Obstructive sleep apnea syndrome and cognition in Down syndrome

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AIM Good-quality sleep is essential for normal learning and memory. Sleep fragmentation and disrupted sleep architecture are commonly observed throughout the lifespan of individuals with Down syndrome, a condition marked by cognitive deficits emerging within the first few months of life. While obstructive sleep apnea syndrome (OSAS) is known to contribute to the loss of sleep quality in Down syndrome, its relation to cognitive and behavioral impairment remains poorly understood.

METHOD Using ambulatory polysomnography, we measured sleep in an unreferred community-based sample of 38 individuals with Down syndrome (15 males, 23 females; mean age 9y 7mo (SD 1y 9mo), range 7–12y). Cognitive outcomes were assessed with the Arizona Cognitive Test Battery, a set of psychometric measures designed and validated for this population.

RESULTS Among children with Down syndrome, mean Verbal IQ score (p=0.006) was 9 points lower in those with comorbid OSAS (apnea–hypopnea index >1.5) than in those without OSAS, and performance on measures of cognitive flexibility was poorer (p=0.03). In addition, those with OSAS showed increased light-stage sleep (p=0.009) at the expense of slow-wave sleep (p=0.04).

INTERPRETATION These findings demonstrate a relation between OSAS and cognitive outcomes in Down syndrome. More work is required to fully understand the mechanisms underlying the links between poor sleep and impaired cognitive function. Overall, these findings highlight the importance of adequate sleep in typically and atypically developing populations.

Down syndrome (trisomy 21) is the most common genetically defined cause of intellectual disability, with over 300 000 affected individuals residing in the United States alone.[1] The condition is characterized by decline of IQ during the infant and toddler years, well-documented deficits in the assimilation and expressive use of language, and impairments in cognitive flexibility and memory.[2] As a result of alterations in craniofacial and oral musculature development and low muscle tone, individuals with Down syndrome are exceptionally vulnerable to obstructive sleep apnea syndrome (OSAS) from infancy, with estimates of the prevalence of the condition ranging from 30% to as high as 80%.[3–5] Ashworth et al.[6] have recently described the extent of sleep disruption in individuals with Down syndrome, noting that such individuals displayed more fragmented sleep than those with Williams syndrome, another intellectual disability. Because of the extent of their sleep disruption, individuals with Down syndrome could potentially suffer ill effects during critical periods of cognitive development.

OSAS occurs when the upper airway becomes intermittently obstructed during sleep, resulting in incomplete ventilation, blood gas irregularities, and sleep fragmentation.[7] It is best diagnosed with polysomnography (PSG), the criterion standard for sleep assessment, and is determined by an apnea–hypopnea index (AHI) score above a high cut-off value as measured using this method. PSG enables the monitoring of sleep states with at least two electroencephalography (EEG) channels, discrimination of nasal airflow, chest and abdominal respiratory effort, and blood oxygenation. AHI is determined by the number of periods of apnea and hypopnea per hour of sleep. While apneas are defined as complete cessation of breathing for two breath cycles, hypopneas involve breathing reduction, but not cessation.

Hypopneas are clinically significant because they result in a reduction in blood oxygen level and central nervous system arousal, as reflected in EEG activity.

In adults and children with typical development, persistent OSAS has been strongly associated with structural differences in the brain's frontal and temporal lobes, and corresponding problems with working memory, executive function, and episodic memory.[8–10] Individuals with persistent OSAS have a neurocognitive profile similar in many respects to that of individuals with Down syndrome.[11,12] This overlap suggests the possibility that OSAS, by virtue of its destabilizing effects on sleep architecture or its reduction of oxygen, might account for some of the cognitive variability seen in individuals with Down syndrome. It also hints at the, albeit more speculative, possibilities that (1) bouts of sleep apnea which occur within the first years of life might significantly influence the trajectory of cognitive development in children with Down syndrome and (2) OSAS might accelerate Alzheimer-like pathology in older adults with Down syndrome, who are already at increased risk for dementia in later life (links between Alzheimer disease and sleep are further discussed by Fernandez and Edgin[13]).

Previous studies have suggested that sleep apnea, measured by PSG and parent-reported sleep disruption, is associated with cognitive impairments in adults with Down syndrome without dementia.[14,15] However, no study has examined the relation between OSAS and cognition in young children with Down syndrome using a comprehensive battery of cognitive measures, and controlling for confounding background factors has not always been possible owing to the small sample sizes in previous studies. In the present study we used PSG to examine the correspondence between OSAS, defined by AHI, and cognition in children with Down syndrome as measured by the Arizona Cognitive Test Battery (ACTB), a battery specifically designed for this population.[16] We also examined which aspects of sleep physiology are most influenced by OSAS in Down syndrome. We hypothesized that OSAS would relate to areas of cognition shown to be impaired in previous studies, including executive function, memory, and verbal learning. We assessed whether particular sleep stages were reduced (e.g. slow-wave sleep), and how differences in sleep physiology, such as level of hypoxemia and EEG arousals, may relate to cognitive outcomes. We examined these relations in light of background medical and demographic factors that could also affect cognition (e.g. body mass index [BMI]). Knowing the extent to which OSAS affects cognitive function in individuals with Down syndrome might increase awareness among health care professionals of the pressing need to screen and treat this often under-recognized medical complication.

METHOD
Participants
A community-based sample of 38 school-aged children with Down syndrome (15 males, 23 females; mean age 9y

What this paper adds
- Obstructive sleep apnea syndrome is associated with some cognitive deficits in children with Down syndrome.
- Verbal IQ was 9 points lower in children with OSAS and Down syndrome, who also showed executive function deficits.
- These differences were found in children of similar age, BMI, and health status.
- Children with a dual diagnosis of Down syndrome and OSAS showed less slow-wave sleep and more light-stage sleep.

7mo (SD 1y 9mo), range 7–12y; mental age calculated from the Kaufman Brief Intelligence Test-2 verbal scale=4.5y) was recruited through advertisements across Arizona and through parent organizations. Exclusion criteria included the presence of Robertsonian translocation, mosaicism, comorbidity for autism, past head injury, or loss of consciousness (>5min). During screening, parents were asked if their child displayed severe vision or hearing loss; children were enrolled only if vision and hearing were corrected. All children in the current study had a confirmed diagnosis of trisomy 21 through medical record verification. Thirty-one sleep studies met the criteria for inclusion; the children included in the present report represented a range of ethnic and income backgrounds (*n*=15 white non-Hispanic, *n*=13 Hispanic, and *n*=3 other, income ranging from $10 000–$200 000). The range of IQ (median=42.00, interquartile range [IQR]=9.0) was similar to previous studies of Down syndrome.[16]

Each child was monitored with PSG off-site at his or her place of residence. Tests selected from the ACTB were administered within 3 months of the sleep measurements by research staff. Questionnaire assessments of parent-reported sleep outcomes and behavior, and medical verifications of parent-reported health outcomes, were also completed. Each child's medical records were collected from the birth hospital, primary care doctor and specialists to verify the diagnosis of Down syndrome (trisomy 21), the presence and type of heart defect, and surgery status (i.e. tonsils and adenoids removal). Table I further compares the background characteristics of children with and without OSAS as determined by PSG.

Written consent was obtained from parents or guardians before the study, and all procedures were approved by the University of Arizona Institutional Review Board.

Assessments
Ambulatory polysomnography
All children underwent unattended PSG in their homes in order to maximize participant compliance (Compumedics Somté PSG system Compumedics USA Inc., Charlotte, NC, USA); data were scored manually according to standard pediatric criteria.[17,18] Previous studies using ambulatory PSG have shown that in-home assessments can be reliable for assessing OSAS.[18] Application of PSG started 1.5 hours before bedtime and was completed by the child's natural sleep time. The following channels were included in the recording montage: electroencephalogram (C3, A2 and C4, A1), electrooculogram, chin electromyogram,

thoracic and abdominal displacement (inductive plethysmography bands), finger pulse oximeter (Nonin 8000J Series Flex SpO2 Sensor; Nonin Medical Inc, Plymouth, MN, USA), a single bipolar electrocardiogram, body position, and ambient light. Flow limitation was evaluated with the use of a nasal cannula, as nasal pressure is considered a sensitive method for detecting flow limitation in both adults and children.

To determine if a child met the criteria for OSAS, we calculated the AHI, which was defined as the number of periods of apnea and hypopnea respiratory events (both obstructive and central) per hour of total sleep time. An AHI cut-off value of 1.5 was set as diagnostic of OSAS as this value is commonly used in children.[19] All results were scored by a registered polysomnographic technologist with 23 years' experience in scoring PSGs in research and clinical settings. Consistent with previous studies examining pediatric OSAS,[20] participants were only included if at least 4 hours of recording time on all channels were obtained. Data for seven participants did not meet the quality criteria, as recording time on some channels was insufficient, and were not included in these analyses. To validate our results, we analyzed the relation between the AHI measured in our study and the AHI generated through sleep studies of these same children conducted by independent clinical sleep laboratories (n=8 gathered from medical records), finding a strong correlation between our estimates and the independent studies (Pearson's r=0.89, p=0.003). Data from eight participants collected for the present research were also blindly recoded by the same sleep technician with a time window of 3 years between each scoring attempt, resulting in high agreement (Spearman's rho=0.93, p=0.001). We tested the data from the seven participants excluded from the study using the same cognitive and behavioral variables (Table II). There were no significant differences (p>0.25 for all); it is therefore likely that our sample was not biased by study loss.

Parent-reported sleep

The Children's Sleep Habits Questionnaire (CSHQ) is a 33-item parent-completed questionnaire designed to examine sleep behavior in children and has been previously used to study Down syndrome.[6,21,22] The CSHQ yields both a total score and eight subscale scores, reflecting key sleep domains in school-aged children. Here we report parent ratings of sleep-disordered breathing and daytime sleepiness subscales, with higher scores reflecting poorer sleep behaviors.

Neurocognitive assessment

Participants' cognition was assessed during a 2-hour testing session. The session included the ACTB for Down syndrome a customized battery of IQ, adaptive behavior, and neuropsychological measures (i.e. hippocampal and prefrontal dependent) that are described fully elsewhere.[16] Each participant was assessed by a trained psychometrician blind to the OSAS diagnosis. The following measures from the ACTB were included.

CANTAB Motor Screening Task. Each child completed the CANTAB Motor Screening Task to gage responses to computer stimuli; all children could interact with the touch-screen successfully by touching an 'X' presented on the screen.

IQ and vocabulary knowledge. The Kaufman Brief Intelligence Test, Second Edition (KBIT-2),[23] is a standardized IQ scale with verbal and non-verbal subtests. The outcome measure of interest was the standardized IQ on the subtests. The verbal scale of the KBIT-2 includes a measure of verbal knowledge, which assesses children's receptive vocabulary.

CANTAB Spatial Paired Associates. The CANTAB Paired-Associates Learning task (http://www.cambridgecognition.com/) assesses the learning of associations between non-verbalizable stimuli and their location within a spatial array on a touch-screen computer. The participant is asked to remember the spatial location associated with each pattern and to touch that place in response to the presentation of the pattern (1–8 patterns are displayed per trial with eight attempts to solve each level until the participant reaches criterion of 100% correct). This task requires specific memory for the originally presented spatial location, and impairments are an early indicator of Alzheimer disease.[24] The outcome measure was the mean number of errors until success across trials.

CANTAB Intra-Extra Dimensional Set Shift. The Intra-Extra Dimensional Set Shift test (IED) is a test of cognitive flexibility. In the initial stages, participants are first presented with two colored shapes, and must learn which shape is 'correct' through trial and error. After several trials of recognizing the correct rule, the 'correct' shape is reversed. In later stages, a second shape is transposed onto each shape, so that the participant must take another dimension into consideration when determining which shape is 'correct'. The task progresses from rule shifts within a dimension (i.e. to a different stimulus of the same type) to responses outside of the trained dimension (i.e. between shapes in which one has never been rewarded) across nine stages of increasing difficulty. The number of stages completed was the main outcome variable.

CANTAB Simple Reaction Time. In the Simple Reaction Time test, participants press a button when a stimulus (a white box with variable onset) appears on a computer screen. The outcome measure is the median reaction time, a measure of processing speed.

Parent- and experimenter-reported behavior

The Connors-3 parent rating scale. The Conners-3 parent rating scale includes a parent questionnaire designed to assess attention-deficit–hyperactivity disorder (ADHD) and its comorbid problems in children and adolescents aged 6 to 18 years.[25] The outcome measure reported here is the mean Conners ADHD Index from the parent-reported results, with higher index scores reflecting more severe ADHD symptoms.

The Scales of Independent Behaviour – Revised. The Scales of Independent Behavior – Revised (SIB-R)[26] is a caregiver-completed checklist-style rating scale designed to assess adaptive functioning and everyday skills. The SIB-R

measures motor, social and communication, personal living, and community living skills. The measure can be applied to individuals of a wide range of ages, from infancy to adulthood. The Standard Score was used as the outcome measure.

Experimenter behavioral ratings. For each individual task, the examiner rated the participant's attention to the task on a 5-point scale relative to the execution of the task, with higher scores reflecting better attention.

Statistical analysis

First, the distributional properties of each measure were examined, including the normality of each continuous measure and the presence of floor/ceiling effects. Tests were considered significant with $p<0.05$. Normality was tested with the Shapiro–Wilks test (normality assumed at $p>0.05$). Non-normal variables were analyzed with non-parametric tests (Mann–Whitney U and Spearman's *rho*). In Table I we compare the child's clinical and family background factors in relation to OSAS using *t*-tests for continuous normal measures, Mann–Whitney U tests for non-normal variables, and Fisher's exact test for dichotomous outcomes. We examined the presence of OSAS in relation to polysomnographic variables and parent report of sleep (Table II) using the *t*-test or Mann–Whitney U test. Finally, we used correlation to examine the extent to which sleep variables that differ in OSAS (e.g. sleep architecture) might correlate with cognitive outcome. Effect sizes are shown for each measure, with Cohen's *d* (small effect=0.2, large effect=0.8) presented for mean differences and odds ratios (small effect=1.44, large effect=4.25) presented for dichotomous outcomes.

RESULTS
Clinical and background characteristics

Table I describes the clinical and family background characteristics of children with Down syndrome with OSAS [nine males, 10 females; mean age 10y 2mo (SD 1y 10mo)] and without OSAS [10 females, two males; mean age 8y 11mo (SD 1y 4mo)], as defined by AHI >1.5. Mean age

did not differ between the groups ($p=0.09$; range 7–12y in both groups; IQR: no OSAS, 2.19 years; OSAS, 3.91y). Children with and without OSAS also did not differ in sex ($p=0.13$), ethnicity ($p=1.00$), tonsil or adenoid surgery status ($p=0.46$), family income level ($n<\$40\,000$, $p=0.68$), mean maternal education ($p=0.89$), or mean BMI ($p=0.24$). An additional analysis examining the distribution of children in the overweight/obese range as compared with the normal range showed no significant differences in children with Down syndrome with and without OSAS; six out of 12 participants in the no OSAS group were overweight/obese and 11 out of 19 participants in the comorbid OSAS group were overweight/obese ($p=0.72$). Further, the OSAS groups did not differ in the number of children with heart defects ($p=0.47$). Heart murmur and patent ductus arteriosus without surgery were not classified as defects. Cyanotic heart disease (Tetralogy of Fallot) was present in one child in the OSAS group and two children in the group without OSAS.

OSAS in relation to polysomnography and parent-reported sleep behavior

Table II shows PSG and parent-reported variables of sleep. OSAS was present in 19 out of 31 children. Examining the PSG data, total sleep time did not differ across the groups ($p=0.44$). However, as the sample was stratified on AHI, AHI naturally differed across groups ($p<0.001$), with differences in the number of apneas ($p<0.001$) and hypopneas ($p=0.007$). The arousal index was significantly elevated in children with OSAS ($p=0.01$), with a greater number of respiratory-related arousals ($p<0.001$). While there was no group difference in oxygen levels while awake ($p=0.25$), oxygen desaturations were larger in the OSAS group during sleep ($p=0.03$). Parent reports correlated poorly with OSAS; we found no significant differences in ratings of daytime sleepiness ($p=0.19$) or symptoms of sleep-disordered breathing ($p=0.34$). Figure 1 shows sleep architecture differences across the groups; the percentage of stage 1 sleep in individuals with Down syndrome and OSAS was increased (Mann–Whitney $U=177.50$, $p=0.009$) at the

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Table I: Child clinical and family social background of children aged 7 to 12 years with Down syndrome with and without OSAS

Measures	No OSAS (*n*=12)	OSAS (*n*=19)	*t* (Mann–Whitney *U*)/Fisher's	*p*	Effect size (odds ratio/*d*)
Clinical characteristics					
Mean age, y (SD)	8.99 (1.49)	10.21 (1.81)	156.00	0.09	−0.74 (*d*)
Males/Females, *n*	2/10	9/10		0.13	0.22
White non-Hispanic *n*	6	9		1.00	1.11
Mean BMI (SD)	18.82(3.49)	19.48 (5.34)	−1.21	0.24	−0.15 (*d*)
Overweight/obese, *n*	6	11		0.72	0.73
Heart defect, *n*	5	11		0.47	0.52
Tonsils or adenoids removed, *n*	8	9		0.46	2.22
Social background factors					
Family income <$40 000, *n*	2	5		0.68	0.56
Mean maternal education,[a] y (SD)	15.00 (2.86)	15.18 (1.76)	−0.14	0.89	−0.08 (*d*)

No OSAS defined as apnea-hypopnea index AHI ≤1.5); OSAS defined as AHI >1.5. [a]All values in Table I were calculated based on *n*=31, with the exception of two missing values for maternal education. OSAS, obstructive sleep apnea syndrome; BMI, body mass index.

Table II: Polysomnographic variables and caregiver reports of sleep in children with Down syndrome

Measure	No OSAS (n=12), mean (SD)	OSAS (n=19), mean (SD)	t (Mann–Whitney U)	p	Effect size (d)
Total sleep time (min)	507.46 (86.38)	491.90 (60.78)	94.00	0.44	0.21
Apnea hypopnea index (events per hour)	0.82 (0.43)	8.93 (11.54)	228.00	<0.001	−0.99
Apnea episodes per hour	0.31 (0.36)	6.37 (10.90)	215.00	<0.001	−0.79
Hypopnea episodes per hour	0.50 (0.36)	2.55 (2.76)	179.00	0.007	−1.04
Arousal index score events per hour	7.13 (2.18)	10.34 (4.35)	−2.72	0.01	−0.93
Respiratory related arousals per hour	0.42 (0.36)	2.75 (2.86)	209.50	<0.001	−1.14
Awake SaO$_2$	96.58 (0.52)	96.16 (1.02)	85.50	0.25	0.52
Average SaO$_2$ desaturation	2.50 (2.02)	4.00 (1.16)	−2.34	0.03	−0.91
Children's Sleep Habits Questionnaire daytime sleepiness subscale	14.78 (3.15)	13.00 (3.16)	1.37	0.19	0.56
Children's Sleep Habits Questionnaire sleep-disordered breathing subscale	5.43 (2.51)	4.40 (1.35)	1.02	0.34	0.51

All polysomnography values were calculated based on n=31. No OSAS defined as apnea-hypopnea index (AHI) ≤1.5; OSAS defined as AHI >1.5. Parent reports were based on no OSAS (n=9) and OSAS (n=17). OSAS, obstructive sleep apnea syndrome; SaO$_2$, saturation of oxygen in hemoglobin.

expense of slow-wave sleep ($t(29)$=2.12, p=0.04). The percentage of REM sleep ($t(29)$=−0.98, p=0.33) and stage 2 sleep ($t(29)$=−0.25, p=0.81) did not differ statistically between groups with and without OSAS.

OSAS in relation to cognitive and behavioral function

Table III describes the performance of children with Down syndrome with and without OSAS on measures of cognition and behavior. Whereas Full-scale (p=0.21) and Non-verbal IQ (p=0.46) did not differ between the groups, Verbal IQ did differ, with scores 9 points lower in the group with OSAS (p=0.006, d=0.91, large effect). The CANTAB IED task, a measure of executive function, was also completed less well by children with Down syndrome
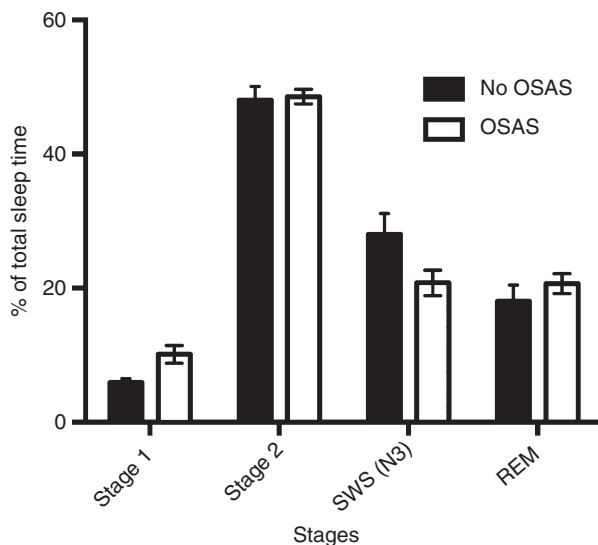

Figure 1: Sleep architecture in children with Down syndrome with and without obstructive sleep apnea syndrome (OSAS). SWS, slow wave sleep; REM, rapid eye movement.

and OSAS (p=0.03, d=1.06, large effect). There were no differences in the adaptive behavior standard score (p=0.31), CANTAB Paired-Associates Learning task mean errors (p=0.13), CANTAB Simple Reaction Time task median reaction time (p=0.42), parent-reported ADHD symptoms (p=0.68), and experimenter-reported ratings of attention (p=0.28).

While several important background factors were not statistically different between the children with and without OSAS (age, BMI), the possibility remains that these factors could influence outcome. Correlations between age, BMI, and OSAS-related cognitive outcomes were all non-significant, suggesting that the relation between OSAS and cognition was not related to these factors (KBIT-2 Verbal IQ standard score and BMI: rho=0.08, p=0.67; BMI and IED stages completed: rho=−0.15, p=0.42; KBIT-2 Verbal IQ standard score and age: rho=−0.04, p=0.84; age and IED stages completed: rho=0.05, p=0.81).

To elucidate the sleep-related mechanisms relating to cognitive differences, we conducted tests of the independent correlations between OSAS-related differences in sleep variables, the Verbal IQ standard score, and CANTAB IED performance. The results showed no significant correlations between mean oxygen desaturation (rho=−0.16, p=0.40), arousals per hour (rho=−0.26, p=0.16), or percentage of time in slow-wave sleep (rho=−0.09, p=0.64) and Verbal IQ. For the cognitive flexibility measure (IED), there were no significant correlations with oxygen desaturation (rho=−0.31, p=0.10), arousals per hour (rho=0.10, p=0.62), or percent time in slow-wave sleep (rho=0.10, p=0.60).

DISCUSSION

In this study we examined relations between OSAS and cognition in an unreferred community cohort of school-aged children with Down syndrome. In total, the results raise concerns regarding the comorbidity of OSAS and Down syndrome; in this population, already at early risk for neurodevelopmental deficits, OSAS could have an

Table III: Cognition and behavior in children with Down syndrome with and without OSAS

Measure	No OSAS (*n*=12), mean (SD)	OSAS (*n*=19), mean (SD)	*t* (Mann–Whitney *U*)	*p*	Effect size (*d*)
KBIT-2, Full-scale IQ	48.92 (10.65)	43.84 (6.18)	82.50	0.21	0.58
KBIT-2, Non-verbal IQ	52.67 (13.55)	48.53 (9.92)	95.50	0.46	0.35
KBIT-2, Verbal IQ	54.42 (11.54)	45.11 (8.83)	48.50	0.006	0.91
Scales of Independent Behavior-Revised standard score	60.25 (29.16)	51.56 (17.36)	1.03	0.31	0.36
CANTAB Paired-Associates Learning task mean errors to success	6.05 (3.89)[a]	8.18 (4.04)	133.00	0.13	−0.54
CANTAB Intra-Extra Dimensional Set Shift stages completed	8.09 (0.83)[a]	5.32 (3.59)	55.50	0.03	1.06
CANTAB Simple Reaction Time task median correct latency	745.05 (203.26)[a]	706.58 (280.64)	85.00	0.42	0.19
Conners ADHD Index[b]	7.67 (5.57)	6.76 (5.75)	0.42	0.68	0.16
Experimenter rating of attention (Scale: 1–5)	4.22 (0.55)	3.93 (0.71)	1.11	0.28	0.46

No OSAS defined as apnea-hypopnea index (AHI ≤1.5); OSAS defined as AHI >1.5. [a]Data from one child were lost owing to computer error. [b]ADHD reports based on no OSAS (*n*=12) or OSAS (*n*=17). OSAS, obstructive sleep apnea syndrome; KBIT-2, Kaufman Brief Intelligence Test – 2nd edition; ADHD, attention-deficit–hyperactivity disorder.

additional impact on cognitive function. Specifically, we found a 9-point difference in Verbal IQ and impairments in cognitive flexibility in children with Down syndrome and comorbid OSAS (AHI >1.5) compared with children below the clinical cut-off generated by PSG (AHI ≤1.5).

The cognitive differences reported here could have a substantial impact on day-to-day functioning in this group. We report reductions in two well-established domains of impairment in this population.[11] While a 9-point difference in Verbal IQ is roughly equivalent to the point-value for findings reported in other populations with OSAS, the functional impact of this difference is dramatically different at this IQ level – quite probably leading to substantial differences in everyday language use. Beyond the impact on verbal learning, OSAS also relates to measures of cognitive flexibility, findings that are in concert with the reported impairments in individuals without Down syndrome suffering from OSAS.[10] Overall, these findings suggest that the cognitive differences due to OSAS in individuals with Down syndrome may be quite specific; the measures used here (e.g. the ACTB) may help guide measurement selection for future outcome studies conducted in larger samples. It should be acknowledged that these findings alone do not allow one to decide the direction of these effects, and longitudinal studies must be conducted to determine if sleep disruption relates to losses or stagnation in cognitive development.

Using the sample reported here, we were able to compare children of equivalent age, BMI, and background health status. These findings help to strengthen our conclusions that the effects reported are indeed related to sleep. Future research should explore the impact of sleep disruption across longitudinal follow-up assessments or through experimental manipulations to add to our understanding of the direction of these effects. Another approach would be to measure if cognition can be improved post-treatment (i.e. after tonsils and adenoids surgery or nasal continuous positive airway pressure treatment, a method delivering airflow that keeps the airway open during sleep).

Given the data presented here, it is also unlikely that the relation between OSAS and these cognitive outcomes is secondary to daytime sleepiness, poor attention during the testing session, or generalized difficulty. Parent ratings of ADHD and laboratory assessments of attention and processing speed were not significantly different between children with and without OSAS. While OSAS related to an IQ measure, this relation was specific to Verbal IQ. No relation between the presence of OSAS and other measures of generalized intellectual function (e.g. adaptive behavior standard scores, Full-scale IQ) was found.

Rather, it is likely that the specific pattern of impacted cognitive functions (e.g. verbal learning and executive function) reflects the disrupted function of specific neural systems and associated learning processes across sleep periods. The concurrent impact on verbal learning and reductions in slow-wave sleep is particularly striking given recent research suggesting that sleep-dependent learning in children may facilitate the acquisition of new word learning and abstraction of rules.[27] Sleep-dependent consolidation of explicit knowledge, such as the vocabulary tested in a Verbal IQ measure, is more likely to occur during slow-wave sleep.[28] Indeed, slow-wave sleep was most affected by the presence of OSAS in this investigation. Although the OSAS-related sleep variables were not independently related to cognitive differences in the current investigation, this finding is not surprising given the time gaps (up to 3mo) between the sleep study and cognitive assessment. Future work should assess the relation between mechanisms of sleep disruption and learning across shorter time intervals.

Some study limitations should be noted. While laboratory PSG is the criterion standard assessment for sleep disorders, we administered PSG in the home environment. The completion of this study with ambulatory PSG allowed for the recruitment of a sample that better represents the full range of children with Down syndrome, not only those whose parents expressed concerns. In further validation of our sleep measurement, we reported a significant correlation (r=0.89) between our studies and independently administered laboratory PSG. We also examined children's outcomes in relation

to completion status of the PSG, finding no differences when studies were poor and could not be included in this report (*n*=7 in total). The current study's sample is unique because it includes a number of children without clinical levels of OSAS; however, the overall size of the sample is an additional limitation. Future studies should examine the effects of sleep and associated medical conditions in larger cohorts of children with Down syndrome.

Given these results and past work highlighting the extensive nature of sleep disruption in this group, effective treatment and screening approaches are needed. Our finding that parent report of OSAS symptoms (e.g. snoring) was not related to objective measures of sleep disruption is of importance and in agreement with past literature; it also demonstrates the need for screening with PSG.[3] Treatment approaches for OSAS are improving and could be beneficial for those in whom OSAS is detected. While the effectiveness of tonsils and adenoids surgery has been debated, new methods of imaging the structure of the airway to guide surgery may prove useful in increasing its efficacy.[29] Other methods for treating OSAS in children are also improving, and some programs have achieved better adherence. Evidence of the success of those efforts comes from a recent study showing that 72% of children with Down syndrome accepted and adhered to nasal continuous positive airway pressure.[30]

While the current study focused on school-aged children, OSAS may be present throughout the life of individuals with Down syndrome, potentially affecting critical periods of cognitive development or periods of developmental risk. Based on these findings in school-aged children, it is important to investigate the impact of OSAS in toddlers with DS, as they often show a decline in IQ and the inability to keep pace with peers.[11] Fernandez and Edgin[13] have recently proposed that OSAS could potentially exacerbate Alzheimer disease-related decline in this group. Future studies should examine the impact of OSAS on cognition from infancy to adulthood.

Broadly, these results suggest that more work is needed to understand the influence of poor sleep on learning in Down syndrome and other neurodevelopmental syndromes, many of which demonstrate disordered sleep to some extent. Beyond the clear implications of these findings for individuals with Down syndrome, they highlight the importance of adequate detection and treatment of OSAS and related sleep disorders across typically and atypically developing populations in general.

Conflict of interest
The authors have stated that they had no interests that might be perceived as posing a conflict or bias.

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