1247.
40. Ogden CL, Kuczmarski RJ, Flegal KM, et al. Centers for Disease Control and Prevention 2000 growth charts for the United States: Improvements to the 1977 National Center for Health Statistics version. *Pediatrics* 2002;109:45-60.
41. Cartwright R, Ristanovic R, Diaz F, Caldarelli D, Alder G. A comparative study of treatments for positional sleep apnea. *Sleep* 1991;14:546-52.
42. Senthilvel E, Krishna J. Body position and obstructive sleep apnea in children with Down syndrome. *J Clin Sleep Med* 2011;7:158-62.
43. Shete MM, Stocks RM, Sebelik ME, Schoumacher RA. Effects of adenotonsillectomy on polysomnography patterns in Down syndrome children with obstructive sleep apnea: A comparative study with children without Down syndrome. *Int J Pediatr Otorhinolaryngo*l 2010;74:241-4.
44. Ferri R, Curzi-Dascalova L, Del Gracco S, Elia M, Musumeci SA, Stefanini MC. Respiratory patterns during sleep in Down's syndrome: Importance of central apnoeas. *J Sleep Res* 1997;6:134-41.
45. Dahlqvist A, Rask E, Rosenqvist CJ, Sahlin C, Franklin KA. Sleep apnea and Down's syndrome. *Acta Otolaryngol* 2003;123:1094-7.
46. Choi JH, Kim EJ, Choi J, et al. The effect of adenotonsillectomy on changes of position during sleep in pediatric obstructive sleep apnea syndrome. *Am J Rhinol Allergy* 2009;23:e56-8.
47. Eiseman NA. Westover MB, Ellenbogen JM, Bianchi MT. The impact of body posture and sleep stages on sleep apnea severity in adults. *J Clin Sleep Med* 2012;8:655-66.
48. Katsantonis GP, Miyazaki S, Walsh JK. Effects of uvulopalatopharyngoplasty on sleep architecture and patterns of obstructed breathing. *Laryngoscope* 1990;100:1068-72.
49. Ishikawa T, Isono S, Aiba J, Tanaka A, Nishino T. Prone position increases collapsibility of the passive pharynx in infants and small children. *Am J Respir Crit Care Med* 2002;166:760-4.
50. Thach BT, Stark AR. Spontaneous neck flexion and airway obstruction during apneic spells in preterm infants. *J Pediatr* 1979;94:275-81.
51. Thut DC, Schwartz AR, Roach D, Wise RA, Permutt S, Smith PL. Tracheal and neck position influence upper airway airflow dynamics by altering airway length. *J Appl Physiol* 1993;75:2084-90.
52. Isono S, Shimada A, Utsugi M, Konno A, Nishino T. Comparison of static mechanical properties of the passive pharynx between normal children and children with sleep-disordered breathing. *Am J Respir Crit Care Med* 1998;157:1204-12.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication May, 2013
Submitted in final revised form August, 2013
Accepted for publication September, 2013
Address correspondence to: Louise O'Brien, Ph.D., M.S., Sleep Disorders Center, Department of Neurology, University of Michigan, Med Inn Room C736, 1500 E Medical Center Dr, Ann Arbor, MI, 48109-5845; Tel: (734) 763-9684; E-mail: louiseo@med.umich.edu

DISCLOSURE STATEMENT

This was not an industry supported study. Dr. O'Brien was partially supported by grants from the National Heart, Lung, and Blood Institute (K23 HL095739, R21 HL089918, and R21 HL087819). She receives equipment support from Philips Respironics Inc., has received sleep-related NIH grant funding, and has received honoraria for speaking on the topic of sleep disordered breathing. The other authors have indicated no financial conflicts of interest.