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SCIENTIFIC INVESTIGATIONS

Clinical predictors of nonadherence to positive airway pressure therapy in children: a retrospective cohort study

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Study Objectives: Despite the importance of treating sleep-disordered breathing, positive airway pressure adherence rates in children are low. Identifying readily available predictors of nonadherence would enable the development of targeted interventions and supports, but literature is limited. Our objective was to identify baseline clinical predictors of 6-month positive airway pressure therapy nonadherence in children with SDB through a retrospective cohort study.

Methods: This study evaluated children (ages 8–17 years) prescribed positive airway pressure therapy for sleep-disordered breathing between 2011 and 2017 at a single pediatric tertiary hospital. The primary outcome was nonadherence at 6 months, measured using both machine downloads and self-report. Candidate baseline predictors included demographics, comorbidities, and sleep-disordered breathing characteristics. Relative risks (RR) and 95% confidence intervals (CI) were estimated using a modified Poisson regression. Missing data were imputed prior to analysis.

Results: The study included 104 children. The independent predictors most strongly associated with greater nonadherence were older age (RR = 1.08 for a 1-year increase; 95% CI, 1.00–1.16) and higher oxygen saturation nadir (RR = 1.03 for a 1% increase; 95% CI, 1.00–1.05), whereas those most strongly associated with lower nonadherence were higher arousal index (RR = 0.97 for a 1 event/h increase; 95% CI, 0.95–1.00), developmental delay (RR = 0.58; 95% CI, 0.30–1.13), and asthma (RR = 0.72; 95% CI, 0.44–1.17).

Conclusions: Overall, children who are older, have less-severe sleep-disordered breathing, or less-disrupted sleep at baseline are more likely to be nonadherent to positive airway pressure therapy and may benefit from additional supports to acclimatize to therapy. As clinical predictors were only weakly associated with nonadherence, nonclinical characteristics may play a larger role in predicting adherence.

Keywords: pediatric, adherence, positive airway pressure, OSA

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BRIEF SUMMARY

Current Knowledge/Study Rationale: To date, literature on predictors of positive airway pressure therapy nonadherence is limited, and adherence rates are low. Our objective was to identify baseline clinical predictors of 6-month nonadherence in children starting positive airway pressure therapy.

Study Impact: The strongest baseline predictors of greater positive airway pressure nonadherence were older age and higher oxygen saturation nadir, whereas the strongest predictors of lower nonadherence were higher arousal index, developmental delay, and asthma. Children with characteristics associated with greater nonadherence may benefit from additional supports to acclimatize to therapy.

INTRODUCTION

Sleep-disordered breathing (SDB) is a condition that encompasses a spectrum of sleep-related breathing disorders, including obstructive sleep apnea (OSA), central sleep apnea, and nocturnal hypoventilation.[1] It affects 1%–5% of healthy children, and can lead to high blood pressure, insulin resistance, behavioral problems, cognitive impairment, and decreased quality of life in children if not adequately managed.[2,3] A common treatment modality for SDB is positive airway pressure (PAP), which is a noninvasive therapy that delivers pressurized air into the lungs through a mask interface to support airway patency and/or ventilation.[1] While highly effective, adherence to therapy in children is poor. A recent systematic review of 20 studies worldwide reported an average PAP adherence rate of 57%.[4] These findings were mirrored in a large-scale study of over 20,000 children with OSA across the United States, of which only 46% met adherence criteria within the first 90 days of PAP use.[5]

To address this concern, our group recently conducted a systematic review to identify predictors of PAP therapy adherence and nonadherence in children. The characteristics most consistently associated with greater adherence were female sex, younger age, Caucasian race, higher maternal education, higher baseline apnea-hypopnea index (AHI), and presence of developmental delay. However, these findings were limited by

several data quality concerns in the included studies. In addition to small sample sizes averaging 51 children per study, many of the included studies measured adherence cross-sectionally, resulting in participants within a study having different lengths of follow-up. Furthermore, almost all of the included studies excluded children with missing adherence data from the analysis, which can affect the generalizability of the study findings if nonadherent participants are preferentially not presenting for follow-up. Finally, very few of the included studies conducted adjusted analyses to evaluate independent associations between baseline characteristics and nonadherence.[6]

To address this gap in the literature, we undertook a larger cohort study following all children newly prescribed PAP therapy at a single-center pediatric tertiary care hospital. This ensured that identified predictors would be generalizable to all children starting PAP therapy, irrespective of whether they obtained a PAP device or had follow-up data available. We specifically chose to identify predictors of nonadherence, so that future interventions could be targeted toward children who require the most support to succeed with PAP therapy. Therefore, this study's primary objective was to identify independent baseline clinical predictors of 6-month PAP therapy nonadherence in children with SDB.

METHODS

Study design and setting

This was a single-center, retrospective cohort study of children diagnosed with SDB and prescribed PAP therapy at the Children's Hospital of Eastern Ontario (CHEO) between January 1, 2011, and December 31, 2017. CHEO is a tertiary-level pediatric hospital with a dedicated sleep laboratory that provides care to children from the provinces of Ontario and Quebec and the territory of Nunavut. We chose 2011 as our start year as that is when our Sleep Laboratory and Respirology clinic first employed an electronic health record system. This study was approved by the CHEO Research Ethics Board prior to commencement (#16/170×).

Data collection for this study took place between August 18, 2016, and September 31, 2019 by 3 reviewers (HB, AB, and SH), and data were entered into REDCap, a secure, online database.[7] All data were verified by a single reviewer (HB) prior to analysis.

Study population

Children were identified through our hospital's electronic medical records. We screened all children aged 8–17 years who had a Respirology Clinic visit between 2011 and 2017 and had a documented PAP prescription, including either continuous positive airway pressure or bilevel positive airway pressure. There was no prespecified sample size, as all eligible children were included.

Children were eligible if they were (1) diagnosed with SDB (specifically OSA, central sleep apnea, or hypoventilation) by polysomnography (PSG); (2) newly prescribed PAP therapy at CHEO between January 1, 2011, and December 31, 2017; and (3) aged 8–17 years at the time of either PAP therapy prescription or start. PAP therapy was indicated for children who had moderate-to-severe SDB or mild SDB with clinically significant daytime symptoms and who were either not surgical candidates or had not been cured by adenotonsillectomy.

Children were excluded if they (1) either lived or were prescribed PAP therapy outside of CHEO's catchment area; (2) did not receive a diagnostic PSG within 1 year (± 1 month) prior to PAP prescription; (3) had been previously prescribed PAP; (4) were ventilated invasively through a tracheostomy; (5) were prescribed PAP therapy for a reason besides SDB (such as respiratory failure due to parenchymal lung disease); or (6) had OSA that resolved with adenotonsillectomy within 3 months of PAP prescription. These exclusions ensured that all children in our study received similar clinical care throughout the study duration and represented a more homogeneous clinical population.

Nonadherence

The primary outcome for this study was nonadherence at 6 months (± 3 months) post-PAP therapy start. In situations where start date was unavailable or the participant had never obtained a PAP device, we used the date of prescription as a proxy for start date. We defined PAP therapy nonadherence as less than 4 hours of PAP use per night for at least 30% of nights. In the absence of a validated pediatric definition of nonadherence, this is a commonly used cutoff in the pediatric literature.[1]

Adherence was evaluated using a combination of objective PAP device downloads (the gold standard) and clinician assessments based on self-reports from clinic visits, phone calls, and faxes from the PAP provider. Missing adherence data were imputed, as described below in the statistical analysis section, to minimize the risk of selection bias.

Predictors

Baseline characteristics evaluated for associations with 6-month adherence status were determined through a previous systematic review on the topic,[6] as well as expert opinion from a pediatric sleep medicine physician (SK). The following baseline characteristics were included as candidate predictors in our study: age, sex, SDB diagnosis, PAP mode, comorbidities (obesity, developmental delay, asthma, mental health disorder, and behavioral disorder), polysomnographic indices (AHI, oxygen saturation nadir, maximum carbon dioxide level, sleep efficiency, and arousal index), and sleep symptoms (daytime somnolence, daytime energy, and headache frequency). We were unable to assess socioeconomic status and psychosocial characteristics as predictors because these data were not documented in the patient records.

Data collection time points

Night of the PSG

All children underwent an in-laboratory nocturnal PSG. PSGs were performed and scored according to the American Academy of Sleep Medicine pediatric guidelines (per *The AASM Manual*

for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications).[8] Children were diagnosed with OSA if they had an obstructive AHI greater than 1 event/h, with central sleep apnea if the AHI was greater than 5 events/h and the obstructive AHI was less than 1 event/h, with hypoventilation if the carbon dioxide level was greater than 50 mm Hg for at least 25% of the sleep time, and with a mixed sleep-related breathing disorder if the child had more than 1 type of SDB (see the AASM Scoring Manual).[2,8] The following data were abstracted from the diagnostic PSG report: SDB diagnosis, sleep efficiency, arousal index, AHI, obstructive AHI, oxygen saturation nadir (ie, lowest oxygen saturation), and maximum carbon dioxide level. In situations where children were started on PAP therapy partway through the night of the sleep study, data were only collected from the diagnostic portion of the study.

During the night of the PSG, parents also completed a locally developed sleep symptom questionnaire based on the Pediatric Sleep Questionnaire.[9] Our study collected parents' responses regarding 3 sleep symptoms of interest: excessive daytime somnolence (daily/weekly/monthly/never), morning headache frequency (1–2 days per week/3–4 days per week/5–6 days per week/7 days per week/never), and daytime energy level (poor/fair/good/excellent). Categories within each self-reported sleep symptom were grouped to compare the top 2 categories (indicating more frequent symptoms) to the lower categories to account for sparseness of data in respective groups.

Clinic visit

Children met with 1 of 2 pediatric sleep medicine physicians at CHEO to review their diagnosis and receive a prescription for PAP therapy. PAP devices were dispensed by local vendors, and families received training by a registered respiratory therapist either at CHEO or by the local vendor. We collected information on the PAP therapy prescription, including date of prescription, PAP mode, mask type, pressure settings, back-up rate, oxygen supplementation, and PAP therapy start date, which was defined as either the date the family received training on their PAP device or the date the family had stated to a clinician that they started using it. Funding for PAP devices was provided through a combination of government-funded programs and private insurance/personal copay of up to 25% of the cost of the device.

We also collected data on individuals' baseline characteristics at the time closest to the PAP therapy prescription from the electronic medical records. This included age, sex, height, weight, province/territory, and presence of comorbidities. Comorbidities of interest included developmental delay, neuromuscular disease, obesity, asthma, mental health disorder (ie, depression, anxiety, bipolar disorder, or obsessive-compulsive disorder), and behavioral disorder (ie, attention-deficit hyperactivity disorder, oppositional-defiant disorder, or conduct disorder). We measured obesity by using the height and weight to calculate age- and sex-adjusted body mass index percentiles, with a body mass index ≥ 95th percentile defined as obese.[10] In patients for whom height or weight was missing, we used physician-reported comorbidities to assess for the presence of obesity. Obesity was used as the predictor rather than body mass index percentile to account for extreme data skewness, as the median body mass index percentile in our data set was greater than the 99th percentile.

Follow-up

After PAP prescription, children were followed at the CHEO Respirology Clinic approximately every 6 months, with intermittent check-in phone calls by a respiratory therapist. Objective adherence downloads were collected either in person when the family brought their device's memory card in during clinic visits, or through faxed reports by the local PAP provider. In the absence of PAP device downloads spanning the entire follow-up period, summary clinician assessments of nonadherence were determined by triangulating all adherence data, including partial adherence downloads (ie, covering only a portion of the follow-up period), clinic notes, phone calls, and follow-up visits.

For our study, we collected nonadherence assessments at the time point closest to 6 months post-PAP therapy start, as well as changes in health status and PAP settings. As we anticipated that not all individuals would have 6-month adherence data available, we also collected 12-month nonadherence for use in our imputation model of missing data.

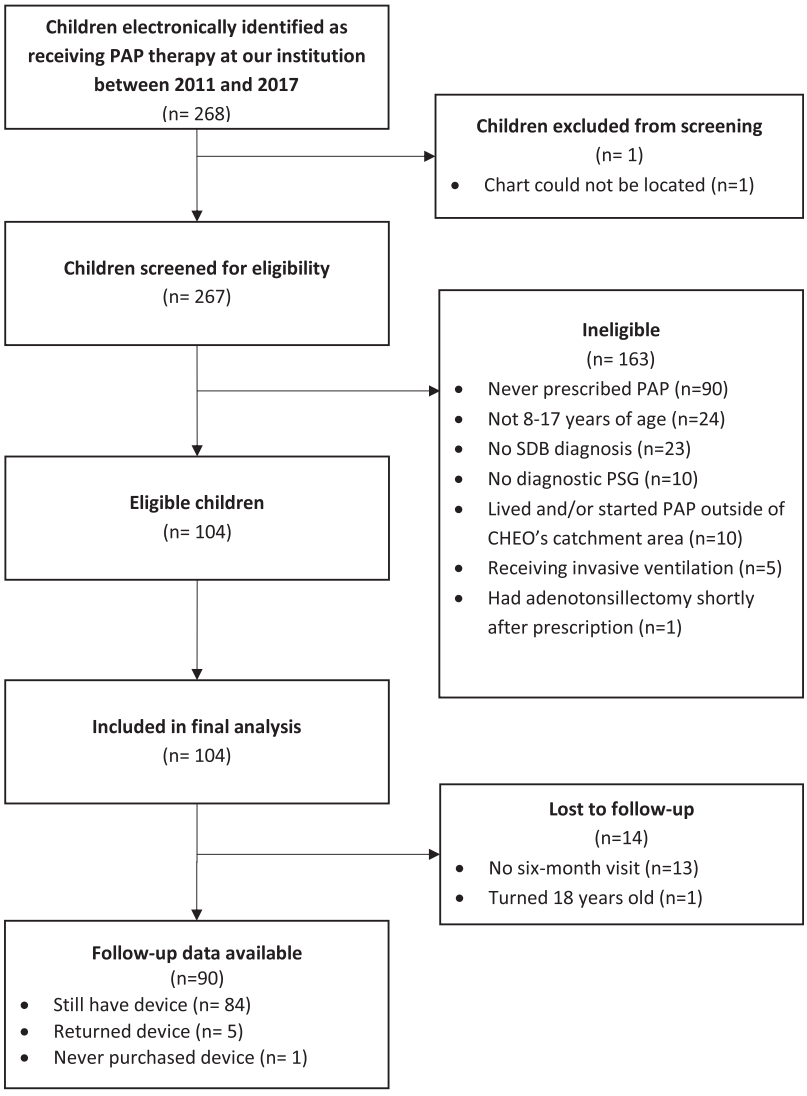
Statistical analysis

All statistical analyses were conducted in R version 3.5.0.[11] Unadjusted and fully adjusted Poisson regression models, with robust sandwich estimators for variance, were used to estimate the relative risks (RRs) and 95% confidence intervals (CIs) for baseline clinical variables, with nonadherence at 6 months as the outcome.[12] Interpretations of the associations were determined based on the magnitude of the RR estimate and the width of the CI, rather than the *P* value.[13,14]

Given the large number of predictors, we conducted a penalized likelihood analysis (ridge regression) to reduce potential overfitting due to sparse data or collinearity.[15] The ridge regression model was fit using the *glmnet* package version 2.0-18 in R.[16] The penalization factor was chosen using cross-validation. Associated CIs were not reported, as this method was used solely to estimate the value of including the predictors in future adjusted prediction modeling after accounting for sparse data issues.

All missing data were imputed prior to analysis. For children who had no reported adherence data within 1 year of PAP therapy prescription or start, we marked them as nonadherent, as it was very unlikely they were receiving follow-up PSGs or clinical support to encourage adherence at another location. For all other missing data, we conducted multiple imputation, a technique that can reduce bias due to missing information in studies with up to 90% missing data.[17–19] Imputations were done using fully conditional specification with predictive mean matching for all variables via the mice package version 3.6.0 in R.[20] The imputation model included all predictor variables and the outcome, as well as nonadherence at 12 months, province of residence, and year of PAP therapy prescription (or start date, if it was available). A total of 10 completely imputed datasets was created. An analysis was also conducted among individuals

Figure 1—Participant flow diagram.



CHEO = Children's Hospital of Eastern Ontario, PAP = positive airway pressure, PSG = polysomnography, SDB = sleep-disordered breathing.

with complete data ("complete case analysis") for the purpose of comparison.

RESULTS

Study sample

A total of 104 children was eligible and included in the final analysis. Reasons for ineligibility are described in **Figure 1.** The study sample had a mean age of 13 (standard deviation [SD] = 3) years. The median AHI and obstructive AHI were 11 events/h (interquartile range = 5–23) and 5 events/h (interquartile range = 2–15), respectively. The mean oxygen saturation nadir was 81% (SD = 10). Sixty-seven percent of children had obesity. Additional baseline demographics are described in **Table 1.** Fifty percent of participants were nonadherent. The average length of follow-up for the 85 children with PAP therapy follow-up visit dates was 168 days (SD = 58). Only 1 child in the study had not picked up the PAP device and was therefore marked as nonadherent.

Missing data

For the full sample of 104 children, there was an average of 7.4% missing data across variables of interest. For PSG data, 8 children (7.7%) were missing maximum carbon dioxide levels, 1 (1.0%) was missing sleep efficiency, and 6 (5.8%) were missing arousal index. This information was missing primarily because the PSGs were conducted at an external institution and the reports were insufficiently detailed, as was the case for 8 of the 11 children (73%) with missing PSG data. Forty children (38.5%) were missing information about both daytime somnolence and daytime energy, and 29 children (27.9%) were missing headache frequency. These symptom questions were missing in children who had PSGs at an external institution, had another PSG within the last few years (these questions are only routinely administered at a child's first PSG), and/or who had a

Table 1—Baseline demographics and follow-up data.

Variable	Entire Study Sample (n = 104)[a]	Subset With Complete Data (n = 44)[b]	Imputed Sample (n = 104)[c]
Demographics			
Age (y), mean (SD)	13 (3)	13 (2)	13 (3)
Male sex, n (%)	80 (77)	36 (82)	80 (77)
SDB diagnosis, n (%)			
OSA	58 (56)	28 (64)	58 (56)
Hypoventilation or CSA	14 (14)	5 (11)	14 (14)
Mixed	32 (31)	11 (25)	32 (31)
PAP mode, n (%)			
CPAP	33 (32)	15 (34)	33 (32)
BPAP	41 (39)	17 (39)	40 (39)
Auto-PAP	31 (30)	12 (27)	31 (30)
Comorbidities			
Developmental delay, n (%)	16 (15)	4 (9)	16 (15)
Obesity, n (%)	70 (67)	33 (75)	70 (67)
Asthma, n (%)	28 (27)	10 (23)	28 (27)
Mental health disorder, n (%)	19 (18)	6 (14)	19 (18)
Behavioral disorder, n (%)	19 (18)	7 (16)	19 (18)
PSG indices			
AHI (events/h), median (IQR)	11 (5–23)	11 (5–20)	11 (5–23)
O_2 saturation nadir (%), mean (SD)	81 (10)	83 (8)	81 (10)
Maximum CO_2 (mm Hg), mean (SD)	51 (8)	50 (7)	51 (8)
Sleep efficiency (%), mean (SD)	84 (13)	82 (13)	84 (13)
Arousal index (events/h), median (IQR)	11 (8–18)	11 (9–19)	11 (8–17)
Self-reported sleep symptoms			
Daytime somnolence (monthly or never), n (%)	18 (28)	13 (30)	28 (27)
Daytime energy (good or excellent), n (%)	26 (41)	20 (46)	53 (51)
Headache frequency (≥3 d/wk), n (%)	13 (17)	8 (18)	20 (19)
Follow-up			
Adherent, n (%)	46 (51)	24 (55)	54 (52)

[a]Demographics for the entire study sample. Missing data were present for CO_2 (n = 8), sleep efficiency (n = 1), arousal index (n = 6), daytime somnolence (n = 40), daytime energy (n = 40), headache frequency (n = 29), and adherence data (n = 14). [b]Demographics for the subset of children not missing any predictor or outcome data. [c]Demographics for 1 imputed dataset. Continuous results were presented as mean (SD) for normally distributed variables and median (IQR) for nonnormally distributed variables. AHI = apnea-hypopnea index, auto-PAP = auto-titrating positive airway pressure, BPAP = bilevel positive airway pressure, CPAP = continuous positive airway pressure, CSA = central sleep apnea, IQR = interquartile ratio, OSA = obstructive sleep apnea, PAP = positive airway pressure, PSG = polysomnography, SD = standard deviation, SDB = sleep-disordered breathing.

PSG earlier in the time frame before the hospital fully switched over to an electronic system and for whom the paper copy of the questionnaire was not kept in the medical records. Finally, 14 children (13.4%) were missing the primary outcome of 6-month nonadherence status. Two of the 14 children (14%) were further missing 12-month follow-up data and were therefore assumed to be nonadherent at 6 months, while the remaining 12 had their nonadherence status imputed. In total, 44 children (42%) had complete data for all of the predictors and the outcome.

Adjusted regression

After conducting unadjusted regressions on all candidate predictors using the imputed data, an adjusted analysis simultaneously controlling for all other predictors was run to evaluate independent associations (see **Table 2**). Nonadherence was greater in children who were older (RR = 1.08 [95% CI, 1.00–1.16] for a 1-year increase), had a lower arousal index (RR = 0.97 [95% CI, 0.95–1.00] for a 1 event/h increase), and had a higher oxygen saturation nadir (RR = 1.03 [95% CI, 1.00–1.05] for a 1% increase, ie, less-severe desaturation). Considering more clinically relevant changes of 5 units (ie, a 5-year increase in age, 5 more arousal events/h, and a 5% increase in oxygen saturation nadir), the RRs were 1.47, 0.87, and 1.44, respectively.

While the CIs were wide, several other potential predictors were identified. Specifically, nonadherence was lower in children

Table 2—Poisson regression estimates evaluating the association between nonadherence at 6 months and baseline characteristics (imputed data analysis, n = 104).

Predictor	Unadjusted Analysis		Adjusted Analysis[a]		Ridge Regression[a]
	RR	95% CI	RR	95% CI	RR
Demographics					
Age (y)	1.07	0.99–1.14	1.08	1.00–1.16	1.03
Male sex	1.12	0.70–1.79	1.06	0.67–1.68	1.03
SDB diagnosis					
Hypoventilation/CSA (reference)	1.00	–	1.00	–	1.00
Mixed diagnosis	0.67	0.41–1.10	0.73	0.36–1.50	0.94
OSA	0.71	0.47–1.07	0.89	0.42–1.87	0.96
PAP mode					
CPAP (reference)	1.00	–	1.00	–	1.00
BPAP	1.25	0.79–1.99	1.62	0.82–3.17	1.08
Auto-PAP	1.21	0.74–1.98	1.54	0.92–2.60	1.06
Comorbidities					
Developmental delay	0.59	0.29–1.22	0.58	0.30–1.13	0.83
Obesity	0.93	0.63–1.36	0.88	0.58–1.33	0.96
Asthma	0.66	0.40–1.10	0.72	0.44–1.17	0.87
Mental health disorder	0.94	0.57–1.56	0.85	0.51–1.43	0.96
Behavioral disorder	1.08	0.68–1.70	1.03	0.68–1.56	1.02
PSG indices					
AHI (events/h)	1.00	0.99–1.01	1.00	0.99–1.01	1.00
O_2 saturation nadir (%)	1.03	1.00–1.05	1.03	1.00–1.05	1.01
Maximum CO_2 (mm Hg)	1.01	0.98–1.03	1.00	0.98–1.03	1.00
Sleep efficiency (%)	1.00	0.98–1.01	1.00	0.99–1.02	1.00
Arousal index (events/h)	0.97	0.95–1.00	0.97	0.95–1.00	0.99
Self-reported sleep symptoms					
Daytime somnolence (monthly or never)	0.93	0.62–1.41	0.91	0.49–1.70	0.99
Daytime energy (good or excellent)	0.86	0.59–1.26	0.77	0.51–1.16	0.93
Headache frequency (≥3 d/wk)	1.03	0.65–1.64	0.97	0.59–1.60	1.00

[a]The reported relative risks in this column are adjusted for all other predictors described in this table. AHI = apnea-hypopnea index, auto-PAP = auto-titrating positive airway pressure, BPAP = bilevel positive airway pressure, CI = confidence interval, CPAP = continuous positive airway pressure, CSA = central sleep apnea, OSA = obstructive sleep apnea, PAP = positive airway pressure, PSG = polysomnography, RR = relative risk, SDB = sleep-disordered breathing.

with developmental delay (RR = 0.58 [95% CI, 0.30–1.13]), asthma (RR = 0.72 [95% CI, 0.44–1.17]), and good or excellent baseline daytime energy (RR = 0.77 [95% CI, 0.51–1.16]). Children using bilevel positive airway pressure (RR = 1.62 [95% CI, 0.82–3.17]) or auto-titrating positive airway pressure (RR = 1.54 [95% CI, 0.92–2.60]) also tended to have greater nonadherence than those using continuous positive airway pressure.

Regarding the remaining predictors, we were unable to interpret the direction and strength of associations between nonadherence and male sex, SDB diagnosis, obesity, mental health disorder, and behavioral disorder, as the CIs included meaningful effect estimates for both directions of association.

Penalized regression

To estimate how well the predictors might perform in future studies, we applied shrinkage modeling to the adjusted regression analysis (see **Table 2**). The most promising predictors of nonadherence using the penalized regression estimates were older age (RR = 1.03 for a 1-year increase), having a lower arousal index (RR = 0.99 for a 1 event/h increase), having a less-low oxygen saturation nadir (RR = 1.01 for a 1% increase), and not having developmental delay (RR = 0.83) or asthma (RR = 0.87).

Complete case analyses

All analyses were also conducted using the subset of 44 participants with complete data on all predictors and the outcome (see **Table 3**). Contrary to the fully imputed data analysis, developmental delay (RR = 0.79 [95% CI, 0.35–1.78]), asthma (RR = 0.89 [95% CI, 0.31–2.58]), and daytime energy (RR = 1.01 [95% CI, 0.56–1.83]) were not identified as predictors of nonadherence in the complete case-adjusted analysis due to wide CIs. Furthermore, obesity was

Table 3—Poisson regression estimates evaluating the association between nonadherence at 6 months and baseline characteristics (complete case analysis, n = 44).

Predictor	Unadjusted Analysis		Adjusted Analysis[a]		Ridge Regression[a]
	RR	95% CI	RR	95% CI	RR
Demographics					
Age (y)	1.18	1.04–1.35	1.18	1.02–1.36	1.03
Male sex	1.56	0.61–3.97	0.96	0.37–2.48	1.06
SDB diagnosis					
Hypoventilation/CSA (reference)	1.00	–	1.00	–	1.00
Mixed diagnosis	0.91	0.51–1.60	0.53	0.13–2.28	1.05
OSA	0.54	0.29–0.99	0.87	0.23–3.20	0.90
PAP mode					
CPAP (reference)	1.00	–	1.00	–	1.00
BPAP	2.29	1.07–4.92	3.42	1.17–9.98	1.15
Auto-PAP	1.50	0.60–3.74	2.34	0.79–6.98	0.99
Comorbidities					
Developmental delay	0.91	0.33–2.52	0.79	0.35–1.78	0.98
Obesity	0.67	0.40–1.10	0.52	0.22–1.25	0.89
Asthma	0.49	0.18–1.30	0.89	0.31–2.58	0.88
Mental health disorder	1.27	0.67–2.41	1.10	0.38–3.18	1.03
Behavioral disorder	1.06	0.52–2.14	0.91	0.47–1.73	0.99
PSG indices					
AHI (events/h)	1.00	0.99–1.01	1.00	0.99–1.01	1.00
O_2 saturation nadir (%)	1.04	1.00–1.08	1.05	1.00–1.10	1.01
Maximum CO_2 (mm Hg)	0.98	0.94–1.03	0.99	0.93–1.04	1.00
Sleep efficiency (%)	0.98	0.97–1.00	1.00	0.98–1.02	1.00
Arousal index (events/h)	0.99	0.95–1.03	0.97	0.94–1.02	1.00
Self-reported sleep symptoms					
Daytime somnolence (monthly or never)	0.79	0.41–1.54	0.86	0.25–2.92	0.96
Daytime energy (good or excellent)	1.02	0.59–1.74	1.01	0.56–1.83	1.01
Headache frequency (≥3 d/wk)	1.18	0.64–2.20	1.06	0.50–2.24	1.03

[a]The reported relative risks in this column are adjusted for all other predictors described in this table. AHI = apnea-hypopnea index, auto-PAP = auto-titrating positive airway pressure, BPAP = bilevel positive airway pressure, CI = confidence interval, CPAP = continuous positive airway pressure, CSA = central sleep apnea, OSA = obstructive sleep apnea, PAP = positive airway pressure, PSG = polysomnography, RR = relative risk, SDB = sleep-disordered breathing.

a predictor of lower nonadherence in the adjusted analysis (RR = 0.52 [95% CI, 0.22–1.25]).

DISCUSSION

Predictors of PAP nonadherence identified in the pediatric literature to date have had limited utility for clinicians aiming to improve PAP therapy adherence rates in their clinical practice, in part due to lack of replicability across studies and methodological shortcomings such as small sample sizes, cross-sectional assessments of adherence, and exclusion of participants with missing data.[6] Furthermore, there is limited literature evaluating independent associations between baseline characteristics and PAP therapy nonadherence. To the best of our knowledge, this larger cohort study is the first to estimate the adjusted RRs of PAP nonadherence at 6 months for a large set of baseline characteristics of children prescribed PAP therapy. Our study found that after adjusting for all other variables and considering potential for overfitting, the characteristics most likely to be independently associated with greater PAP therapy nonadherence were older age and higher oxygen saturation nadir (ie, less-severe oxygen desaturations), whereas those most likely associated with lower nonadherence were higher arousal index, developmental delay, and asthma.

Despite the generally small point estimates and wide CIs estimated for many of our predictors, the congruency between our findings and previous literature on the topic corroborates these clinical predictors as potentially valuable for identifying at-risk children. Our previous systematic review identified older age as a predictor of nonadherence in children, while developmental delay was associated with lower nonadherence.[6] Of

note, this difference in adherence based on developmental status is possibly attributable to differences in PAP acclimatization, as children with developmental delay often undergo a much more prolonged desensitization protocol to adjust to PAP use compared to children with typical development. The association between asthma and lower nonadherence has also been reported in another study, which reported an adjusted odds ratio of 15.9 (95% CI, 2.1–122.4).[21] Lower arousal index was also reported as a predictor of nonadherence in 1 study, with a mean difference of arousal index between adherent and nonadherent groups of 4.9 (SD = 21.4) vs 17.0 (SD = 14.1) ($P < .01$), respectively.[22] While oxygen saturation (either mean or nadir) was not associated with nonadherence in any other study besides ours,[22–24] these differences in findings can be explained by several factors, including different eligible populations and different definitions of adherence used, among others.

While our study did not find an association between AHI and nonadherence, our findings suggest that SDB severity may still play a role in pediatric PAP therapy nonadherence. We found that children with less-severe oxygen desaturations, a measure of SDB severity, were more likely to be nonadherent. We also found that lower arousal index, an indicator of higher-quality sleep, was associated with greater nonadherence. It is possible that children who sleep poorly at baseline may perceive the benefits of PAP therapy more strongly than those who feel otherwise well. Similarly, children in our study who did not have asthma were more likely to be nonadherent. As there is a known bidirectional relationship between SDB and asthma, it is possible that children with asthma are more likely to use PAP therapy if they also perceive improvement in their asthma symptoms with PAP use.[25]

There were several additional variables, such as SDB diagnosis and PAP mode, which were not identified as meaningful predictors of nonadherence in the ridge regression but may still be predictive of nonadherence. In the unadjusted analyses, children with OSA or a mixed SDB diagnosis had lower nonadherence than those with hypoventilation or central sleep apnea. Similarly, children on bilevel positive airway pressure or auto-titrating positive airway pressure had greater nonadherence compared to those on continuous positive airway pressure. While it is possible that these variables were simply less predictive of nonadherence after adjusting for all other variables, an association may have been seen with a larger sample size, as the CIs were very widespread. Results from previous studies regarding PAP mode as a predictor are mixed; some studies have reported greater adherence with bilevel positive airway pressure, while others have reported greater adherence with continuous positive airway pressure.[3,21,26] Interestingly, only 1 study in our previous systematic review evaluated indication for PAP as a predictor, likely because the majority of studies only included children with OSA.[6] Ramirez et al[27] compared children with OSA to those with neuromuscular disease and found no meaningful differences in adherence. Additional investigation of these variables as predictors of nonadherence may be helpful.

Other than 1 study published in 2006 by Marcus et al[28] of 29 children, this cohort study is the first to consider the impact of excluding participants with missing data from an analysis of PAP adherence. We noted very different results between the fully imputed data analysis and the complete case analysis. While likely in part due to noise and differences in sample size, these differences also point toward selection bias that may be present in the complete case analysis. While our imputation method likely did not remove all bias associated with missing data, using an expanded imputation model that included additional factors that may have been associated with missing information and loss to follow-up, such as year of PAP therapy start and nonadherence at 12 months, ensured that bias was minimal. The inclusion of a proxy outcome assessment in an imputation model has been shown to substantially reduce bias in epidemiological studies.[29] Based on the differences in results between the complete case analysis and fully imputed data analyses, it is clear that results obtained only from children who present for follow-up cannot be generalized to the larger population of children prescribed PAP therapy without careful consideration.

After conducting a penalized ridge regression to estimate how the predictors would perform in future prediction modeling applications, we found that many of our predictors were generally weakly associated with nonadherence. This suggests that clinical characteristics may play a smaller role in nonadherence compared to nonclinical factors. This has been supported by recent research. Studies have identified maternal social support,[30] having a family member on PAP,[31] and caregiver-reported self-efficacy[32] as associated with a clinically meaningful increase in pediatric adherence. Furthermore, several qualitative studies in children using PAP therapy for SDB reported that the most common barriers to adherence were technical difficulties such as tubing and mask fit, lack of perceived benefits, inadequate support to troubleshoot problems, and family environment.[33–35] It is therefore vital that future studies of predictors of PAP therapy nonadherence collect information on psychosocial factors and family environment, as these factors may ultimately prove to be more strongly associated with nonadherence than the clinical factors evaluated in our study.

This study was limited by several factors. Due to the study's retrospective design and reliance on routinely collected data, we were unable to assess additional predictors of nonadherence such as socioeconomic status and psychosocial factors. In addition, location of PAP training may have affected rates of adherence. While a registered respiratory therapist provided training in all instances and families could always contact the CHEO Respirology Clinic for assistance, instructions and degree of follow-up likely varied depending on whether PAP initiation took place at CHEO or with a local PAP provider. Due to the age limits of our eligible population chosen to allow for evaluation of sleep symptoms using our institution's sleep symptom questionnaire, our findings may not be generalizable to children younger than age 8 years. Furthermore, we used a combination of downloaded adherence reports and clinician summary assessments to evaluate nonadherence. Although triangulating these data increased the robustness of our outcome and enabled us to evaluate adherence in children who did not have downloaded adherence reports, this may have resulted in misclassification bias if the clinician summary assessments

were inaccurate. Using clinician summary assessments also limited our ability to evaluate nonadherence continuously, which may have masked more complex relationships between predictors and nonadherence. Finally, our study had some missing data, although this was mainly limited to self-reported daytime symptoms and was robustly handled. All data were multiply imputed with the exception of 2 children who had no follow-up adherence data for over 1 year following prescription and were therefore assumed to be nonadherent. Of note, cost of the PAP device was unlikely to be a barrier to adherence in our study as the majority of this is covered by government funding in Canada.

CONCLUSIONS

This cohort study is the largest to date to estimate the RRs of baseline characteristics of children prescribed PAP therapy with respect to nonadherence to PAP therapy. We found that the clinical baseline characteristics most strongly associated with greater nonadherence were older age, not having a diagnosis of developmental delay or asthma, less-severe oxygen desaturations, and lower arousal index. Ultimately, these results should be used to inform a larger prospective cohort study that concurrently evaluates clinical characteristics, psychosocial factors, and family environment to develop a prediction model to more effectively identify children likely to struggle with adherence. This will ensure that children at greatest risk of nonadherence to PAP therapy are identified early, thereby allowing them to receive timely intervention before poor adherence behaviors become ingrained. Early success with PAP therapy may ultimately prevent secondary health consequences of SDB in children that carry into adulthood.

ABBREVIATIONS

AHI, apnea-hypopnea index
CHEO, Children's Hospital of Eastern Ontario
CI, confidence interval
OSA, obstructive sleep apnea
PAP, positive airway pressure
PSG, polysomnography
RR, relative risk
SDB, sleep-disordered breathing
SD, standard deviation

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