

A predictive model for obstructive sleep apnea and Down syndrome

Brian G. Skotko^{1,2} | Eric A. Macklin³ | Marco Muselli^{4,5} | Lauren Voelz⁶ | Mary Ellen McDonough¹ | Emily Davidson^{2,6} | Veerasathpurush Allareddy⁷ | Yasas S. N. Jayaratne⁸ | Richard Bruun⁹ | Nicholas Ching¹⁰ | Gil Weintraub¹¹ | David Gozal¹² | Dennis Rosen^{2,13}

¹ Down Syndrome Program, Division of Medical Genetics, Department of Pediatrics, Massachusetts General Hospital, Boston, Massachusetts

² Department of Pediatrics, Harvard Medical School, Boston, Massachusetts

³ Biostatistics Center, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts

⁴ Rulx, Inc., Boston, Massachusetts

⁵ Institute of Electronics, Computer, and Telecommunication Engineering, Italian National Research Council, Genoa, Italy

⁶ Down Syndrome Program, Division of Developmental Medicine, Department of Medicine, Boston Children's Hospital, Boston, Massachusetts

⁷ Department of Orthodontics, The University of Iowa College of Dentistry and Dental Clinics, Iowa City, Iowa

⁸ Division of Orthodontics, Department of Craniofacial Sciences, University of Connecticut School of Dental Medicine, Farmington, Connecticut

⁹ Department of Dentistry, Boston Children's Hospital, Boston, Massachusetts

¹⁰ Children's Dentistry, El Cerrito, California

¹¹ Beth Israel Deaconess Medical Center, Boston, Massachusetts

¹² Department of Pediatrics, University of Chicago, Chicago, Illinois

¹³ Division of Respiratory Diseases, Department of Medicine, Boston Children's Hospital, Boston, Massachusetts

Obstructive sleep apnea (OSA) occurs frequently in people with Down syndrome (DS) with reported prevalences ranging between 55% and 97%, compared to 1–4% in the neurotypical pediatric population. Sleep studies are often uncomfortable, costly, and poorly tolerated by individuals with DS. The objective of this study was to construct a tool to identify individuals with DS unlikely to have moderate or severe sleep OSA and in whom sleep studies might offer little benefit. An observational, prospective cohort study was performed in an outpatient clinic and overnight sleep study center with 130 DS patients, ages 3–24 years. Exclusion criteria included previous adenoid and/or tonsil removal, a sleep study within the past 6 months, or being treated for apnea with continuous positive airway pressure. This study involved a physical examination/medical history, lateral cephalogram, 3D photograph, validated sleep questionnaires, an overnight polysomnogram, and urine samples. The main outcome measure was the apnea-hypopnea index. Using a Logic Learning Machine, the best model had a cross-validated negative predictive value of 73% for mild obstructive sleep apnea and 90% for moderate or severe obstructive sleep apnea; positive predictive values were 55% and 25%, respectively. The model included variables from survey questions, medication history, anthropometric measurements, vital signs, patient's age, and physical examination findings. With simple procedures that can be collected at minimal cost, the proposed model could predict which patients with DS were unlikely to have moderate to severe obstructive sleep apnea and thus may not need a diagnostic sleep study.

KEYWORDS

Down syndrome, obstructive sleep apnea, trisomy 21

Abbreviations: 5-HIAA, 5-hydroxyindoleacetic acid; AHI, obstructive apnea-hypopnea index; CSHQ, Children's Sleep Habits Questionnaire; DOPAC, 3,4-dihydroxyphenylacetic acid; DS, Down syndrome; GABA, γ -aminobutyric acid; LLM, logic learning model; NPV, negative predictive value; OSA, obstructive sleep apnea; PEA, phenylethylamine; PPV, positive predictive value; SpO₂, wake peripheral oxyhemoglobin saturation; SRBD, Sleep-Related Breathing Disorders (SRBD) Scale of the Pediatric Sleep Questionnaire; TST, total sleep time.

Correspondence

Brian G. Skotko MD, MPP, Down Syndrome Program, Massachusetts General Hospital, 185 Cambridge Street, Room 2.224, Boston, MA 02114.

Email: bskotko@mgh.harvard.edu

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1 | INTRODUCTION

Down syndrome (DS) is the most common chromosomal condition, occurring in an estimated one out of every 792 live births (de Graaf, Buckley, & Skotko, 2015), with approximately 206,000 Americans living with this genetic variance (de Graaf, Buckley, & Skotko, 2016). Obstructive sleep apnea (OSA) is prominent in this population, with an estimated prevalence ranging between 55% and 97% (Austeng et al., 2014; Ng et al., 2006; Shott et al., 2006), compared to 1–4% in the otherwise healthy pediatric population (Lumeng & Chervin, 2008). Persons with DS are prone to developing OSA because of associated anatomical and medical differences (Fung, Witmans, Ghosh, Cave, & El-Hakim, 2012; Shott, 2006).

In the typically developing population, OSA is associated with significant morbidities that include short- and long-term cognitive deficits (Halbower et al., 2006), behavioral disturbances (Mitchell & Kelly, 2007), hypertension (Li et al., 2008), altered glycemic homeostasis (Tamura, Kawano, Watanabe, & Kadota, 2008), increased cardiovascular and cerebrovascular disease (Nishibayashi, Miyamoto, Miyamoto, Suzuki, & Hirata, 2008; Parish & Somers, 2004), failure to thrive (Brouillette, Fernbach, & Hunt, 1982), pulmonary hypertension (Brouillette et al., 1982), and even death (Bradley & Phillipson, 1985). In people with DS, who already have intellectual disabilities, sleep disruption can also lead to executive functioning deficits (Chen, Spano, & Edgin, 2013). Further, OSA in this population is associated with a decrease in verbal IQ, cognitive flexibility (Breslin et al., 2014), visuoperceptual skills (Andreou, Galanopoulou, Gourgoulanis, Karapetsas, & Molyvdas, 2002), and an increase in mood disorders (Capone, Aidikoff, Taylor, & Rykiel, 2013). Thus, detecting OSA early in people with DS may help reduce the incidence of these comorbidities and improve neurocognitive functioning.

The American Academy of Pediatrics recommends that all children with DS undergo a sleep study evaluation—the gold standard for OSA detection—by the age of 4, or sooner if symptoms are present (Bull & Committee on Genetics, 2011). Even after surgical treatment, however, OSA may persist or recur and must therefore be screened for annually, often necessitating multiple sleep studies over a lifetime (Bull & Committee on Genetics, 2011). Polysomnograms, while noninvasive, are generally uncomfortable and often poorly tolerated

by individuals with DS, as they are asked to sleep in an unfamiliar environment. Parents must spend a night in the hospital along with their children, and one technician is often required for each patient with DS. Pediatric sleep studies are also expensive and are not readily available in many parts of the country. Given the limited availability, inconvenience, cost, and intolerance of overnight polysomnography, many have highlighted the need for better screening tools to predict OSA in individuals with DS, thereby reducing the need for polysomnography (Lin, Davey, Horne, & Nixon, 2014; Rosen, Lombardo, Skotko, & Davidson, 2011). Although a few studies, to date, have attempted to examine this, none has been able to identify a practical screening tool for OSA that could replace polysomnography in at least some cases (de Miguel-Diez, Villa-Asensi, & Alvarez-Sala, 2003; Marcus, Keens, Bautista, von Pechmann, & Ward, 1991; Shott et al., 2006).

The objective of the present study was to construct a clinically useful predictive model combining signs, symptoms, craniofacial anatomical measurements, and metabolic markers to screen for OSA in patients with DS.

2 | PATIENTS AND METHODS**2.1 | Patients**

All patients with DS, over the age of 3, already attending the Down Syndrome Program at Boston Children's Hospital were sequentially invited to participate. Exclusion criteria included having an adenotonsillectomy, adenoidectomy, tonsillectomy, sleep study within the past 6 months, or being treated for OSA with continuous positive airway pressure. We applied these criteria because we did not want to assume that recurrent OSA would be modeled similarly to primary OSA. Patients from both English- and Spanish-speaking families were recruited. Informed consent/assent was obtained from participants.

2.2 | Study Procedures

This was an observational, prospective cohort study, approved by the institutional review boards of Boston Children's Hospital (protocol

10-03-0092) and Massachusetts General Hospital (protocol 2012P002062). This protocol involved 2–3 study visits at Boston Children's Hospital with the first taking place during a regularly scheduled visit to the Down Syndrome Program and included a physical examination/medical history, lateral cephalogram, three-dimensional photography, and completion of survey instruments. In some instances, the lateral cephalograms and three-dimensional photographs were arranged for a subsequent visit. After these measures were completed, the participant returned for an overnight polysomnogram, where evening and next morning urine samples were also collected.

2.2.1 | Survey instruments

Parents or legal guardians completed the Sleep-Related Breathing Disorders (SRBD) Scale of the Pediatric Sleep Questionnaire and the Children's Sleep Habits Questionnaire (CSHQ), previously validated instruments to assess OSA in the general pediatric population (Chervin, Hedger, Dillon, & Pituch, 2000; Owens, Spirito, & McGuinn, 2000). Since we were using these measures as potential predictive variables of OSA—and not for reporting summary statistics or trends of sleep behaviors—validation in people with DS was not necessary. The survey instruments were available in both English and Spanish.

2.2.2 | Physical examination/medical history

Demographic data were collected for each participant: age, sex, ethnicity, and race. Two independent sets of anthropometric measurements were collected for each participant: height, weight, body mass index, sedentary blood pressure, and wake peripheral oxyhemoglobin saturation (SpO_2) by transcutaneous pulse oximetry on the index finger. A medical history was collected followed by a standardized physical examination which included neck circumference, subjective presence of macroglossia, a Mallampati score classification (Class I: Soft palate, fauces, uvula, pillars visible; Class II: Soft palate, fauces, uvula visible; Class III: Soft palate, base of uvula visible; Class IV: Soft palate not visible at all), and a Friedman/Brodsky score classification (Class I: tonsils are hidden within the pillars; Class II: tonsils extend to the pillars; Class III: tonsils extend beyond the pillars but not to the midline; Class IV: tonsils extend to the midline). Any current use of medications for asthma, gastrointestinal reflux (GERD), or thyroid disease was also documented. A standardized dental examination was performed, which included assessment for maxillary hypoplasia, retrognathia, and macroglossia. Overbite was recorded as a percentage, and overjet was recorded in millimeters.

2.2.3 | Lateral cephalograms

A lateral cephalogram was attempted for each patient using the Sirona ORTHOPHOS XG Plus lateral cephalograph system (Sirona Dental Systems, Inc., Charlotte, NC). Two authors (N.C. and V.A.) analyzed 72 anthropometric measurements estimated from the cephalograms (Dolphin version 11.7, Dolphin Imaging & Management, Chatsworth, CA), some already shown to be predictors of OSA in the general population (Lee, Chan, Grunstein, & Cistulli, 2009; Wong et al., 2008) (e-Figure 1; e-Tables 1–3).

2.2.4 | Three-dimensional digital photography

The 3dMDface stereophotography system (3dMD, Atlanta, GA) was used for capturing 3D facial images. The system consists of six synchronized cameras (four grayscale and two color) positioned at specific angulations. The six images acquired simultaneously are then merged using a complex triangulation algorithm to generate a lifelike 3D image of the face. We used anthropometric landmarks identified in previous research on facial morphology (Jayaratne, Deutsch, & Zwahlen, 2013; Jayaratne, Deutsch, & Zwahlen, 2014a,b; Jayaratne & Zwahlen, 2014), and additional ones, which we hypothesized might be associated with OSA (e-Tables 4 and 5).

2.2.5 | Urine metabolic markers

On the evening before and the morning after their polysomnograms, each participant was asked to provide a urine sample, which was analyzed using a previously validated, multiplexed, enzyme-linked immunosorbent assay method for assessment of several neurotransmitters in the lab of one author (D.G.) (Kheirandish-Gozal, McManus, Kellermann, Samiei, & Gozal, 2013). Assays included epinephrine, norepinephrine, dopamine, serotonin, glycine, taurine, γ -aminobutyric acid (GABA), glutamate, phenylethylamine (PEA), aspartic acid, histamine, 3,4-dihydroxyphenylacetic acid (DOPAC), 5-hydroxyindoleacetic acid (5-HIAA), tyramine, and tryptamine. All samples were assayed in duplicate and values were retained if they were within 10% of each other. Urine creatinine level was measured for each sample, and individual urine neurotransmitter levels were corrected for corresponding urine creatinine concentration. Creatinine-corrected assay levels from a sample of 43 age- and gender-matched neurotypical children without OSA were used to calculate normative values. Previous studies have identified alterations in some of these metabolic markers in neurotypical children with OSA with cognitive deficits (Gozal et al., 2009).

2.2.6 | Polysomnograms

All overnight polysomnographic studies were performed in the Boston Children's Hospital Sleep Laboratory. The sleep session was recorded by video and audio. Parameters measured included 10-lead electroencephalogram; electrooculogram; submental electromyogram and anterior tibial electromyography; airflow measurement with oronasal thermistor and nasal pressure transducer; thoracoabdominal movement measured via impedance pletysmography; pulse oximetry; capnography; and video and microphone recording to assess snoring, breathing patterns, and movement. The polysomnogram was performed using digital polysomnographic equipment (Natus Sleepworks, Natus Medical Incorporated, San Carlos, CA), and oximetry was done using Masimo Rad 9 with SET Technology, using a 2-sec window.

All participants were monitored and continuously observed by a trained technician. One board-certified clinician (D.R.) analyzed each polysomnogram based upon the American Academy of Sleep Medicine (AASM)'s Manual for the Scoring of Sleep and Associated Events Respiratory Rules for Children (American Academy of Sleep Medicine, 2015). Sleep stages, total sleep time, leg movements, and arousal index were routinely scored. Obstruction was scored per the 2007 AASM

manual for scoring of sleep and associated events as follows. Events were scored as obstructive apnea when they were lasting for two breath cycles or greater, associated with a $\geq 90\%$ reduction in airflow measured by thermistor compared to baseline for $\geq 90\%$ of the discrete respiratory event, and were associated with ongoing respiratory effort for the duration of the decreased flow. Events were scored as obstructive hypopnea when they were lasting for two breath cycles or greater, associated with a $\geq 50\%$ reduction in airflow measured by nasal-pressure signal amplitude compared to baseline for $\geq 90\%$ of the discrete respiratory event, were associated with ongoing respiratory effort for the duration of the decreased flow, and were associated with arousal, awakening or desaturation of $\geq 3\%$. Sleep was scored in 30-sec epochs. The apnea-hypopnea index (AHI), calculated as total hypopneas and apneas per hour, was the main outcome measure and expressed as number of obstructive events per hour of total sleep time (TST). Only epochs in which definable EEG and respiratory signals were present for $> 50\%$ of the 30-sec period were counted. A minimum of 480 scored epochs (240 min) was necessary for a polysomnogram to be included in this study.

2.3 | Statistical Analysis

The sample size of 100 participants with completed sleep studies was selected in order to have greater than 80% power to declare an independent predictor of OSA significant in both the discovery and validation analyses with the following assumptions: the predictor is normally distributed, the odds ratio over one standard deviation for predicting OSA is at least 2.0, a two-tailed test with $P < 0.05$ is considered significant, and the prevalence of OSA is 50% in our sample. Study data were collected and managed using REDCap electronic data capture tools hosted at Boston Children's Hospital (Harris et al., 2009). A model to predict three levels of OSA severity (none: $\text{AHI} \leq 1/\text{hrTST}$; mild: $1 < \text{AHI} \leq 5/\text{hrTST}$; moderate to severe: $\text{AHI} > 5/\text{hrTST}$) was developed using a Logic Learning Machine (LLM) by using the Rulex 3.1 suite (www.rulex-inc.com) (see e-Section 1).

3 | RESULTS

3.1 | Participants

We enrolled a total of 130 patients with DS of whom 102 completed polysomnography and were included in analyses, achieving our targeted sample size (Table 1). The median age of patients included in our study was 5.6 years with a range of 3–24.4 years.

3.2 | Predictive Model

In our sample, 45 (44.1%) patients had some degree of OSA (Table 2). The best LLM model had a cross-validated negative predictive value (NPV) of 72% (95%CI: 64.1–80.9%) for an $\text{AHI} > 1$ and 90% (95%CI: 84.7–95.7%) for $\text{AHI} > 5$. The positive predictive values (PPV) were 55% (95%CI: 45.2–64.5%) and 25% (95%CI: 17.2–33.8%), respectively. The specificity was 51% and 55% and the sensitivity was 76% and 72%, respectively. The false negative rates were 24% and 28%,

and the false positive rates were 49% and 45%, respectively (Table 2). For $\text{AHI} > 5$, the negative likelihood ratio was 0.51, and the positive likelihood ratio was 1.6. As such, the diagnostic odds ratio was 3.1, meaning that there was a 3.1-fold higher odds of the model being negative when the patient does not have moderate/severe OSA than when the patient does have moderate/severe OSA, or conversely, a 3.1-fold higher odds of the model being positive when the patient does have moderate/severe OSA than when the patient does not have moderate/severe OSA.

The variables used in the final model included CSHQ and SRBD survey questions, the patient's medication history (e.g., currently being treated for thyroid disease, asthma, or GERD), anthropometric measurements (e.g., BMI percentile, height percentile, weight percentile, sedentary blood pressure percentile, awake SpO_2), the patient's age, sex, race, and physical examination findings (e.g., Mallampati score, presence of macroglossia, neck circumference). The 15 most relevant variables (of 101 in total) were particular CSHQ questions, SRBD questions, and the hypertension percentile (Figure 1), indicating that parental responses on sleep questionnaires best discriminated patients with versus without OSA. The complete set of 300 rules used for this model is available as an online data supplement (e-Spreadsheet 1 and e-Spreadsheet 2).

Variables from the lateral cephalograms, 3D photographs, dental examinations, and urine metabolic markers did not improve the positive predictive value or negative predictive value of our model. Only half of participants were able to complete these items, mostly due to younger patients being unable or unwilling to tolerate these study components. As such, these variables are not included in our final model (e-Spreadsheet 2), but the results from alternative models are described in e-Table 5. The 15 most relevant variables for “no OSA” and “mild OSA” from these alternative models are described in e-Figure 2.

4 | DISCUSSION

Using measures that can be collected at minimal cost and effort in a primary care setting, we have identified a predictive model of OSA in patients with DS. Our model's most promising feature for clinical practice is its NPV for moderate and severe OSA in children with DS: a negative result predicts with 90% accuracy that moderate to severe OSA is not present. There was a threefold higher odds of the model being negative when the patient did not have moderate/severe OSA than when the patient did have moderate/severe OSA. This may obviate the need for sleep studies particularly when it seems unlikely they will be tolerated or when such studies are unavailable or unaffordable. A positive result from our model would need to be confirmed by polysomnogram given the relatively high frequency of false positives.

The cost and time to implement would be minimal: a parent/guardian would need to complete two short questionnaires, and physicians would need to add a few items to their routine assessments. To be specific, the physician would need to collect the following variables: age, gender, race, height, weight, body mass index, sedentary

TABLE 1 Participant characteristics (N = 102)^{a,b}

Variable	Details	Overall	OSA Status, % (N)		P
			No OSA	OSA	
Age group, % (N)	3–5 years	54.9 (56)	63.2 (36)	44.4 (20)	0.30
	6–10 years	29.4 (30)	24.6 (14)	35.6 (16)	
	11–15 years	10.8 (11)	8.8 (5)	13.3 (6)	
	16–24 years	4.9 (5)	3.5 (2)	6.7 (3)	
Gender, % (N)	Male	59.8 (61)	57.9 (33)	62.2 (28)	0.69
	Female	40.2 (41)	42.1 (24)	37.8 (17)	
Ethnicity, % (N)	Not Hispanic	71.6 (73)	70.2 (40)	73.3 (33)	0.95
	Hispanic/Latino	17.6 (18)	19.3 (11)	15.6 (7)	
	Unknown	10.8 (11)	10.5 (6)	11.1 (5)	
Race, % (N)	White	59.8 (61)	63.2 (36)	55.6 (25)	0.36
	Black	7.8 (8)	8.8 (5)	6.7 (3)	
	Asian	5.9 (6)	1.8 (1)	11.1 (5)	
	Other race	8.8 (9)	7.0 (4)	11.1 (5)	
	Multiracial	4.9 (5)	7.0 (4)	2.2 (1)	
	Unknown	12.7 (13)	12.3 (7)	13.3 (6)	
BMI status, % (N)	Underweight	3.9 (4)	3.5 (2)	4.4 (2)	0.089
	Normal	42.2 (43)	35.1 (20)	51.1 (23)	
	Overweight	30.4 (31)	40.4 (23)	17.8 (8)	
	Obese	23.5 (24)	21.1 (12)	26.7 (12)	
Awake SpO ₂ (%)	(mean ± SD)	97.5 ± 2.8	97.6 ± 2.7	97.3 ± 3.0	0.761
% of Night with SpO ₂ ≥ 95%	Median (range)	89.9 (1.2, 100)	92.5 (10.0, 100)	88.9 (1.2, 100)	0.548

^aA total of 28 participants of the original 130 withdrew prior to completing a polysomnogram: 20 caregivers decided that they no longer wanted to have their child complete a polysomnogram; four participants were not able to tolerate the polysomnogram and no useable data were gathered; two participants had clinically warranted adenotonsillectomies after consenting, excluding them from further participation; one caregiver felt the commuting time to our Sleep Center was a burden; and one felt their child with DS had too many other clinical obligations to dedicate time to research.

^bOf these patients who completed a polysomnogram, 101 of their caregivers completed the SRBD, and 100 completed the CSHQ; 102 participants had medical histories taken and physical exams performed; 85 had 3D photographs; 56 completed a dental exam; 26 had lateral cephalograms; and 54 were able to give night-time urine samples, and 51 morning samples.

blood pressure, wake peripheral SpO₂, neck circumference, assessment of macroglossia, a Mallampati score classification, a Friedman/Brodsky score classification, and documentation of current medical treatment for asthma, gastrointestinal reflux (GERD), or thyroid disease. Before we recommend implementation, however, we will be validating the model in a new set of patients over the next several years. Once this is done, the model will be automated on a web page, giving providers a quick online tool to calculate the risk of OSA in their patients with DS and determine whether a diagnostic sleep study might be warranted.

TABLE 2 Cross-tabulation of cross-validated predictions of OSA severity versus observed OSA severity by polysomnography

	Results from polysomnograms		
	AHI ≤ 1	1 < AHI ≤ 5	AHI > 5
Predicted results			
AHI ≤ 1	29	8	3
1 < AHI ≤ 5	3	6	2
AHI > 5	25	13	13

Our study differs from previous research attempts to identify a predictive model for OSA in patients with DS by including a more robust set of independent variables, many of which proved to be important (de Miguel-Diez et al., 2003; Shott et al., 2006). In 1991, researchers compared sedated nap recordings to non-sedated overnight polysomnographies in 16 children with DS (Marcus et al., 1991). The nap studies underestimated the sleep abnormalities identified in the overnight studies by 30%. In 2006, researchers asked parents of 35 children with DS to complete three questions related to nighttime snoring or difficulty breathing from the CSHQ (Shott et al., 2006). Afterwards, all children with DS had polysomnograms, and the parental reports on the questionnaire were not found to be predictive of the results. Only 36% of the children whose parents reported sleep problems had evidence of OSA; conversely, 54% of the children whose parents reported no problems had abnormal sleep study results. Their study's primary aim was prevalence estimation, so the evaluation of predictors for OSA was limited. In another prospective study of 108 children with DS, ages 1–18 years, researchers gathered anthropometric measurements (e.g., body mass index) prior to overnight polysomnograms (de Miguel-Diez et al., 2003). Three variables were

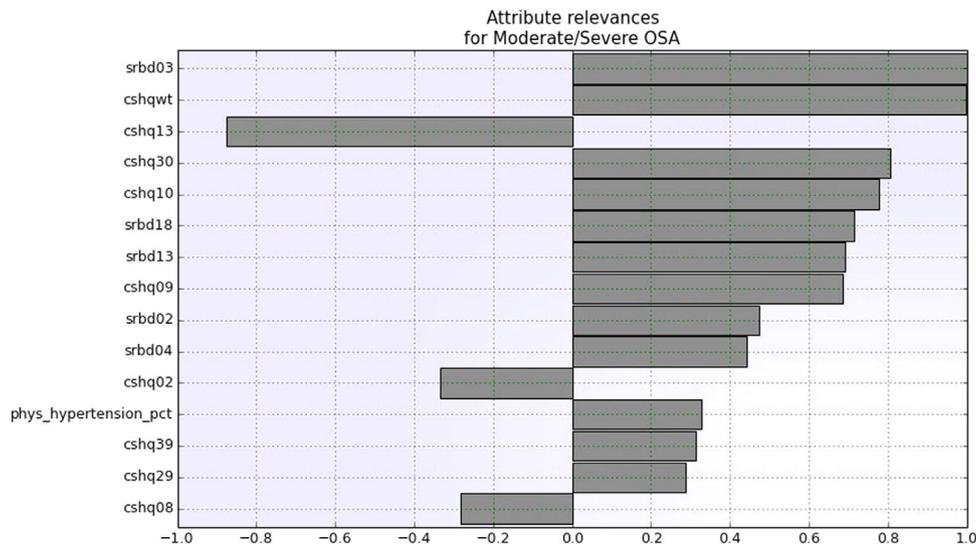


FIGURE 1 The 15 most relevant variables for predicting moderate or severe OSA. srbd03: While sleeping, does your child snore loudly?, cshqwt: wake time; cshq13: child sleeps too little; cshq30: child awakens alarmed by a frightening dream; cshq10: child struggles at bedtime (cries, refuses to stay in bed, etc.); srbd18: this child often has difficulty organizing tasks and activities; srbd13: this child often has difficulty organizing tasks and activities; cshq09: child resists going to bed at bedtime; srbd02: while sleeping, does your child always snore?; srbd04: while sleeping, does your child have heavy or loud breathing?; cshq02: while sleeping, does your child have heavy or loud breathing?; phys_hypertension_pct: hypertension percentile; cshq39: adults or siblings wake up child; cshq29: child awakens during the night screaming, sweating, and inconsolable; cshq08: child is ready to go to bed at bedtime. Variables further defined in e-Spreadsheet 1 in Supplementary Materials. Relevance is a sensitivity-weighted measure of increase in false positive rate when a given predictor is dropped from the model defined mathematically in e-Section 2 in Supplementary Materials

noted to be predictors of OSA: age less than 8 years, male gender, and tonsillar hypertrophy. Predictive accuracy of the model was not reported. A separate group of researchers found that higher BMI was associated with OSA among individuals with DS, as has been observed in the general population (Shires et al., 2010). Lastly, in a study of 31 children with DS, ages 2–16 years, researchers demonstrated that daytime speech difficulties and snoring were significantly associated with a reduction in overnight blood oxygen levels as measured by at-home oximeters (Stores & Stores, 2014). Other research, however, has demonstrated that overnight pulse oximetry has a poor sensitivity for OSA in patients with DS when used in isolation (Jheeta, McGowan, & Hadjikoumi, 2013). Overall, the results of all of these studies did not translate into a practical screening tool for OSA in persons with DS that could be used by physicians before ordering an overnight polysomnography.

Our study, however, is not without limitations, including participant compliance. Whereas 102 participants completed a polysomnogram, satisfying our target sample size, only half were able to complete the dental exams, lateral cephalograms, and urine samples. This was mostly due to younger patients being unable or unwilling to tolerate these study items. While a higher completion rate of these measures might have identified their importance as predictors and contributed to improved accuracy of OSA prediction, we consider the noncompliance, itself, to be clinically meaningful, demonstrating the practical challenges that physicians may encounter if trying to implement these measures. Only one board-certified physician scored the sleep studies to simulate real-world practice; it is possible that another physician might have scored some studies differently, although this is mitigated by the strict criteria of the AASM's Manual for the Scoring of Sleep and

Associated Events Respiratory Rules for Children (American Academy of Sleep Medicine, 2015).

In the end, our model included the variables that were easily collected and of prognostic importance. In our study population, 44% of patients had some form of OSA, compared to 55–97% of patients with DS reported to have OSA in the literature. These prevalence numbers, however, are all based on convenience samples, so the true population prevalence of OSA in patients with DS is unknown. Since NPV is dependent on the prevalence of disease (in this case, OSA), we also calculated a ratio independent of this probability. We found that there was a threefold higher odds of the model being negative when the patient did not have moderate/severe OSA than when the patient did have moderate/severe OSA, making it worthy of further validation testing.

Our model's NPV for mild OSA is not as high as it is for moderate or severe OSA. To this extent, implementation of our model might lead to false negatives for mild OSA. Our model's strength lies in excluding moderate or severe OSA. There will still be some false negatives; so in resource-rich areas, physicians may still elect to pursue polysomnograms as the first-line screen. However, in areas of the country where polysomnograms are less available or affordable or when patients with DS are unable or unwilling to tolerate a sleep study, our model might offer, after validation, a viable alternative for providers looking to exclude moderate or severe OSA.

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CONFLICT OF INTEREST

The authors have no financial conflict of interests related to the content of this study. B.G.S. serves in a non-paid capacity on the Board of Directors for the Band of Angels Foundation, a non-profit organization, and on the Medical and Science Advisory Board for the Massachusetts Down Syndrome Congress. He is a non-paid clinical advisory to the National Center for Prenatal and Postnatal Down Syndrome Diagnoses Resources. B.G.S. occasionally gets remunerated from Down syndrome non-profit organizations for speaking engagements about Down syndrome. He receives research support from Hoffmann-La Roche, Inc. B.G.S. receives annual royalties from Woodbine House, Inc., for the publication of his book *Fasten Your Seatbelt: A Crash Course on Down Syndrome for Brothers and Sisters*. B.G.S. is occasionally asked to serve as an expert witness for legal cases where Down syndrome is discussed. B.G.S. has a sister with Down syndrome. E.A.M. receives research support from Biotie Therapies, Inc. and serves on Data and Safety Monitoring Boards for Acorda Therapeutics and Shire Human Genetic Therapies.

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Additional Supporting Information may be found online in the supporting information tab for this article.

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