# Predictors of Non-Adherence to Positive Airway Pressure Therapy in Children

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A thesis submitted in partial fulfillment of the requirements for the
Master's degree in Epidemiology

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## PREFACE

Approval to conduct the research described in this thesis for partial fulfillment of the requirements for the Master's degree in Epidemiology was obtained from the School of Epidemiology and Public Health.

This entire thesis, from commencement to completion, represents original work undertaken by me (Henrietta Blinder) as part of the requirements for the MSc degree in Epidemiology. Dr. Franco Momoli and Dr. Sherri Katz (the co-supervisors for this thesis), as well as Dr. Dhenuka Radhakrishnan (a member of the author's Thesis Advisory Committee), oversaw the author's work and provided critical methodological and clinical guidance and feedback. The remaining co-authors, namely Dr. Vanessa Bacal, Ms. Julia Bokhaut, Dr. Reuben Goldberg, Ms. Anna Blinder, and Mr. Stephen Holland, were involved in the collection of study data and revision/approval of the final manuscripts. Author contributions are described in detail in the preface for each manuscript.

**Manuscript 1**

**Title:** Predictors of adherence to positive airway pressure therapy in children: A systematic review and meta-analysis

**Authors:** Henrietta Blinder, Dr. Franco Momoli, Julia Bokhaut, Dr. Vanessa Bacal, Dr. Reuben Goldberg, Dr. Dhenuka Radhakrishnan, and Dr. Sherri L Katz.

**Additional approvals:** None.

**Publication:** This manuscript was submitted to *Sleep Medicine* for review on July 26, 2019.

**Manuscript 2**

**Title:** Clinical predictors of non-adherence to PAP therapy in children – A retrospective cohort study

**Authors:** Henrietta Blinder, Dr. Franco Momoli, Stephen H Holland, Anna Blinder, Dr. Dhenuka Radhakrishnan, and Dr. Sherri L Katz.

**Additional approvals:** Approval was obtained from the Children's Hospital of Eastern Ontario (CHEO) Research Ethics Board to conduct the cohort study at CHEO (#16/170X).

## ABSTRACT

In children with sleep-disordered breathing, adherence to positive airway pressure (PAP) therapy is poor. Literature on predictors of PAP non-adherence is limited by lack of rigorous reviews and inconsistent findings across studies. This thesis aimed to address this dearth of information through both a systematic review and a retrospective cohort study. Our review summarized the literature on predictors of non-adherence in children, including identifying common methodological concerns. These results informed the development of our cohort study, which identified clinical predictors of PAP non-adherence at six months. Overall, we identified that non-adherence was greater in children of older age, without developmental delay or asthma, with lower baseline apnea-hypopnea index, less low oxygen saturation nadir, lower arousal index, and lower maternal education. Ultimately, this thesis provides a foundation to help clinicians prioritize limited resources towards children requiring more support to succeed with PAP therapy adherence, before negative long-term habits of non-adherence form.

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## ACKNOWLEDGEMENTS

I could never have gotten to where I am now without the help and support of so many individuals.

I'd like to thank my co-supervisors, Dr. Sherri Katz and Dr. Franco Momoli, who were so understanding and convinced me to finish my degree when life threw some very fast curveballs. Sherri, you were my first mentor in Ottawa, and provided me with support, guidance, and friendship over the last four years. Franco, thank you for taking a chance on me, and pushing me to think critically, independently, and learn all that I could in this (relatively) short period.

I'd also like to thank Dr. Dhenuka Radhakrishnan, who, between finding time in her busy schedule to share her expertise and keep me on track for graduation, always asked how I was doing. I'd like to thank Dr. Vanessa Bacal, Ms. Julia Bokhaut, Mr. Stephen Holland, and Dr. Reuben Goldberg, who spent long hours collecting and evaluating data and without whom this research would not have been possible. I'd like to thank Dr. Margaret Sampson for creating and running the search strategy for the systematic review, and the Clinical Research Unit (including Dr. Dayre McNally and Ms. Catherine Glass) for preparing the data on CrowdScreen and allowing me to use the software. A special thanks to Charmaine Mohipp, who shared the secret to finishing grad school.

To Vincent LeBlanc, my partner, thank you for everything. You made sure I took care of myself and kept me grounded no matter what was going on. Anna Blinder, my sister – thank you for feeding me salads when I was too busy to eat properly, for the dark humour, and for the nomadic chocolate.

Lastly, I'd like to thank the first statistics professor I ever had, Dr. Gary Umphrey. Your unique teaching style, colourful collection of suits, and use of entomological examples are the reason I fell in love with statistics in the first place.

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# 1. Introduction

## 1.2. Sleep-disordered breathing

In the last decade, public awareness of the importance of sleep for healthy childhood development has greatly increased. A novel update to the *Canadian 24-hour Movement Guidelines for Children and Youth* in 2016 integrated sleep as a key component of daily healthy active living.[1] This notion has also been supported by the American Academy of Sleep Medicine, who released a consensus statement in 2016 recommending the amount of sleep children should get on a nightly basis.[2] Knowing the importance of sleep for childhood development, adequate treatment of sleep-related breathing disorders, which interfere with quality of sleep, is more crucial than ever.

During normal transition to sleep, there are several physiological changes that occur in children. Respiratory rate decreases, along with a decrease in tidal volume, or the amount of air being moved in and out of the body during respiration. The upper airway tone also becomes more relaxed, resulting in relaxation of surrounding soft tissue and narrowing of the airway passage. These physiological changes result in breathing that is slower and shallower during sleep compared to wakefulness. In some cases, this can lead to pauses in breathing, called 'apneas', or extremely shallow breathing, called 'hypopneas'. When there is insufficient air entering and exiting the body, the gas exchange of oxygen and carbon dioxide becomes impaired, leading to desaturations and build-up of carbon dioxide in the blood. Occasional respiratory events such as these are normal, and the body defends against these events by waking up, called 'arousals', so that breathing can return to normal.[3]

When the normal physiological processes of breathing become compromised during sleep, sleep-disordered breathing (SDB) develops. SDB is a term that covers a spectrum of sleep-related breathing disorders, including obstructive sleep apnea (OSA), central sleep apnea (CSA), and nocturnal hypoventilation. OSA is the most common, and affects 1-5% of typically developing children.[4] In children with comorbid Down syndrome or obesity, this prevalence can rise to as high as 60% and 78%, respectively.[5,6] OSA is characterized by repeated airway obstructions during sleep. This typically occurs due to a combination of lower airway muscle tone and adenotonsillar hypertrophy, ultimately resulting in a blocked airway passage.[3] In children with obesity, this airway blockage can be further aggravated by external compression due to excess soft tissue mass.[7] CSA is much rarer; it is typically the result of a congenital malformation of the brain, increased pressure on the brainstem which triggers respiration, or acquired neurological illness like brain trauma. With CSA, the brain does not signal the respiratory

muscles to breathe, resulting in absence of or inadequate respiration. Lastly, nocturnal hypoventilation is caused by insufficient respiratory effort to move the chest wall, often secondary to neuromuscular disease or obesity. This leads to build-up of carbon dioxide in the blood, which can be dangerous for the body.[8]

The gold standard test to diagnose all types of SDB is by polysomnography (PSG), an overnight in-laboratory sleep study. During a PSG, there are several leads, bands, and sensors attached to the child to monitor their brain wave activity, gas exchange, airflow, and respiratory rate, among others. This allows the clinician to monitor for respiratory events such as apneas and hypopneas, oxygen desaturations, carbon dioxide retention, and arousals. A common measure of SDB severity calculated using PSG data is the apnea-hypopnea index (AHI), which is the number of apneas and hypopnea events per hour. Higher AHI, more severe and/or more frequent oxygen desaturations, higher carbon dioxide levels, and greater sleep fragmentation (measured as the 'arousal index', or number of arousals per hour), are all indicative of more severe SDB.[9]

Getting early treatment for SDB is imperative, as untreated SDB is associated with cardiovascular and behavioural problems, growth failure, cognitive impairment, excessive daytime sleepiness, and decreased quality of life that can carry into adulthood.[4] While an adenotonsillectomy is the first line of treatment for OSA in young children, not all children will respond to surgery. Adenotonsillectomies have been reported to fail to cure OSA in over 50% of children with obesity and in children who are older than 7 years.[10,11] For children who have surgical contraindications or who are not cured by surgical intervention, as well as those with non-obstructive forms of SDB such as CSA and nocturnal hypoventilation, positive airway pressure (PAP) therapy is a safe, non-invasive, and viable treatment alternative.[12,4]

### 1.3. PAP therapy

PAP therapy is a form of airway and/or ventilatory support that delivers pressurized air into the airways and lungs through a mask interface.[4] It can be administered through three main modes: continuous PAP (CPAP), bi-level PAP (BPAP), and auto-titrating PAP (auto-PAP). CPAP, which is often prescribed for children with OSA, delivers air into the airways and lungs at one continuous pressure to keep the upper airway open and prevent alveolar collapse.[8] BPAP is prescribed for children with CSA, hypoventilation, and for severe cases of OSA if CPAP is inadequate. It delivers air into the airways and lungs at two different pressures (inspiratory and expiratory pressures), in time with the individual's respiratory efforts, to increase the amount of air being inspired, assist with clearance of carbon dioxide and ensure

a minimum number of breaths are taken per minute. Finally, auto-PAP is a newer modality that exists for both CPAP and BPAP models, and is useful for initiating children on PAP therapy before they have undergone a titration PSG.[13] It delivers a variable pressure within a defined range by monitoring the patient's airflow and adjusting the pressure according to the amount of airflow limitation.[8] Differences between the modes are summarized in Table 1. With the exception of auto-PAP, prescription of PAP therapy generally requires a titration PSG to determine the optimal pressure setting. All three modes have shown success in managing SDB.[9]

The gold standard measurement for PAP therapy adherence is the use of PAP device downloads. Depending on available technology, downloads can be obtained directly by the clinic or by the local PAP provider during a patient's follow-up visit.[14] Some newer PAP devices have functionality that allows adherence data to be directly uploaded onto an online server each night,[15] but this is a fairly novel development that has not been readily available in the past. As such, the availability of PAP adherence downloads often depends not only on a child presenting for follow-up, but on them physically bringing their memory card to clinic or to a PAP provider. In the absence of objective data downloads, self-reports of adherence are often used as a proxy.

Despite all the benefits of PAP therapy use for SDB, adherence poses a major barrier to its use in children.[8] To be effective, PAP therapy must be worn consistently at night for an extended period of time. Many studies, however, cite extremely poor adherence of less than four hours per night.[15] While no empiric definition of PAP therapy adherence exists for children , many pediatric clinicians have adopted the adult definition of adherence (≥4h per night for ≥70% of nights) as minimum criteria, and some researchers suggest that a longer duration of nightly use may be necessary as children require more sleep than adults.[8] Although several interventions aimed at improving adherence in children have shown some success, there are insufficient clinical resources to pro-actively address non-adherence in all children starting PAP therapy.[15–17] Identifying characteristics associated with PAP non-adherence would allow clinicians to direct their finite resources towards the children who require the most support to succeed with PAP therapy.

Current research on predictors of PAP therapy non-adherence in children is limited. To the best of our knowledge, there are no systematic reviews on this topic. Two comprehensive narrative reviews on pediatric PAP therapy adherence have been published, but their methodological rigor was considered to be very low as they did not report their search strategies or use critical appraisal tools.[15,14] Several retrospective and prospective cohort studies have been conducted in this field of research which have

reported a range of potential baseline predictors. These include maternal education, age, race, sex, body mass index (BMI), developmental delay, asthma, social support, caregiver self-efficacy, mask type, having a family member on PAP therapy, PAP pressure level, and apnea-hypopnea index (AHI).[18–24] However, the majority of these predictors were unadjusted estimates identified by single studies, while other studies found contrary or null results. This discrepancy in findings is likely due to the wide variability in study population, adherence definitions, and lengths of follow-up across studies. Another factor to consider is sample size. With the exception of two studies of 140 and 141 children, sample sizes ranged from 27 to 62 participants, limiting the studies' evaluations to few characteristics simultaneously.[26,18,20,22,24,23,21,25,19,27–29] This variability in findings across studies has made identification of robust predictors challenging.

### 1.4. Prediction modelling

With the advent of 'Big Data' and machine-learning, the use of prediction modelling in the clinical research field has risen sharply. In the last five years, a search in PubMed of primary studies evaluating 'clinical prediction models' in humans yielded over 6000 results. Prediction models aim to combine multiple characteristics to predict – with a certain level of accuracy – the likelihood of a patient having a specific clinical outcome. In contrast to aetiological research, prediction modelling does not attempt to explain causal relationships, but to determine a patient's absolute risk for having an outcome so that their clinical care can be personalized.[30]

Constructing a robust prediction model requires well thought-out research questions, a good-quality dataset, and extensive analyses and validation of the final model. In particular, good prediction models depend on the presence of strong predictors.[30] This is especially important in pediatric research, where small sample sizes are often the norm and statistical power is low. A characteristic's utility as a predictor is determined by both the magnitude of its association with an outcome, as well as its prevalence within a population. For example, if a body mass index (BMI) of less than 10 was strongly associated with an adverse event, this may not be helpful for identifying patients at risk in a population where very few individuals have such low BMIs. It is ideal to identify strong predictors before developing a prediction model, particularly if obtaining data will require undergoing an expensive cohort study, as this will promote an accurate and discriminating final model.[30]

### 1.5. Rationale and study objectives

Identifying children at greatest risk of non-adherence is necessary to prioritize limited health resources towards those who require the most support to succeed. However, more preparation needs to be done before a prediction model to identify children at risk of PAP therapy non-adherence can be developed. The literature has not been systematically synthesized yet, therefore, it is unclear which variables may serve as meaningful candidate predictors of non-adherence. Furthermore, current individual studies reported in the literature are often composed of small sample sizes and unadjusted analyses focused on whether a variable is statistically significant, with inconsistent findings across studies. As such, it is unclear whether sufficiently 'strong' predictors have been identified yet. Modern prediction modelling strategies typically avoid primarily data-driven selection of variables, often additionally relying on expert judgement for the initial choice of candidates. An important input to planning a prediction modelling study would then be a robust assessment of characteristics that are prognostic of PAP use.

Therefore, the purpose of this thesis was to build upon existing literature to identify predictors of non-adherence to PAP therapy. These results will provide preliminary information on predictors to inform a larger prospective cohort study aimed at creating a prediction model to identify children at risk of PAP non-adherence.

The objectives of this thesis were to:

- Identify clinical and non-clinical predictors of PAP therapy adherence and non-adherence in children with SDB through a systematic review of the literature; and
- Identify predictors of six-month PAP therapy non-adherence in children with SDB starting PAP therapy through a retrospective cohort study at a pediatric tertiary care centre.

### 1.6. A comment on the primary outcome

For this thesis, we were primarily interested in factors associated with non-adherence to PAP therapy. Non-adherence is a more clinically relevant outcome for healthcare practitioners, as opposed to adherence, as it enables them to identify children who require additional resources to be successful with their PAP therapy. The methodological distinction in outcomes ('adherence' or 'non-adherence') is less critical in studies estimating odds ratios, mean differences, and linear beta coefficients, as either outcome results in exactly inverse or opposite findings and can therefore be easily compared. In studies of relative risks, however, the distinction between adherence and non-adherence becomes important, as results vary depending on the reference outcome level. Put simply, the factors associated with

adherence may not be the same as factors associated with non-adherence. As such, studies estimating relative risks are not directly comparable if they use different reference levels for their outcome.

Since no previous systematic reviews had been conducted in our field of research, we were inclusive and considered both predictors of adherence and non-adherence in our review. As all studies in the systematic review identified 'adherence' as their primary outcome, we framed the results solely in the context of 'adherence' for clarity of reporting. However, given the intent of this thesis was to identify predictors of non-adherence, our cohort study assessed 'non-adherence' as the outcome of interest. This was necessary as we were estimating relative risks. To enable easy comparison between the results of the systematic review and the cohort study, where methodologically appropriate, all subsequent discussion of the systematic review results (in Chapters 3 and 4) were reframed with the outcome as 'non-adherence'.

### 1.7. Structure of the thesis

This thesis will be presented in a thesis-by-manuscript format. Each research objective will be addressed in a separate chapter in the form of a manuscript. A preface will introduce each manuscript to provide its relevance within the context of the overall thesis.

**Chapter 2** presents the full work of the systematic review. This manuscript, titled "Predictors of adherence to positive airway pressure therapy in children – A systematic review and meta-analysis," was authored by Henrietta Blinder, Dr. Franco Momoli, Julia Bokhaut, Dr. Vanessa Bacal, Dr. Reuben Goldberg, Dr. Dhenuka Radhakrishnan, and Dr. Sherri L Katz. We systematically reviewed the literature and identified baseline predictors of PAP therapy adherence in children with SDB using PAP therapy.

**Chapter 3** reports on the findings of the retrospective cohort study, conducted at the Children's Hospital of Eastern Ontario. This manuscript, titled "Clinical predictors of non-adherence to PAP therapy in children – A retrospective cohort study," was authored by Henrietta Blinder, Dr. Franco Momoli, Stephen H Holland, Anna Blinder, Dr. Dhenuka Radhakrishnan, and Dr. Sherri L Katz. We evaluated children with SDB who were newly prescribed PAP therapy and identified baseline clinical characteristics which were predictive of PAP therapy non-adherence at six months.

Finally, **Chapter 4** consists of an overarching discussion to unify the findings of the two research studies and describe their utility within the current clinical and research landscape. Next steps for this work will be discussed.

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**Table 1.** Description of the three main PAP modes.

| | CPAP | BPAP | Auto-PAP |
|---|---|---|---|
| **Pressure support** | • One constant pressure level | • Two pressure levels (inspiratory and expiratory pressures)<br>• Can also have back-up respiratory rate | • Ideal pressure level calculated with each breath within a defined range |
| **Common indications** | • OSA | • Hypoventilation (secondary to neuromuscular disease or obesity)<br>• CSA | • Children who have not had a titration study<br>• Children requiring variable pressures throughout the night |
| **Mechanical function** | • Maintains the upper airway open<br>• Prevents alveolar collapse | • Increases the volume of air being inspired<br>• Assists with clearance of $CO_2$<br>• Maintains minimum breathing rate | • Available in both CPAP and BPAP modes<br>• Adjusts the pressure according to the amount of airflow limitation |

# 2. Predictors of adherence to positive airway pressure therapy in children – A systematic review and meta-analysis

## PREFACE

**Objective addressed**: to identify clinical and non-clinical predictors of PAP therapy adherence and non-adherence in children with SDB through a systematic review of the literature.

**Author contributions:** Henrietta Blinder developed the protocol, screened eligible studies for inclusion, abstracted data, conducted risk of bias assessment and quality of evidence assessments, conducted the statistical analysis, and wrote the manuscript. Dr. Sherri Katz and Dr. Franco Momoli provided clinical and methodological expertise on the development of the protocol, supervised all stages of research, and provided guidance on the writing of the manuscript. Julia Bokhaut screened eligible studies for inclusion, abstracted data, and conducted risk of bias assessments. Dr. Vanessa Bacal abstracted data and conducted risk of bias assessment. Dr. Reuben Goldberg screened eligible studies for inclusion. Dr Dhenuka Radhakrishnan provided clinical and methodological expertise on the protocol and guidance throughout the study. All authors reviewed and approved the final manuscript.

**Publication:** This manuscript was submitted to *Sleep Medicine* for review on July 26, 2019. The confirmation of submission is in Appendix 1, located at the end of this chapter.

**Ethics:** No ethics approval was required for this study.

## TITLE PAGE

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**Keywords:** Pediatric, sleep-disordered breathing, adherence, positive airway pressure, predictor

**Abbreviations: 95%CI** = 95% confidence interval; **AHI** = apnea-hypopnea index; **BPAP** = bi-level positive airway pressure; **BMI** = body mass index; **CPAP** = continuous positive airway pressure; **GRADE** = Grading of Recommendations Assessment, Development, and Evaluation; **IQR** = inter-quartile range; **OR** = odds ratio; **PAP** = positive airway pressure; **QUIPS** = Quality in Prognostic Studies tool; **SD** = standard deviation; **SDB** = sleep-disordered breathing.

**Funding**: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

**Declarations of interest:** None.

## ABSTRACT

**Background:** While positive airway pressure (PAP) is effective for treating sleep-disordered breathing (SDB) in children, adherence is poor. Studies evaluating predictors of PAP adherence have inconsistent findings, and no rigorous reviews have been conducted. This systematic review aims to summarize the literature on predictors of PAP therapy adherence in children.

**Methods:** Studies evaluating baseline predictors of PAP therapy adherence in children (≤20 years) with SDB were included. We searched MEDLINE, Embase, CENTRAL, CINAHL, Clinicaltrials.gov, and the last four years of conference abstracts. Results were described narratively, with random-effects meta-analyses performed where feasible. Risk of bias and confidence in the evidence were assessed.

**Results:** We identified 50 factors evaluated across twenty-eight studies (21 full text articles, seven abstracts). The highest rates of PAP therapy adherence were most consistently found with female sex, younger age, Caucasian race, higher maternal education, greater baseline apnea-hypopnea index (AHI), and presence of developmental delay. Pooled estimates included odds ratios of 1.48 (95%CI: 0.75-2.93) favoring female sex, 1.26 (95%CI: 0.68-2.36) favoring Caucasian race, and a mean difference in AHI of 4.32 (95%CI: -0.61-9.26) events/hour between adherent and non-adherent groups. There was low quality evidence to suggest that psychosocial factors like health cognitions and family environment may predict adherence.

**Conclusion:** In this novel systematic review, we identified several factors associated with increased odds of PAP therapy adherence in children. These findings may help guide clinicians to identify and support children less likely to adhere to PAP therapy and should be considered when developing interventions to improve adherence.

## 2.1. Introduction

Sleep-disordered breathing (SDB) is a condition characterized by impaired breathing during sleep. It affects 1-5% of the pediatric population,[1] and 30-60% of children in high-risk groups such as those with obesity or Down syndrome.[2,3] Many long-term consequences have been associated with SDB, including cardiovascular disease, behavioural problems, cognitive impairment, and decreased quality of life, eventually leading to irreversible end-organ damage.[4] With treatment, however, these sequelae can be mitigated, highlighting the importance of early intervention.

A commonly prescribed therapy for SDB in children with surgical contraindications or failure, complicating comorbid conditions, or non-obstructive forms of SDB, is positive airway pressure (PAP) therapy.[1,5] PAP is a form of non-invasive ventilatory support that delivers pressurized air into the lungs to assist with breathing.[1] It may include stenting the airway open with a continuous pressure (CPAP) for treatment of obstructive sleep apnea, or bi-level positive airway pressure (BPAP) to assist with ventilation. While effective, adherence to PAP therapy is challenging.[1] A narrative review by King and colleagues in 2014 found that most pediatric populations used PAP less than four hours per night; this is less than half the recommended amount of high-quality sleep based on Canadian guidelines for children aged 8-17 years.[6,7]

Given the limited pediatric sleep resources in Canada,[8] identifying children at risk for nonadherence would enable clinicians to dedicate their time and tailor their therapies to those who need the most support to be successful with PAP therapy. To date, there have been a limited number of published studies that focus on predictors of adherence in children. Previously identified predictors of adherence include female sex, African American race, and presence of a family member on PAP.[9–13] However, findings have been inconsistent across studies, and there are currently no published reviews specifically designed to identify PAP adherence predictors in children.[1] To address this gap, our aim was to conduct a rigorous and systematic review of the literature to identify predictors of pediatric PAP therapy adherence.

## 2.2. Materials and methods

The study has been registered (PROSPERO #CRD42016046275), and this manuscript was prepared according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement.[14]

Several changes were made to the protocol since its initial registration on PROSPERO. These changes were made through consensus by investigators (SK, FM, DR) who were not familiar with the results of the literature search and/or the included studies. Changes include:

The risk of bias tool was changed from the JBI Critical Appraisal tool for Descriptive/Case Series studies to the Quality in Prognosis Studies (QUIPS) tool, [15,16] as the latter tool was found to better account for potential sources of bias in studies of prognostic factors;

The eligible age range was widened to include children up to 20 years, as some studies reported outcomes on pediatric cohorts up to 20 years of age.

### 2.2.1. Eligibility criteria

***Population***

Studies of children (≤20 years old) newly prescribed non-invasive PAP therapy for SDB were included. Any method of SDB diagnosis which collected overnight respiratory data was accepted, including sleep study and nocturnal oximetry. Both CPAP and BPAP therapy were eligible for inclusion.

***Predictors***

All baseline factors evaluated quantitatively by study authors were considered for inclusion. Interventions introduced to enhance adherence, for example, the addition of a respiratory therapist to the team, were not included.

***Outcome***

The outcome of interest was adherence to therapy. There was no pre-specified definition or measure of adherence, nor a minimum length of follow-up time, to allow capture of as many studies reporting on predictors of adherence as possible. The impact of using a broad definition is addressed in the discussion.

***Study design***

This review considered studies reporting on factors associated with adherence, including randomized trials, cohort studies, and cross-sectional studies which reported on baseline data. Studies with sample sizes less than five, protocols, guidelines, and letters to the editor were excluded.

***Setting***

Regardless of where PAP therapy was initiated, only studies that followed patients in an outpatient setting were included.

***Report characteristics***

There were no *a priori* restrictions on language or publication date. All exclusions were reported in the study screening flowchart.

### 2.2.2. Information sources

A comprehensive literature search was conducted in MEDLINE including Epub Ahead of Print, In-Process & Other Non-Indexed Citations (1946 – March 21, 2019), Embase (1980 – March 21, 2019), and the CENTRAL Trials Registry of the Cochrane Collaboration (Mar 2019 Issue) using the Ovid interface. CINAHL was searched from inception using the EbscoHost interface. All final searches were conducted on Mar 21, 2019.

Reference lists of all primary studies and identified narrative/systematic reviews were hand-searched for relevant studies. We conducted a grey literature search of clinicaltrials.gov, and conference abstracts presented at the American Thoracic Society, American Academy of Sleep Medicine, European Respiratory Society, World Association of Sleep Medicine, and Canadian Sleep Society between 2015 – 2019. Authors of eligible studies were contacted up to two times via email, if available, to obtain additional study details. We also supplemented missing study details with those reported in their clinicaltrials.gov registry and related publications on the same study population (e.g. where more than one paper was published), where available.

### 2.2.3. Search strategy

The search strategy was designed and conducted by a librarian experienced in systematic reviews, using a method designed to optimize term selection.[17] Keywords were derived based on the concepts 'sleep-disordered breathing', 'positive airway pressure therapy', 'children', and 'adherence'. Previous systematic reviews on adherence were examined to determine search terms for that concept. After screening a sample of records, the strategy was revised to only include studies with indexing or text terms suggesting a pediatric age group. Search strategies are presented in Appendix 2.

### 2.2.4. Data collection and analysis

***Data management***

After initial online duplicate removal, records retrieved by the electronic search were downloaded and imported into a Reference Manager database,[18] and any remaining duplicate references were removed. Throughout the review, newly identified records were integrated into the set for screening. Records were then uploaded to CrowdScreen, an online platform to facilitate appraisal of records against the inclusion criteria.[19] All final data collection was performed in REDCap, a secure online electronic database.[20]

***Selection process***

Screening of eligibility criteria occurred independently and in duplicate by two reviewers at each phase of the review. Studies identified as eligible by at least one reviewer at the title and abstract screening phase were included for full text screening. To ensure predictors identified only in the full text were not missed, all eligible studies mentioning assessment of 'adherence' or 'compliance' to PAP therapy were considered eligible for full text review. Discrepancies in eligibility at the full text screening phase were resolved by consensus or by a clinical expert if necessary. The entire study selection process is presented below.

***Data collection process***

Data were extracted using electronic data collection forms created in REDCap.[20] These forms were piloted a priori with three records. Data extraction was performed in full by one reviewer (HB), with results verified by a second reviewer (VB or JB).

The following data was abstracted:

***Publication characteristics*:** study title, first author, year of publication, study timeframe, country of study origin, source of funding.

***Study characteristics****:* study design, sample size, age, apnea-hypopnea index (AHI), percent male sex, primary sleep diagnosis, method of sleep diagnosis, comorbidities, type of ventilation device, ventilator settings, length of time on ventilation, clinical support.

***Outcome characteristics***: method of assessment, definition of adherence, means with standard deviations (SD) or medians with interquartile ranges (IQR) for continuous measures, event rates for dichotomous measures, sample size per group, length of follow-up time. Only outcome data that informed the analysis of factors associated with adherence was reported.

***Predictor characteristics***: factors assessed, associated point estimates and 95% confidence intervals (95%CI) (both adjusted and unadjusted).

### 2.2.5. Risk of bias

Risk of bias for each included study was assessed independently by two reviewers (HB, JB) using the QUIPS tool, with disagreements resolved by consensus, or a third reviewer with clinical expertise when consensus could not be reached. The QUIPS tool is recommended by the Cochrane Prognosis Methods Group to assess risk of bias in prognostic factor studies. It considers bias across six domains: participation, attrition, prognostic factor measurement, confounding measurement, outcome measurement, and analysis and reporting.[16] This tool has been used in other recent systematic reviews with similar methodology.[21–24]

We made two modifications to the QUIPS tool. The domain of confounding measurement was removed from our bias assessment as we were not aiming to examine causal relationships at this stage of research. Further, we added a question to assess for a possible risk of selection bias in retrospective cohort studies: "Were patients with missing adherence data excluded from the eligible study cohort?" By only selecting participants with complete adherence data for inclusion in the study, bias may have been introduced if there was systematic loss of follow-up primarily in those who were non-adherent to PAP therapy.

### 2.2.6. Data synthesis

Baseline demographics were reported descriptively as mean±SD or median (IQR) for continuous variables, and percentages for categorical variables. Data on factors evaluated with respect to adherence were presented as point estimates with associated 95% confidence intervals. Where feasible, crude odds ratios (OR) were calculated by hand and differences between groups were transformed into mean differences.

Where pooling of outcome data was appropriate, we used the metafor package in R version 3.3.2.[25,26] Random-effects meta-analyses were conducted using the method of restricted maximum likelihood estimation. Study outcomes were transformed into different data types using metafor's *escalc* function in cases where pooling was feasible, such as transforming differing continuous outcomes into standardized mean differences. Appropriateness of pooling was assessed by examining studies for clinical heterogeneity in terms of severity of disease, presence and type of comorbidities, length of

follow-up, and adherence measure used. In the presence of clinical heterogeneity, pooling of data was not performed, and the results were presented narratively with the use of summary tables and figures.

In line with the 2016 recommendations by the American Statistical Association and a timely issue of the *American Statistician* journal consisting of 43 articles advocating to eliminate the use of p-values in null hypothesis significance testing, we did not report p-values in our results nor use them to draw conclusions.[27,28] We interpreted our findings based on the magnitude of the association, the level of variability, and the sample size.

We had intended to conduct sensitivity analyses informed by the risk of bias. A group consensus was reached by three authors who had not been involved in the study screening and data extraction (SK, FM, DR) to conduct a sensitivity analysis including only studies without high risk of bias across any domain, and at least three domains with low risk of bias. Due to limited reporting of quantitative data, we were unable to conduct any sensitivity analyses. We had likewise intended to assess for publication bias via funnel plots and conduct sub-group analyses for the three most predominant underlying causes of SDB (neuromuscular disease, obesity, or Down syndrome), but this was not possible due to data constraints.

#### 2.2.7. Confidence in the evidence

The strength of the body of evidence was assessed using a modified version of the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach, developed for systematic reviews of prognostic factor research.[29,30] Given very few studies were eligible for inclusion in meta-analyses, the quality of evidence was assessed using a narrative analysis.

### 2.3. Results

#### 2.3.1. Results of the search

The comprehensive literature search yielded 392 records after removal of duplicates, of which 28 were included in the final analysis. One Chinese text was excluded because an English language translation was unavailable.[31] There was one full text article identified through the grey literature search which replaced a previously included abstract of the same study.[32,33] A randomized controlled trial conducted by Marcus et al in 2012 resulted two publications on the same study population,[9,34] so only the publication by DiFeo et al was included in our review as it had the most complete data with respect to our primary outcome.[9] Twenty-one of the included studies were full text articles,[2,9–13,32,35–48] and seven were published conference abstracts.[49–55] A flowchart outlining the study selection process is shown in Figure 1.

### 2.3.2. Study characteristics

This review included eight prospective studies and 20 retrospective studies. Studies were conducted in the United States of America (n=15),[9,10,12,32,38–41,43,46,48,49,51,52,55] Canada (n=3),[2,36,42] Australia (n=3),[13,35,50] France (n=3),[37,45,54] the United Kingdom (n=2),[44,53] Mexico (n=1),[47] and Singapore (n=1).[11] The sample size of participants included in the analysis ranged from 9–240 children (median=50.5). Identification of factors associated with adherence was the primary study objective in 14 of the studies (50%),[9–13,35,40,42,49–53,55] of which six were abstracts. Study details are described in Table 1.

### 2.3.3. Adherence outcomes

Definitions of adherence and factors assessed by each study in relation to adherence are described in Table 2. Of the 24 studies which reported their method of adherence assessment, 20 (83%) studies used a PAP device download. Fourteen (50%) studies measured adherence between one- and six-months' post-treatment start.

Adherence was either measured dichotomously (using a cut-off) or continuously. The most common definition used to group participants into 'adherent' or 'non-adherent' categories was *>4 hours use per night for >70% nights* (n=6; 40% of studies with dichotomous assessments), with 11-75% of the study population meeting the criteria for adherence. The most commonly used continuous measure of adherence was *hours per night* (n=8; 62% of studies), with an average use of 2.8 – 7.0 hours per night.

### 2.3.4. Evaluated factors

We identified a total of 50 factors, which have been organized into five overarching categories: demographics, disease characteristics, technological factors, comorbidities, and psychosocial factors. Summary results are described below, with quantitative findings summarized in Table 3. A comprehensive list of all study results, organized by factor, is presented in Appendix 3.

***Demographics***

The most prominent demographic factors evaluated by study authors were sex, age, race, body mass index (BMI), maternal education, and socio-economic status. Of note, race was evaluated inconsistently across studies, with comparisons primarily being Caucasians to Blacks, Hispanics/Latinos, or no description of the groups being compared.

Study findings generally identified a trend towards better adherence with both female sex and Caucasian race. Several of the reported point estimates had wide confidence intervals, but overall

described a positive relationship with adherence. A meta-analysis of three studies[12,32,38] found that females had an OR of 1.48 (95%CI: 0.75, 2.93) of being adherent to PAP therapy compared to males (Figure 2A). Similarly, a meta-analysis of two studies[12,32] found that Caucasian race was associated with 1.26 (95%CI: 0.68, 2.36) greater odds of being adherent compared to non-Caucasian race (Figure 2B).

Several studies also reported better adherence with younger ages and with having a mother with higher levels of education. A dose-response relationship was seen in both cases. Of note, the relationship between younger age and adherence was only seen when evaluating adherence continuously; no relationship was identified between age and adherence when directly comparing adherent and non-adherent participants.

Most of the included studies that reported on BMI and socio-economic status had ambiguous or contradictory findings. All but one study examined adherence dichotomously, limiting the opportunity to assess for continuous trends. A meta-analysis of three studies[2,32,38] evaluating BMI resulted in a pooled standardized mean difference of -0.14 (95%CI: -0.47, 0.19) between the adherent and non-adherent groups (Figure 2C).

All the above factors were considered to be of very low quality of evidence, except for sex, age, and maternal education, which were all considered to be of low quality.

***Sleep-disordered breathing characteristics***

The most common SDB characteristics evaluated by study authors were AHI, obstructive AHI, level of oxygen saturation, and arousal index.

A higher baseline AHI tended to be associated with better adherence across studies. Point estimates of the included studies had high variability, but consistently identified a positive relationship. A meta-analysis of three studies[12,32,38] found that adherent children had 4.32 (95%CI: -0.61, 9.26) more events/hour compared to non-adherent children (Figure 2D) .

Evidence suggested that oxygen saturation was not associated with adherence in one study,[38] and other studies reported ambiguous findings with small point estimates.[12,38] However, all of the studies evaluating oxygen saturation examined adherence dichotomously, therefore no evaluations of continuous relationships of adherence with oxygen saturation were conducted.

We were unable to comment on other clinically relevant factors identified by study authors, including subjective symptoms, obstructive AHI, carbon dioxide retention, sleep efficiency, and arousal index, due to limited data with ambiguous findings. A higher baseline arousal index was associated with better

adherence in one study (mean difference between adherent and non-adherent participants of 7.9 arousal events/hour).[38] Apart from AHI and oxygen saturation, which had moderate and low qualities of evidence, respectively, all of the factors in this domain were considered to be of very low quality of evidence.

***Treatment characteristics***

The main treatment characteristics assessed for associations with adherence included PAP mode, PAP pressure level, and mask type.

Studies evaluating PAP mode either compared auto-CPAP to CPAP, or BPAP to auto-CPAP/CPAP. Studies evaluating auto-CPAP and CPAP generally reported similar adherence rates; no differences between groups were found in two studies.[47,49] Conversely, studies comparing BPAP and auto-CPAP/CPAP reported inconsistent results. One study[11] found BPAP use to be associated with better adherence, while others[2,39] reported lower adherence in BPAP users, no clinically significant difference between groups[9], or ambiguous findings.[48] A meta-analysis of two studies[2,39] reported that children using BPAP had an OR of adherence of 0.17 (95%CI: 0.05, 0.64). While this indicates that children using BPAP may have lower adherence than their counterparts using auto-CPAP/CPAP, our confidence in this finding was very low as the meta-analysis was unable to include three studies which reported either inverse (i.e. strongly favoring BPAP for improving adherence) or ambiguous findings with smaller magnitudes of association.

Results of studies evaluating an association between PAP pressure level and adherence were generally ambiguous, with small associations and wide confidence intervals reported.[12,46] One study noted a moderate correlation between increasing PAP pressure level and adherence (r=0.30).[53]

Several other factors, such as mask type, setting where PAP initiated for the first time (i.e. hospital or at-home), humidification, improvement in AHI on PAP, and difference between the final treatment pressure determined by polysomnography and the initial estimated PAP pressure, were assessed but there was insufficient quantitative data to report on. All treatment characteristics were of very low quality of evidence.

***Comorbidities***

The primary comorbid conditions evaluated by study authors in relationship to PAP therapy adherence were obesity, developmental delay, and asthma/atopy.

In general, presence of developmental delay was consistently associated with better adherence, with large magnitudes of effect reported.[9,12,55] However, several studies reported ambiguous findings.[35,55] Two studies further reported that children with obesity tended to have worse rates of adherence (ORs of 0.65 (95%CI: 0.31, 1.34) and 0.83 (95%CI: 0.51, 1.35)), but the associated confidence intervals were too large to draw meaningful conclusions.[11,12]

It was unclear whether asthma and atopy were associated with PAP adherence. One study[11] reported a higher odds of adherence in patients with asthma (OR = 3.00; 95%CI: 0.87, 10.3), but the inverse was seen when evaluating asthma and atopy combined, or allergic rhinitis alone (ORs of 0.45 (95%CI: 0.20, 1.03) and 0.73 (95%CI: 0.22, 2.45), respectively).[11,12]

The only other comorbid conditions evaluated with respect to PAP therapy adherence were presence of a genetic syndrome and having an orofacial cleft (as compared to craniosynostosis or a branchial arch anomaly). The comorbid conditions were each evaluated by one study, with ORs of 3.00 (95%CI: 0.87, 10.3)[11] and 1.83 (95%CI: 0.75, 4.44)[38] reported, respectively. The quality of evidence was very low for all comorbid conditions evaluated, except for developmental delay, which was of low quality.

***Psychosocial factors***

The OSA-18 tool, a measure of SDB-related quality of life, and level of school attended were the only psychosocial factors evaluated by more than one study each. In terms of the OSA-18, one study reported a lower overall total score in adherent participants compared to non-adherent participants, and two studies reported a statistically significant association between the 'level of caregiver concern' subscale and adherence. Level of school was evaluated by two studies conducted by the same research team, who found that children in primary school tended to have better adherence compared to children in middle/high school. No magnitudes of effect were reported by the study authors.

There were several other psychosocial factors evaluated by single studies that may have been associated with adherence. Children who perceived having a 'worse than usual night of sleep' had an adjusted OR of 0.20 (95%CI: 0.04. 0.90) for adherence compared to their counterparts.[52] A correlation of 0.50 was reported between amount of social support and nights of PAP use per month, or 5.5±1.40 more nights per month with a one unit increase in social support.[9] Those with a family member on PAP used their device 1.3 more hours per night (95%CI: 1.03, 1.57), 1.0 more hours per nights used (95%CI: 0.73, 1.27), 3.4% more nights of use (95%CI: 0.53, 6.27), and 12.5% more nights used greater than four hours (95%CI: 9.19, 15.81) compared to those without a family member on PAP.[10] One study identified that caregiver-reported self-efficacy and risk perception were associated with 0.81 (95%CI: 0.22, 1.39)

and 0.16 (95%CI: -0.30, 0.63) more hours of use per night with a one unit increase in score, respectively.[40]

The quality of evidence for all evaluated psychosocial factors was predominantly very low.

### 2.3.5. Risk of bias

Risk of bias was assessed for each included study using the QUIPS tool. Individual study results by risk of bias domain are presented in Figure 3. Abstracts were generally given moderate or high risk of bias ratings due to limited reported information.

For full text evaluations, risk of selection bias and risk of attrition bias were concerning for retrospective and prospective cohort studies, respectively, as all of the included studies but one[48] categorically excluded participants with missing adherence data from their analyses. Percentage of participants excluded from analyses due to missing data ranged from 0% to 61%.

Risk of bias due to measurement of predictive factors was generally low as most factors were clinical characteristics commonly measured using objective methods. Adherence outcomes were also predominantly measured using objective data downloads from the PAP device, as compared to subjective parent/child reports. However, many of these studies were still identified as having a moderate risk of bias associated with outcome measurement as they assessed adherence cross-sectionally. Rather than measuring adherence after a set length of time on PAP therapy, such as three months, cross-sectional studies measured adherence of all presenting children at a single point in time, regardless of whether they had just started therapy or had been on it for years.

The last domain was risk of statistical reporting bias, which was low in all but two full-text studies which did not report sufficient information and/or had conflicting results in their text and figures for their measured outcomes.[11,45]

Based on our pre-determined criteria, the studies by Castorena et al, DiFeo et al, Ennis et al, Katz et al, Marcus et al, Nixon et al, Roberts et al and Simon et al were qualified as having a low risk of bias.[2,9,35,38,42,43,47,48]

## 2.4. Discussion

To the best of our knowledge, this is the first review to systematically examine the literature for predictors of adherence to PAP therapy in children. We identified a total of 50 clinical and non-clinical factors assessed by study authors for their association with adherence, across a wide range of domains.

The highest rates of adherence tended to be found with female sex, younger age, Caucasian race, a higher level of maternal education, greater AHI, and presence of developmental delay. While many psychosocial factors were identified by study authors and showed potential as predictors, such as level of social support, parental self-efficacy, and having a family member on PAP, they were often only assessed by single studies with small sample sizes, limiting their generalizability for application to the larger pediatric population.

***Contextualization within the current literature***

Factors associated with adherence have been studied in populations of children with other chronic medical conditions requiring long-term therapy, such as children with cystic fibrosis receiving physiotherapy, and children with diabetes treated with insulin. These studies identified some similar predictors to ours, including child age, level of maternal education, and parental beliefs regarding therapy.[56–63] This cohesiveness across pediatric medical conditions increases our confidence in our study findings, and suggests that there may be an underlying pattern of adherence exhibited by children, regardless of disease and type of therapy.

As was shown in our study, treatment adherence often decreases as children grow older and begin making health decisions independently of their parents. Previous literature has theorized that children gaining autonomy may become less adherent because they do not understand the severity of their illness, or are responding negatively to feeling pressured to use their therapy.[58,60,64] This may also explain the higher PAP adherence rates seen in children with developmental delay, who often remain dependent on their parents as they age and may be less affected by the notion of needing to use PAP therapy. It should be noted that, while our study did identify higher rates of adherence in children with developmental delay, PAP therapy is not offered for all children. The family and the doctor must come to an agreement before PAP therapy is prescribed, therefore it is possible that only children with developmental delay who had a greater likelihood of accepting PAP therapy were given a PAP device to trial.

Compared to studies in adults, which often identified multiple markers of SDB-disease severity as predictors of PAP therapy adherence,[65] AHI was the only marker of disease severity in our study which may be associated with adherence. This discrepancy across age groups may simply be due to limited information, as the majority of disease-severity markers reviewed in our study had inconclusive findings. There may also be differences in disease-related knowledge and perception. In addition to having a better understanding of the long-term consequences of untreated severe illness,[58,60,64] adults may be

better at comprehending the illness' impact on their quality of life due to having more experience with ill health.[66]

In line with other health outcomes, lower maternal education and racial minority status tended to be correlated with poor adherence in our study. Improving adherence in these groups is essential.[67] Promisingly, many psychosocial factors, such as health cognitions and family environment, also tended to be associated with better adherence, indicating that interventions aimed at altering child and parent perceptions may be effective in improving PAP therapy adherence rates.[68,69] The association between adherence and caregiver factors, such as level of caregiver concern and caregiver-reported risk perception, may also partially explain why children with developmental delay and greater SDB severity tended to have better adherence. Parents with children who either have more severe disease or are more medically complex may perceive a greater risk of negative outcomes due to untreated SDB, which may result in greater motivation to encourage good adherence in their child. As parents are the first-line decision-makers regarding their child's health, parental buy-in and encouragement to use the therapy is crucial to ensure children learn its importance and develop good habits.[70] Further, engaging youth to understand the importance of PAP therapy and supporting them in its use autonomously may help foster greater adherence to treatment. Given that health habits in childhood often continue into adulthood, intervening earlier in the health trajectory is critical to mitigate these health inequalities.

While preliminary, these identified characteristics can serve as a starting point for clinicians aiming to improve rates of PAP therapy adherence in children. Based on our findings, adherence tended to be lower in children who were male, more autonomous, of a non-Caucasian race, with a lower level of maternal education, and who had less severe SDB. Clinicians can use these characteristics to identify a target population of children to consider including in future studies aimed at developing and evaluating interventions to improve PAP adherence in children with SDB. Considering the relationship between these characteristics and adherence may also help identify methods to improve adherence. For example, if adherence decreases with child autonomy, educating and supporting the parent may become less important with increasing age, compared to using supports tailored towards the youth, such as text reminders and check-ins.

***Methodological concerns***

Despite growing interest, there are still many challenges affecting the quality of research in this field. Many of the associations identified were either weak in strength or had high variability, limiting our ability to draw robust conclusions. Almost all of the included studies excluded participants with missing

adherence data from their review, and attrition rates were generally high. If children who were non-adherent were less likely to return for follow-up than those who were adherent, the study populations may have been biased towards having higher rates of adherence. Our data quality was also affected by the large number of cross-sectional studies. This increased the within-study heterogeneity as these studies included both patients newly started on PAP and those who had been on it for years, potentially masking predictors of PAP therapy adherence.

Another challenge was the lack of a unified approach to reporting adherence. We identified over 10 different definitions/measures of adherence in our review alone, limiting the number of results which could be pooled. This further may have affected the robustness of our data, as using different cut-points might alter the thresholds at which predictors are identified. Many studies, in the absence of a definition, dichotomized their outcome into 'adherent' and 'non-adherent' groups for simplicity. While convenient, this limits opportunities to evaluate trends that might only be noticed on a continuous, dose-response scale,[71] and can be especially problematic in pediatric studies often already at a disadvantage due to smaller sample sizes. Additionally, 17% of studies used subjective patient or clinician reports of adherence rather than objective downloads, which may have resulted in over-reporting of adherence.

Poignantly, the variability across studies was also our study's main strength. We intentionally used broad inclusion criteria aimed at capturing as many predictors as possible. We used an inclusive search strategy, reported on findings from conference proceedings, and did not pre-specify a measure of adherence. These steps minimized the risk of publication bias and promoted identification of less-publicized studies. We also assessed the risk of bias and the quality of the evidence using tools specifically designed for studies of prognostic factors to increase the rigor of our work. Combined, these steps ensured our review was meticulous and inclusive in its search and evaluation of the literature.

***Conclusion***

This systematic review is the first to comprehensively summarize the literature on predictors of PAP therapy adherence in children. We identified several factors which may be associated with adherence, including sex, age, race, level of maternal education, AHI, and developmental delay. Although the overall quality of evidence was poor, our findings suggest a pattern of PAP therapy adherence parallel to that seen in children using long-term therapies for other chronic medical conditions. Clinicians should gauge the above factors, and the role they might play with respect to PAP therapy adherence, when developing and evaluating interventions to enhance adherence.

***Acknowledgements****:* We would like to thank Catherine Glass, BScH, MA(c) (Children's Hospital of Eastern Ontario Research Institute) for methodological assistance and Margaret Sampson, MLIS, PhD, AHIP (Children's Hospital of Eastern Ontario) for developing the electronic search strategies.

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## Figure, Table, and Appendices.

**Figures:**



**Tables:**



**Appendices:**

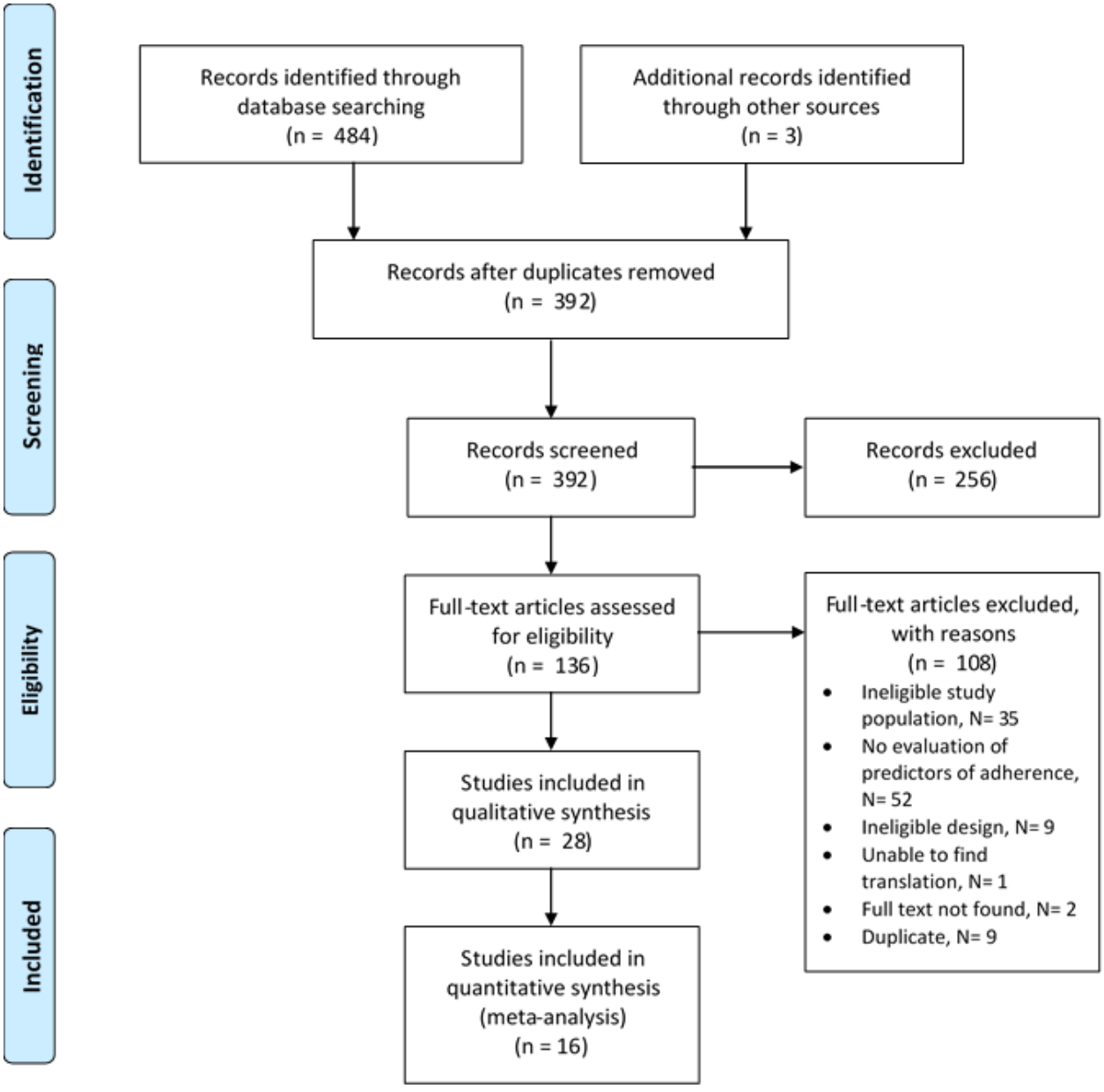


**Figure 1.** PRISMA flow diagram.

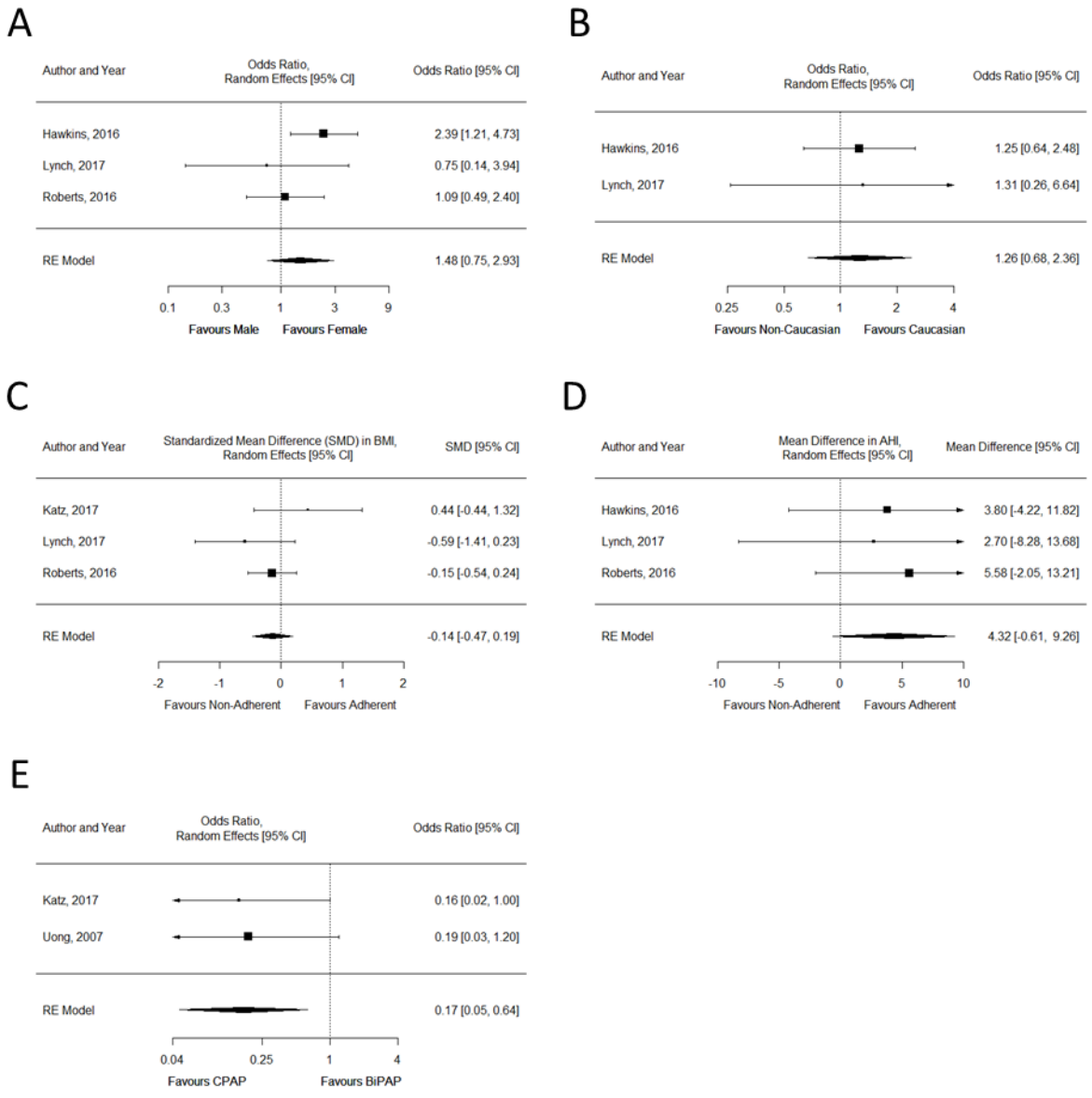


**Figure 2.** Meta-analyses of the associations between selected factors and adherence to PAP therapy.

(A) Association with female sex. (B) Association with Caucasian race. (C) Association with body mass index (BMI). (D) Association with apnea-hypopnea index (AHI). (E) Association with PAP mode.

| Study | Bias Domains | | | | |
|---|---|---|---|---|---|
| | Study participation | Study attrition | Predictive factor measurement | Outcome measurement | Statistical Reporting |
| **Full text** | | | | | |
| Beebe 2011 | 🟢 | 🔴 | 🟢 | 🔴 | 🟢 |
| Castorena-Maldonado 2008 | 🟢 | 🟢 | 🟢 | 🟡 | 🟢 |
| Com 2015 | 🔴 | ○ | 🟢 | 🟢 | 🟢 |
| DiFeo 2012 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 |
| Ennis 2015 | 🟡 | 🟢 | 🟢 | 🟡 | 🟢 |
| Hawkins 2016 | 🔴 | ○ | 🟢 | 🟡 | 🟢 |
| Katz 2017 | 🟢 | 🟢 | 🟢 | 🟡 | 🟢 |
| Lynch 2017 | 🟢 | 🔴 | 🟢 | 🟢 | 🟢 |
| Machaalani 2016 | 🟡 | ○ | 🟡 | 🟢 | 🟡 |
| Marcus 2006 | 🟡 | 🟡 | 🟢 | 🟢 | 🟢 |
| Nathan 2013 | 🔴 | ○ | 🟢 | 🔴 | 🔴 |
| Nixon 2011 | 🟢 | ○ | 🟢 | 🟢 | 🟢 |
| O'Donnell 2006 | 🔴 | ○ | 🟢 | 🟡 | 🟢 |
| Perriol 2019 | 🔴 | 🔴 | 🟢 | 🔴 | 🔴 |
| Puri 2016 | 🔴 | ○ | 🟢 | 🟢 | 🟢 |
| Ramirez 2013 | 🔴 | ○ | 🟢 | 🟡 | 🟢 |
| Roberts 2016 | 🟡 | ○ | 🟢 | 🟢 | 🟢 |
| Simon 2012 | 🟡 | 🟢 | 🟢 | 🟡 | 🟢 |
| Trucco 2018 | 🔴 | ○ | 🟢 | 🟢 | 🟡 |
| Uong 2007 | 🔴 | ○ | 🟢 | 🟡 | 🟢 |
| Xanthopoulos 2017 | 🔴 | ○ | 🟢 | 🟢 | 🟢 |
| **Abstract** | | | | | |
| Brockbank 2015 | 🔴 | 🔴 | 🟢 | 🟢 | 🟡 |
| Chan 2009 | 🔴 | ○ | 🟡 | 🔴 | 🔴 |
| Kang 2018 | 🔴 | ○ | 🟢 | 🟡 | 🟡 |
| Kiel 2012 | 🔴 | ○ | 🟡 | 🟡 | 🔴 |
| Paruthi 2014 | 🔴 | ○ | 🟡 | 🔴 | 🔴 |
| Perriol 2018 | 🔴 | ○ | 🟢 | 🔴 | 🟡 |
| Vincent 2015 | 🔴 | ○ | 🟢 | 🟡 | 🔴 |

**Legend:**
🟢 Low risk of bias 🟡 Moderate risk of bias 🔴 High/unsure risk of bias ○ N/A

**Figure 3.** Summary assessments of the risk of bias by domain for the included studies.

**Table 1.** Study characteristics

| Study | Study design | N | Condition(s) of interest | Method of diagnosis | Age[a] | AHI[a] | Primary objective |
|---|---|---|---|---|---|---|---|
| **Full Texts** | | | | | | | |
| **Beebe 2011** | Prospective cohort | 13 | OSA and obesity | PSG | 14.8±1.8 (A)<br>14.4±1.5 (NA) | 10.0±6.8[b] (A)<br>9.3±5.7[b] (NA) | To determine whether PAP use improves academic functioning among adolescents with obesity-related OSA |
| **Castorena-Maldonado 2008** | Prospective cohort | 48 | severe OSA and scheduled for surgery | Home sleep study | 6 (4-7) | 6 (3.3-8.0) | To describe preoperative PAP compliance in children with OSA |
| **Com 2015** | Retrospective cohort | 36 | Children with OSA and obesity | PSG | -- | -- | To describe characteristics and surgical outcomes of obese children with OSA |
| **DiFeo 2012** | RCT | 56 | OSA | PSG | 12±4 | 19±16 | To evaluate factors predicting PAP adherence in children referred for PAP initiation |
| **Ennis 2015** | Qualitative study with retrospective cohort data | 9 | Nocturnal hypoventilation and obesity/ neuromuscular disease | PSG | 13.0±2.2 | 22.6±28.6 | To explore factors relating to BPAP adherence, and compare these between youth with underlying obesity or neuromuscular disease |
| **Hawkins 2016** | Retrospective cohort | 140 | OSA | --[c] | 12.0±5.7[d] (A)<br>12.7±4.7[d] (NA) | 20.3±26.8[e] (A)<br>16.5±21.2[e] (NA) | To examine demographic and disease-specific characteristics in relation to PAP adherence |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Katz 2017** | Prospective cohort | 27 | Moderate-severe SDB and obesity | PSG | 14.5 (12.6-16.5) | 15.5 (7.4-25.2) | To evaluate the change in HOMA-IR and 24 blood pressure after PAP treatment for children with obesity |
| **Lynch 2017** | Prospective cohort | 25 | OSA | PSG | 10.5±2.2 (A)<br>13.5±2.3 (NA) | 13.2±19.6 (A)<br>10.5±7.6 (NA) | To examine the relationship between CPAP adherence and quality of life in youth with OSA |
| **Machaalani 2016** | Retrospective cohort | 55 | SDB | PSG | 6.9±5.5 | 24.9±22.8 | To objectively measure adherence and effectiveness of PAP in children and determine factors associated with adherence |
| **Marcus 2006** | RCT | 21 | OSA | PSG | 10±4 (BPAP group)<br>11±4 (CPAP group) | 27±32 | To determine adherence to and effectiveness of PAP in children with OSA |
| **Nathan 2013** | Retrospective cohort | 51 | OSA | PSG | 11 (8-13) | 26.7 (12.0-79.7)[b] | To determine NIV compliance in children with OSA and the factors affecting compliance |
| **Nixon 2011** | Retrospective cohort | 30 | OSA | --[c] | 9.6±6.5 (A)<br>8.8±4.9 (NA) | 22.6±16.0[b] (A)<br>22.9±22.6[b] (NA) | To determine predictors of CPAP adherence |
| **O'Donnell 2006** | Retrospective cohort | 50 | OSA | PSG | 10.0±5.1 | 11.3[f] | To describe CPAP use and adherence among children |
| **Perriol 2019** | Prospective cohort | 34 | OSA | PSG | 10.4±3.2 | 12.2±10.6 | To evaluate CPAP adherence and its evolution over 24 months in non-syndromic children with OSA |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Puri 2016** | Retrospective cohort | 56 | OSA | PSG | 13.2±3.7 | 25.2±28.7 | To examine whether the presence of a family member on PAP therapy would be associated with better PAP adherence |
| **Ramirez 2013** | Retrospective cohort | 62 | SDB | --[c] | 10.0±4.7[d] | -- | To assess the adherence of children to long-term PAP therapy |
| **Roberts 2016** | Retrospective cohort | 100 | OSA and a craniofacial condition | PSG | 9.6±4.3 (A)<br>9.5±4.6 (NA) | 17.6±19.8 (A)<br>12.0±19.1 (NA) | To characterize and quantify the effects of PAP to the growing midface and maxillary dentition in children with OSA and craniofacial conditions. |
| **Simon 2012** | Qualitative study with retrospective data | 51 | OSA | PSG | 13.26±2.45[d] | 17.7±21.7[d] | To provide descriptive data on adherence in youth with OSA, and to develop a psychometrically sound measure of barriers for adherence to PAP use |
| **Trucco 2018** | Retrospective cohort | 25 | SDB and Down syndrome | PSG | 2.15 (0.7-5.3) | 11.1 (4.4-24.9) | To describe the prevalence and nature of SDB in children with Down syndrome |
| **Uong 2007** | Retrospective cohort | 27 | OSA | PSG | 13.6±3.1 | 28.4±31.8 | To describe PAP effectiveness and adherence among school-aged children |
| **Xanthopoulos 2017** | Retrospective cohort | 141 | OSA | --[c] | 11.9 (7.9-15.5) | 13.8 (7.1-29.7) | To examine the relationship between health cognitions prior to starting CPAP and CPAP adherence |

| Abstracts | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Brockbank 2015** | Cross-over RCT | 13 | OSA | PSG | 14.3±2.7 | 10.5±5.8 | To determine whether auto-CPAP provides an accurate pressure estimation, and better treatment adherence and outcomes compared to fixed CPAP |
| **Chan 2009** | Retrospective cohort | 45 | SDB | PSG | -- | -- | To investigate the effectiveness of and compliance to PAP, and identify factors associated with compliance |
| **Kang 2018** | Retrospective cohort | 240 | OSA | --[c] | 7.9 (3.2-13.1) (Developmental delay)<br>11.0 (5.5-16.1) (No developmental delay) | -- | To compare PAP adherence between children with developmental disabilities and typically developing children |
| **Kiel 2012** | Retrospective cohort | 113 | OSA | --[c] | 11.7[f] | 15.4[f] | To determine what factors are associated with PAP compliance |
| **Paruthi 2014** | Retrospective cohort | 104 | OSA | PSG | -- | -- | To determine whether a positive in-lab titration experience is associated with improved adherence |
| **Perriol 2018** | Retrospective cohort | 66 | SDB | PSG | 10±3 | 13.2±11 | To describe patients' compliance with 12-month treatment |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Vincent 2015** | Retrospective cohort | 102 | SDB | --[c] | 13[g] | -- | To describe and analyze NIV adherence among established patients, and determine which factors significantly affect it |

[a]Results are described as either mean ± SD or as median (IQR 1 – IQR 3).

[b]Obstructive index reported

[c]Type of diagnostic test done not specified.

[d]Collected at time of download, not at baseline.

[e]AHI collected from earliest titration PSG, which may or may not have been the diagnostic PSG at baseline.

[f]SD was not reported.

[g]IQR not reported.

**Abbreviations**: **A** = adherent group; **BPAP** = bi-level positive airway pressure; **CPAP** = continuous positive airway pressure; **NA** = non-adherent group; **OSA** = obstructive sleep apnea; **PAP** = positive airway pressure; **PSG** = polysomnography; **RCT** = randomized-controlled trial; **SDB** = sleep-disordered breathing.

**Table 2.** Adherence characteristics and outcomes

| Study | Adherence definition[a] | Adherence results[b] | Length of follow-up | Assessment method[c] | Predictors assessed |
|---|---|---|---|---|---|
| **Full text** | | | | | |
| **Beebe 2011** | ≥21% of sleep time spent with PAP use | 46% | 4 months | R | Sex, age, race, BMI, OAHI, self-reported grades, self and parent-reported school QOL, vigilance, PAP pressure |
| **Castorena-Maldonado 2008** | ≥3h/night<br>h/night | 73%<br>4.5±2.6 | From baseline to surgery, median days (IQR)= 26 (8-71) | D | Weight, BMI, PAP mode, PAP pressure, number of apneas and hypopneas |
| **Com** | >4h/night for >70% of nights | 11% | 4 years | D | Race |
| **DiFeo 2012** | h/night<br><br>Nights/month | 3±3<br>2.8±2.7<br><br>22±8<br>19±9 | 1 month<br>3 months<br><br>1 month<br>3 months | D | Age, race, developmental delay, social support, parent stress, maternal education, sex, nasal symptoms, mESS questionnaire, AHI, PAP pressure, obesity, PAP mode |
| **Ennis 2015** | >4h/night for >50% of nights in preceding month | 77.8% | Most recent download | D | AHI |
| **Hawkins 2016** | ≥4h/night for >70% of nights | 49% | Most recent download | D | Sex, race, AHI, oxygen saturation, % total sleep time with oxygen saturation <90%, residual AHI, insurance status, developmental delay, obesity, atopy, Down syndrome, PAP pressure, PAP mode |
| **Katz 2017** | ≥4h/night for ≥50% of nights | 64% | 6 months | D and R | BMI, PAP mode |

| | | | | | |
|---|---|---|---|---|---|
| **Lynch 2017** | >4h/night for ≥50% of nights | 60% | 3 months | D | Sex, age, race, BMI, household income, maternal education, AHI, OSA severity, total sleep time, sleep efficiency, OSA-18 questionnaire |
| **Machaalani 2016** | ≥4h/night for ≥70% of nights | 75% | First assessment post-treatment start; approximately 4-6 weeks | D | Age |
| **Marcus 2006** | ≥3h/night | -- | 6 months | D | PAP mode, sex, age, race, subjective symptoms (standardized set of questions), AHI, oxygen saturation, arousal index, PAP pressure |
| **Nathan 2013** | ≥4 nights/week | 41% | All adherence data available | R | Sex, age, obesity, allergic rhinitis, asthma, genetic syndrome, OAHI, PAP mode, humidification, titration, PAP counselling, PAP device funding |
| **Nixon 2011** | h/night | 4.7±2.7 | 3 months | D | Sex, age, OAHI, oxygen saturation, arousal index, location of PAP initiation, developmental delay, presence of a significant comorbidity, difference between prescribed and final pressure, SES |
| **O'Donnell 2006** | % nights used, median (IQR)<br>h/night (IQR)<br>h/night for nights used (IQR) | --<br>4.7 (1.4-7.0)<br>6.3 (3.3-8.5) | All days of follow-up Median (IQR) = 207 (50-450) days | D | Age, mask type, psychology support, sex, AHI, developmental delay |
| **Perriol 2019** | h/night | 7.0±2.7 | --[d] | -- | Age, AHI, developmental delay, school level |
| **Puri 2016** | h/night | *Family member with vs without PAP*<br>3.6±2.2 vs 3.4±1.8<br>3.0±2.6 vs 2.8±2.2 | 1 week<br>1 month | D | Age, sex, OAHI, obesity, presence of a family member on PAP |

| | | | | | |
|---|---|---|---|---|---|
| | | 3.6±2.6 vs 2.4±2.4 | 3 months | | |
| | h/night for nights used | 4.0±2.6 vs 3.8±2.7 | 1 week | | |
| | | 3.9±2.6 vs 3.8±2.4 | 1 month | | |
| | | 4.8±2.6 3.8±2.4 | 3 months | | |
| | % of nights | 82±26.1 vs 77±24.3 | 1 week | | |
| | | 65±21.8 vs 65±24.3 | 1 month | | |
| | | 58±26.2 vs 55±24.3 | 3 months | | |
| | % of nights used >4h | 38±21.7 vs 37±30.4 | 1 week | | |
| | | 33±30.5 vs 31±30.4 | 1 month | | |
| | | 36±30.5 vs 23±30.4 | 3 months | | |
| **Ramirez 2013** | h/night for nights used | 08:17±02:30 | Most recent download | D | Indication for PAP, mask type |
| **Roberts 2016** | ≥4h/night on ≥70% of nights for ≥6months | 50% | At least 6 months. Compliant group: 2.6 ± 1.2 years; noncompliant group: 2.5 ± 1.3 years | D and R | Sex, age, height, weight, BMI, AHI, oxygen saturation, carbon dioxide retention, arousal index, sleep efficiency, craniofacial diagnosis, LeFort rating, mandibular advancement prior to PAP |
| **Simon 2012** | h/night | 3.35±2.79 | Last 3 months prior to clinic visit. Reports covered 89 ± 86.5 days | D | PAP mode, device brand, mask type, home healthcare provider |
| **Trucco 2018** | >4h/night for >50% of nights | 52.0% | 4 months | D | PAP mode |
| | | 45.8% | Latest download | | |
| **Uong 2007** | >4h/night for ≥70% of nights | 70.4% | Follow-up of 18.1 ± 11.8 months | D | AHI, PAP mode, difference between baseline and residual AHI, sex, age, race, BMI, subjective symptoms (standardized set of questions), |
| | h/night | 7.0±2.1 | | | |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | oxygen saturation, carbon dioxide retention |
| **Xanthopoulos 2017** | Minutes of PAP use over all nights<br>>20 min/night | 176.4 (37.3-350.2)<br>79% | 1 month | D | Caregiver-reported and patient-reported risk perception of OSA, self-efficacy regarding PAP use, and outcome expectations of PAP use |
| **Abstract** | | | | | |
| **Brockbank 2015** | % nights used | *Auto-CPAP vs fixed CPAP*: 62.5±27.2 vs 63.2±26.9 | 4 weeks | D | PAP mode |
| **Chan 2009** | -- | 6.45[e] | Cross-sectional assessment | D | Age, PAP pressure, humidification |
| **Kang 2018** | | *Developmental delay vs no developmental delay* | | -- | Age, sex, race, developmental delay, PAP pressure, obesity, OAHI |
| | h/night on nights used | 5.0 (1.4-7.9) vs 4.6 (1.9-7.2) | 3 months | | |
| | | 6.4 (1.8-8.3) vs 5.7 (2.5-7.3) | 6 months | | |
| | % nights used | 86.7 (33.9-97.9) vs 62.9 (30.8-87.8) | 3 months | | |
| | | 90.0 (53.3-100) vs 70.7 (29.2-90.8) | 6 months | | |
| **Kiel 2012** | -- | Not reported | First clinic visit | D | OSA-18 questionnaire, mESS questionnaire, whether parents stayed to hear the results of the PSG the following morning, AHI, PAP mode, mask type |
| **Paruthi 2014** | >4h/night for >70% of nights over 30 consecutive days | 55.8% | 3 months | -- | Sex, age, BMI, AHI, perceiving the titration to be a 'worse' night of sleep |

| | | | | | |
|---|---|---|---|---|---|
| **Perriol 2018** | -- | 90% | 12 months | -- | PAP mode, obesity, school level, location of PAP initiation |
| **Vincent 2015** | % of nights with ≥4h of use | 64.2[e] | Cross-sectional collection, adherence data covered 30-182 days | D | Sex, age, AHI, PAP pressure |

[a]This was the definition reported by study authors in their quantitative assessment of predictors of adherence. Definitions either constituted of continuous measures (e.g. h/night) or a cut-off (e.g. >4h per night).

[b]Adherence results are described dichotomously (percent adherent) or continuously (mean ± standard deviation). Units of measure are defined by the adherence definition used by study authors, described in the preceding adjacent column.

[c]R= Report (parent or clinical report); D = Download of adherence data from PAP device.

[d]Unclear reporting regarding length of follow-up for assessment of predictors of adherence; between 1-24 months.

[e]No standard deviation reported.

**Abbreviations**: **AHI** = apnea-hypopnea index; **BMI** = body mass index; **h** = hours; **HOMA-IR** = Homeostatic Model Assessment of Insulin Resistance; **mESS** = modified Epworth Sleepiness Scale; **OAHI** = obstructive apnea-hypopnea index; **OSA** = obstructive sleep apnea; **PAP** = positive airway pressure; **QOL** = quality of life; **SES** = socio-economic status.

**Table 3.** Summarized quantitative findings of selected factors assessed as predictors of PAP therapy adherence[a].

| Assessed factor | Total number | | Relationship with adherence: number of studies; range of point estimates[b] | | | | Meta-analysis estimate (95%CI) | GRADE score |
|---|---|---|---|---|---|---|---|---|
| | Participants | Studies[c] | Suggestive of ↑ adherence | Suggestive of ↓ adherence | Suggestive of no association | Ambiguous | | |
| **Demographics** | | | | | | | | |
| **Female sex** | 359 | 6 | **n = 3;** $OR_{unadj}$ = 2.10 – 4.00[11,12,35]; $OR_{adj}$ = 5.22[11] | -- | -- | **n = 3;** $OR_{unadj}$= 0.75 – 1.25[32,38,46] | **n = 3;** $OR_{unadj}$ = 1.48 (0.75 – 2.93) [12,32,38] | ** |
| **Older age** | 482 | 9 | -- | **n = 3;** $MD_{adh-nonadh}$ = -3 yrs[32]; $MD_{high-low}$ =-3.6 h/night[36], -2.8 h/nights used[36], -36.7% nights used[36]; r = -0.5[9] | **n = 2;** $MD_{adh-nonadh}$ = 0.2 – 0.4 yrs[38,46] | **n = 4;** $MD_{adh-nonadh}$ = 0.8 yrs[35]; $MD_{high-low}$ = -1.1 h/night[13], -5.6% days used >4h[13], 16.7% lower adherence[11]; r = 0.05[53] | -- | ** |
| **Caucasian race[d]** | 234 | 4 | **n = 1;** $MD_{yes-no}$ = 1.7 h/night[9]; $\beta_{adj}$= 1.94 more h/night[9] | -- | -- | **n = 4** $OR_{unadj}$ = 1.31 – 6.00[32,46]; $MD_{yes-no}$ = 5.7% greater adherence[12], 1.6 nights/month[9] | **n = 2;** $OR_{unadj}$ = 1.26 (0.68 – 2.36) [12,32] | * |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Higher BMI** | 165 | 4 | **n = 1;** $MD_{adh\text{-}nonadh}$ = 0.2 z-score units[2] | **n = 1;** $MD_{adh\text{-}nonadh}$ = -13.4 BMI units[32]; -0.6 z-score units[32] | -- | **n = 2;** $MD_{adh\text{-}nonadh}$ = -3 BMI units[46], -0.0 z-score units[46], -4.7 percentile units[38] | **n = 3;** $SMD_{adh\text{-}nonadh}$ = -0.14 (-0.47, 0.19)[2,32,38] | * |
| **Higher maternal education** | 81 | 2 | **n = 2;** $MD_{high\text{-}low}$ = 37.1% greater adherence[32]; r = 0.3 – 0.4[9]; $\beta_{adj(high\text{-}low)}$ = 3.4 more nights/month[9] | -- | -- | -- | -- | ** |
| **Higher socio-economic status** | 291 | 3 | -- | **n = 1;** $OR_{unadj}$ = 0.59[11] | -- | **n = 3;** $MD_{high\text{-}low}$ = 7.1% lower adherence[38]; $OR_{unadj}$ = 1.19[12] $OR_{adj}$ = 0.34[11] | -- | * |
| **Disease factors** | | | | | | | | |
| **Higher AHI** | 367 | 4 | **n = 1;** $MD_{adh\text{-}nonadh}$ = 5.6 events/hr[38] | -- | -- | **n = 3**; $MD_{adh\text{-}nonadh}$ = 2.7 – 3.8 events/hour[12,32]; r = 0.08[53] | **n = 3**; $MD_{adh\text{ - }nonadh}$ = 4.32 (-0.61 – 9.26) events/hour[12,32,38] | *** |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Higher OAHI** | 94 | 3 | -- | -- | -- | **n = 3;** $MD_{adh\text{-}nonadh}$ = 0.3 – 0.7 events/hr[35,46]; $MD_{high\text{-}low}$ = 8.6% greater adherence[11] | -- | * |
| **Higher oxygen saturation** | 270 | 3 | -- | -- | **n = 1;** $MD_{adh\text{-}nonadh}$ = 0.0 – 0.1%[38]; | **n = 2;** $MD_{adh\text{-}nonadh}$ = 2.1%[12]; r = 0.17[35] | -- | ** |
| **Higher arousal index** | 130 | 2 | **n = 1;** $MD_{adh\text{-}nonadh}$ = 7.9[38] | -- | -- | **n = 1;** r = -0.1[35] | -- | * |
| **Treatment characteristics** | | | | | | | | |
| **Auto-CPAP mode[e]** | 61 | 2 | -- | -- | **n = 2;** $MD_{yes\text{-}no}$ = 0.0 h/night[47], -0.7 % nights used[49] | **n = 1;** $OR_{unadj}$ = 1.35[47] | -- | * |
| **BPAP mode[e]** | 105 | 5 | **n = 1;** $OR_{unadj}$ = 3.60[11] | **n = 2;** $OR_{unadj}$ = 0.16 – 0.19[2,39] | **n = 1;** $MD_{yes\text{-}no}$ = -2 – 1 nights/month[9] | **n = 3;** $MD_{yes\text{-}no}$ = -0.3 – 1.2 h/night[f; 9,48]; $OR_{adj}$ = 1.38[11] | **n = 2;** $OR_{unadj}$ = 0.17 (0.05 – 0.64)[2,39] | * |
| **Higher PAP pressure** | 255 | 3 | **n = 1;** r = 0.30[53] | -- | -- | **n = 2;** $MD_{yes\text{-}no}$ = 0.4[g] – 0.8[12,46] | -- | * |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Nasal mask** | 112 | 2 | -- | -- | -- | **n = 2;** $MD_{yes-no}$ = 0.08 h/night[37], 3.5 h/night[g; 36], 3.2 h/night used[g; 36], 30% nights used[g; 36] | -- | * |
| **Comorbidities** | | | | | | | | |
| **Obesity** | 191 | 2 | -- | -- | -- | **n = 2;** $OR_{unadj}$ = 0.65 – 0.83[11,12] | -- | * |
| **Developmental delay** | 466 | 4 | **n = 3;** $MD_{yes-no}$[g] = 19.3 – 23.8% more nights used[56]; $\beta_{adj}$ = 2.4 more h/night[9] ; $OR_{unad}$ = 2.55[12] | -- | -- | **n = 2;** $MD_{yes-no}$[g] = 0.4 – 0.7 h/nights used[56]; $OR_{unadj}$ = 0.82[35] | -- | ** |
| **Atopy/Asthma** | 191 | 2 | **n = 1;** $OR_{unadj}$ = 3.00[11]; $OR_{adj}$ = 15.9[11] | **n = 1;** $OR_{unadj}$ = 0.45[12] | -- | **n = 1;** $OR_{unadj}$ = 0.73[11] | -- | * |

[a]Only studies which reported point estimates were included in this table.

[b]Estimates with moderate-to-large magnitudes of associations and confidence intervals which primarily only included one direction of association were considered as **evidence of a predictor**. Estimates with small magnitudes of associations and small confidence intervals centered around the null were considered as evidence that the characteristic **did not predict adherence**. Estimates with confidence intervals that spanned large magnitudes of association in both directions, or which did not report the variability of their point estimate, were considered to show **ambiguous evidence**.

[c]The total number of studies which evaluated the predictor. As some studies are referenced in more than one column if they evaluated adherence using multiple measures (e.g. h/night and nights/month), this number may be less than the sum of the following four columns.

[d]Breakdown by race was not exact. The 'other' category for Hawkins et al was predominantly Hispanic/Latino (64%) and Black (25%)[12]. Both Beebe et al and Lynch et al did not specify who was represented in their 'non-Caucasian' race category[3246]. The 'Caucasian' category for DiFeo et al was predominantly Caucasian (87%) but also included 3 participants of more than one race, while their 'Other' category was African American (100%)[9].

[e]Comparison group is children using CPAP.

[f]Marcus et al assessed the association between BPAP use and adherence by both excluding children with missing adherence data from the analysis, and by assuming all children with missing data were non-adherent. Results of both analyses are included in this report[48].

[g]Median and interquartile ranges were used instead of the mean and standard deviation.

**Abbreviations**: **BPAP** = bi-level continuous positive airway pressure; **CPAP** = continuous positive airway pressure; **$MD_{adh\text{-}nonadh}$** = mean difference between the adherent and non-adherent groups; **95%CI** = 95% confidence interval; **$MD_{high\text{-}low}$** = mean difference in outcome between the highest level category and lowest level category (e.g. those at the highest SES level and those at the lowest level); **$MD_{yes\text{-}no}$** = mean difference in outcome between participants with and without the variable of interest (e.g. comparing those with and without developmental delay); **$OR_{adj}$** = adjusted odds ratio; **$OR_{unadj}$** = unadjusted odds ratio; **SDM** = standardized mean difference.

**Appendix 1.** Email confirmation of manuscript submission to *Sleep Medicine*.



uOttawa

**Track your recent Co-Authored submission to SLEEP**
1 message

Fri, Jul 26, 2019 at 3:22 PM

*** Automated email sent by the system ***

Dear Dr. Henrietta Blinder,

You have been listed as a Co-Author of the following submission:

Journal: Sleep Medicine
Title: Predictors of adherence to positive airway pressure therapy in children: A systematic review and meta-analysis
Corresponding Author: Sherri Katz
Co-Authors: Henrietta Blinder; Franco Momoli; Julia Bokhaut; Vanessa Bacal; Reuben Goldberg; Dhenuka Radhakrishnan;

To be kept informed of the status of your submission, register or log in (if you already have an Elsevier profile).

Thank you,

Sleep Medicine

## **Appendix 2.** Electronic search strategies

### 2A. MEDLINE, Embase and CENTRAL multi-database search strategy

Searches for MEDLINE, Embase and CENTRAL were conducting as an Ovid multi-database search. Lines 1-6 are optimized for Embase and the main question constructs are broken out in separate lines for clarity. Line 7 is optimized for MEDLINE and lines 8-12 are optimized for CENTRAL. The next lines isolate the records to the database the search was designed for, combine those sets, remove duplicate records and final isolate the records from each database again so each can be downloaded and imported into the citation manager using a database-specific import filter.

| | |
|---|---|
| 1 | exp Patient Compliance/ or (adher* or nonadher* or complian* or comply or noncomplian* or cooperat*).ti,ab,kw. |
| 2 | exp Sleep Disordered Breathing/ or (hypersomnia adj3 periodic respiration).tw,ab,kw. or ((Sleep or nocturnal or obstruct*) adj3 (breath* or apnea* or apnoea* or hypopn*)).ti,ab,kw. or (hypoventil* or SBD or OSA or CSA or IMV).ti,ab,kw. |
| 3 | exp Positive End Expiratory Pressure/ or Noninvasive Ventilation/ or (Positive adj3 Pressure).ti,ab,kw. or ((PAP not (PAP test* or pap smear*)) or BIPAP or CPAP).ti,ab,kw. or ((noninvas* or non-invas* or home or domicill* or hyperbaric) adj4 (respirat* or ventila*)).ti,ab,kw. |
| 4 | 1 and 2 and 3 |
| 5 | 4 and (baby or babies or newborn* or infan* or neonat* or preschool* or pre-school* or child* or pediatr* or paediatr* or teen* or adolescen*).mp. |
| 6 | limit 5 to embase [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained] |
| 7 | (exp Patient Compliance/ or (adher* or nonadher* or complian* or comply or noncomplian* or cooperat*).ti,ab,kf.) and (exp Sleep Apnea Syndromes/ or (hypersomnia adj3 periodic respiration).tw,ab,kf. or ((Sleep or obstruct*) adj3 (breath* or apnea* or apnoea* or hypopn*)).ti,ab,kw. or (hypoventil* or SBD or OSA or CSA or IMV).ti,ab,kf.) and (exp Positive-Pressure Respiration/ or Noninvasive Ventilation/ or (Positive adj3 Pressure).ti,ab,kf. or ((PAP not (PAP test* or pap smear*)) or BIPAP or CPAP).ti,ab,kf. or ((noninvas* or non-invas* or home or domicill*) adj4 (respirat* or ventila*)).ti,ab,kf.) and (child* or adolescent* or infan*).mp. |
| 8 | (adher* or nonadher* or complian* or comply or noncomplian* or cooperat*).ti,ab,kw. |
| 9 | (hypersomnia adj3 periodic respiration).tw,ab,kw. or ((Sleep or nocturnal or obstruct*) adj3 (breath* or apnea* or apnoea* or hypopn*)).ti,ab,kw. or (hypoventil* or SBD or OSA or CSA or IMV).ti,ab,kw. |

10 ((Positive adj3 Pressure) or ((PAP not (PAP test* or pap smear*)) or BIPAP or CPAP) or ((noninvas* or non-invas* or home or domicill* or hyperbaric) adj4 (respirat* or ventila*))).ti,ab,kw.

11 (baby or babies or newborn* or infan* or neonat* or preschool* or pre-school* or child* or pediatr* or paediatr* or teen* or adolescen*).mp.

12 8 and 9 and 10 and 11

13 6 use emez

14 7 use ppez

15 12 use cctr

16 or/13-15

17 remove duplicates from 16

18 17 use ppez

19 17 use emez

20 17 use cctr

**2B. CINAHL search strategy**

| | | | |
|---|---|---|---|
| S4 | S1 and S2 and S3 | Limiters<br>All Child | 16 |
| S3 | (MH "Positive-Pressure Respiration+" or MH "Noninvasive Ventilation+" or (Positive N3 Pressure).ti,ab,kf. or ((PAP not (PAP test* or pap smear*)) or BIPAP or CPAP) or ((noninvas* or non-invas* or home or domicill*) N4 ventila*) OR ((noninvas* or non-invas* or home or domicill*) N4 ventila*) ) | Limiters<br>All Child | 574 |
| S2 | (MH "Sleep Apnea Syndromes+" or (hypersomnia N3 periodic respiration) or (sleep N3 (breath* or apnea* or apnoea* or hypopn*) OR (obstruct* N3 (breath* or apnea* or apnoea* or hypopn*) or (hypoventil* or SBD or OSA or CSA or IMV) | Limiters<br>All Child | 1881 |
| S1 | (MH "Patient Compliance+" or (adher* or nonadher* or complian* or comply or noncomplian* or cooperat*)) | Limiters<br>All Child | 10487 |

**Appendix 3.** Individual study findings by factor of interest**.**

| Factor | Measurement | Findings by study |
|---|---|---|
| **DEMOGRAPHICS** | | |
| **Sex** | Female vs male | OR= 2.39 (1.21, 4. 73)[12]; 1.09 (0.49, 2.40)[38]; 0.75 (0.14, 3.94)[32]; 2.10 (0.99, 4.40) [11]; 1.25 (0.12, 13.34)[46]; 4.00 (0.76, 20.92)[35]<br>$OR_{adj}$ = 5.22 (1.02, 26.77) (adjusted for PAP mode, funding and comorbidities)[11] |
| | -- | Point estimate not reported for eight studies (p>0.05 for all)[9,10,36,39,48,52,53] |
| **Age** | Adherent vs non-adherent | Mean years = 9.6 ± 4.3 vs 9.5 ± 4.6 (p>0.05)[38]; 10.5 ± 2.2 vs 13.5 ± 2.3) (p=0.01)[32]; 14.8 ± 1.8 vs 14.4 ± 1.5 (p>0.05)[46]; 9.6 ± 6.5 vs 8.8 ± 4.9 (p>0.05)[35] |
| | Correlations between age and adherence | r = 0.05 (p> 0.05)[53]; r = -0.483 (p<0.01) (after removing children with developmental delay)[9] |
| | <1y vs 1-6y vs 6-12y vs >12y | % adherent = 66.7 vs 33.3 vs 33.3 vs 50 (p>0.05)[11] |
| | <6y vs 6-12y vs 13-18y | Mean h/night = 7.2 ± 3.8 vs. 4.2 ± 2.7 vs. 3.6 ± 3.1 (p= 0.01)[36]<br>Mean h/night on nights used = 7.7± 3.3 vs. 5.7± 3.2 vs. 4.9 ± 3.0 (p= 0.08)[36]<br>Median (IQR) % nights used = 94.6 (87.5 – 99.7) vs. 74.2 (57.8 – 87.7) vs. 57.9 (32.0 – 93.0) (p = 0.02)[36] |
| | <2y vs >2y | Mean ages = 7.6 ± 4.0 vs 6.5 ± 2.1 h/night[13]; 84.2 ± 16.6 vs 78.6 ± 19.5 % of days used>4h (p = 0.3)[13] |
| | -- | Point estimates not reported for seven studies: positive association for two (p<0.05 for both[50,56], one of which only reported it with children with developmental delay after adjusting for age, race, sex, PAP pressure, obesity, and OAHI)[56], negative association for two (p<0.05 for both [10,45]), not reported for three (p>0.05)[39,41,48] |
| **Race** | Caucasian vs Hispanic vs Black vs More than one race vs Asian | % adherent = 52.7 vs 46.3 vs 28.6 vs 100 vs 100 (p>0.05)[12] |
| | Caucasian vs non-Caucasian | OR = 6.00 (0.42, 85.25)[46], 1.31 (0.26, 6.64)[32] |
| | Black vs non-Black | Mean h/night = 2.5 ± 2.4 vs 4.2 ± 2.8 at 1 month (p = 0.02); beta coefficient after adjusting for PAP at 1 |

| | | |
|---|---|---|
| | | month = -1.94 ± 0.73 (p =0.01); no difference at 3 months (p>0.05)[9]<br>Mean nights/month = 21.6±8.6 vs 23.2±8.0 (p=0.63) at 1 month, no difference at 3 months (p>0.05)[9] |
| | -- | Point estimates not reported by four studies: p<0.05 for one study favouring Caucasian race[56], p>0.05 for three studies[39,41,48] |
| **Height** | Adherent vs non-adherent | Mean cm = 129.7 ± 26.4 vs 128.9 ± 29.2[38] |
| **Weight** | Adherent vs non-adherent<br>>30 kg vs <30k | Mean kg = 34.2 ± 18.8 vs 34.8 ± 21.2[38]<br>OR = 16 (1.9, 137.0) (based on defined adherence cut-off of ≥3h/night). Study also evaluated higher adherence cut-offs, including: ≥4h/night (OR = 14.25; CI: 3.26, 62.30), and ≥5h/night (OR = 5.94; CI = 1.69, 20.86)[47] |
| **BMI** | Adherent vs non-adherent | Mean BMI = 30.8 ± 8.9 vs 44.2 ± 12.6 (p = 0.01)[32]; 42.4 ± 6.1 vs 45.4 ± 15.1 (p>0.05)[46]<br>Mean BMI % = 56.4 ± 30.3 vs 61.1 ± 32.4 (p>0.05)[38];<br>Mean BMI z-score = 2.0 ± 1.1 vs 2.6 ± 0.5 (p>0.05)[32]; 2.6 ± 0.2 vs 2.6 ± 0.3 (p>0.05) (adjusted for age and sex)[46]; 2.7 ± 0.4 vs 2.5 ± 0.3 (p=0.56)[2] |
| | -- | Point estimates not reported by three studies: one reported a positive statistical association (p<0.05)[47], and two studies reported no statistically significant association (p>0.05)[39,52] |
| **Maternal education** | <High school diploma vs. some college vs. college degree | % adherent = 42.9 vs 58.3 vs 80.0 (p>0.05)[32] |
| | Some high school vs high school grad vs some college vs college grad vs postgraduate degree | Correlation for h/night = 0.29 at 1 month (p = 0.03); 0.31 at 3 months (p = 0.02)[9]<br>Correlation for nights/month = 0.41 at 1 month (p<0.01); 0.40 at 3 months (p< 0.01)[9]<br>Linear beta coefficient for nights/month after adjusting for PAP mode = 3.4 ± 1.02 at 1 month (p<0.01)[9] |
| **SES** | <$20k vs $20-39k vs $40-59k vs >$60k | % adherent = 57.1 vs 50.0 vs 100.0 vs 50.0 (p>0.05)[32] |
| | Public insurance vs no public insurance | OR = 0.84 (0.43, 1.64) [12] |
| | Monetary assistance to purchase PAP vs no assistance | OR = 1.69 (0.96, 2.97)[11]<br>$OR_{adj}$ = 2.90 (0.59, 14.35) after adjusted for PAP mode, sex, and comorbidities[11] |
| | -- | No point estimate reported for one study (p>0.05)[35]. |

| | | |
|---|---|---|
| **DISEASE FACTORS** | | |
| **Indication for PAP** | Obstructive sleep apnea vs neuromuscular disease | Mean h/night on nights used = 08:22 ± 2:25 vs 07:54 ± 2:56 hh:mm (p=0.60)[37] |
| **Subjective symptoms** | -- | No point estimates reported by four studies looking at nasal symptoms using the NOSE questionnaire (p>0.05 for one study)[9], sleepiness symptoms using the mESS (p>0.05 for one study[9], p<0.05 for one study[51]), and a standardized set of questions assessing sleep symptoms, behavior, and school performance (p>0.05 for two studies[39,48]). |
| **AHI** | Adherent vs non-adherent | Mean AHI = 20.3 ± 26.8 vs 16.5 ± 21.2 (p = 0.25)[12]; 17.6 ± 19.8 vs 12.0 ± 19.1 (p>0.05)[38]; 13.2 ± 19.6 vs 10.5 ± 7.6 (p = 0.68)[32] |
| | Correlation between AHI and adherence | r = 0.08 (p>0.05)[53]) |
| | -- | No point estimates reported by nine studies, which either examined AHI (p<0.05 for one study (positive association)[39] and p>0.05 for seven studies[9,36,42,45,48,51,52])((positive association reported in one[45]), or the absolute number of apneas and hypopneas (p<0.05 for one study)[47] |
| **OAHI** | Adherent vs non-adherent | Mean OAHI = 10.0 ± 6.8 vs 9.3 ±5.7 (p=0.89)[46]; 22.6 ± 16.0 vs 22.9 ± 22.6 (p=0.98)[35] |
| | Mild vs moderate vs severe OAHI | % adherent = 33.3 vs 45.5 vs 41.9 (p=0.86)[11]) |
| | -- | No point estimates reported for two studies (p>0.05)[10,56]) |
| **Oxygen saturation** | Adherent vs non-adherent | Mean $O_2$ = 96.6±1.3 vs 96.6±1.3 (p>0.05)[38]<br>Nadir $O_2$ = 89.2±5.3 vs 89.3±6.2y (p>0.05)[38]; 77.8±9.6 vs 79.9±7.7[12] |
| | Correlation between $O_2$ nadir and adherence | r= 0.17 (p= 0.40)[35] |
| | -- | No point estimates reported in two studies (p>0.05)[39,48] |
| **Carbon dioxide retention** | Adherent vs non-adherent | Mean $CO_2$ = 42.6±4.5 vs 43.7±4.5 (p>0.05)[38]<br>Max $CO_2$ = 49.5±5.1 vs 49.7±5.1 (p>0.05)[38] |
| | -- | No point estimate reported in one study (p>0.05)[39] |
| **Sleep efficiency** | Adherent vs non-adherent | Mean sleep efficiency = 80.5±17.2 vs 79.5±12.3 (p>0.05)[38]; 83.8±13.2 vs 89.0±4.1 (p=0.18)[32] |
| **Arousal index** | Adherent vs non-adherent | Mean arousal index = 24.9±21.4 vs 17.0±14.1 (p<0.01))[38]. |

| | | |
|---|---|---|
| | Correlation between arousal index and adherence | r = -0.1 (p = 0.76)[35] |
| | -- | No point estimate reported in one study (p>0.05)[48] |
| **TST** | Adherent vs non-adherent | Mean TST = 455.7±67.9 vs 444.0±27.2 (p=0.61)[32]<br>%TST with $O_2$<90% = 19.5±28.3 vs 14.2±24.6 (p=0.26)[12] |
| **Obstructive sleep apnea severity** (no definition given) | Severe OSA vs no severe OSA | OR = 0.50 (0.10, 2.56)[32] |
| **TREATMENT CHARACTERISTICS** | | |
| **Location of PAP initiation** | Adherent vs non-adherent | % who commenced PAP at home = 70 vs 65 (p=1.00)[35] |
| | -- | No point estimate reported in one study (p>0.05)[73] |
| **Titration PSG** | Undergoing a titration PSG vs no titration PSG | OR = 0.90 (0.57, 1.71)[11] |
| **PAP mode** | Auto-CPAP vs CPAP | OR = 1.35 (0.37, 4.95)[47]<br>Mean h/night = 4.5±2.6 vs 4.5±2.7 (p=0.92)[47]<br>Mean % nights used = 62.5±27.2 vs 63.2±26.9 (p=0.74)[49] |
| | BPAP vs CPAP | Mean h/night = 6.0 (3.2, 8.8) vs 4.8 (2.4, 7.2)(p>0.05) (participants with missing data excluded); 4.0 (0.3, 7.7) (SD=7.55) vs 3.6 (0.4, 6.8) (p>0.05) (participants with missing data assumed to be non-adherent)[48]; 3.08±2.75 vs 3.35±2.25 (p>0.05) at month 1[9]; 3.05±2.82 vs 2.08±2.45 (p>0.05) at month 3[9]<br>Median (IQR) h/night = 8 (2-8) vs 5 (2-8) (p>0.05)[44]<br>Mean nights/month = 22±9 vs 24±6 (p>0.05) at month 1[9]; 19±9 vs 18±10 (p>0.05) at month 3[9]<br>% adherent = 50 vs 57(p>0.05)[44]<br>OR = 0.19 (0.03, 1.20)[39]; 0.16 (0.02, 1.00)[2]; 3.60 (2.39, 5.10)[11]<br>$OR_{adj}$ = 1.38 (0.70, 26.9)[11] |
| | -- | No point estimates reported (p>0.05 for four studies; one compared auto-PAP to CPAP[73], two compared BPAP to CPAP[12,43], and one did not report their comparison groups[51]) |
| **PAP pressure** | Adherent vs non-adherent | Mean cm $H_2O$ = 9.2±2.2vs 10.0±2.7 (p=0.67)[46]<br>Mean cm $H_2O$ (range) = 8.7 (5.4-13.0) vs 8.3 (3.5-15) (p>0.05)[12] |

| | | |
|---|---|---|
| | Correlation between pressure and adherence | r = 0.30 (p> 0.05)[53] |
| | -- | No point estimates reported by four studies; three studies identified a positive relationship between PAP pressure and adherence (p<0.05)[47,50,56], and two reported no associations (p>0.05)[9,48] |
| **Difference between initial and final PAP pressure** | Correlation between difference in pressure and adherence | r = -0.4 (p= 0.04) (i.e. a greater difference in estimated initial pressure and final titrated pressure was associated with worse adherence)[35] |
| **Mask type** | Nasal mask vs full face mask vs nasal cannula | Mean h/night = 8:17±2:16 vs 8:12±3:17 vs 8:23±2:44 (p=0.86)[37] |
| | Nasal mask vs full face mask | Median h/night = 5.2 vs 1.7 (p>0.05)[36] |
| | | Median h/night on nights used = 6.9 vs 3.7 (p>0.05)[36] |
| | | Median % nights used = 82 vs 52 (p>0.05)[36] |
| | -- | No point estimates reported by two studies (p>0.05)[43,51] |
| **Residual AHI** | Adherent vs non-adherent | Mean AHI = 4.7±4.3 vs 5.4±8.3 (p=0.52)[12] |
| **Improvement in AHI on PAP** | -- | No point estimate reported by one study which reported a positive relationship between AHI improvement and adherence (p=0.02)[39] |
| **Humidification** | Humidification vs no humidification | OR = 1.50 (0.85, 1.37)[11] |
| | -- | No point estimate reported by one study (p>0.05)[50] |
| **CPAP counselling** | Counselling vs no counselling | OR = 0.87 (0.55, 1.37)[11] |
| **Device brand** | -- | No point estimate reported by one study (p=0.35)[43] |
| **Home healthcare provider** | -- | No point estimate reported by one study (p=0.09)[43] |
| **COMORBIDITIES** | | |
| **Obesity** | Obesity vs no obesity | OR = 0.65 (0.31, 1.34)[11]; 0.83 (0.51, 1.35)[12] |
| | -- | No point estimates reported by four studies: (p>0.05 for three studies[9,10,56], p<0.01 in favor of children with obesity in one study[73]) |
| **Development delay** | Developmental delay vs no developmental delay | Linear beta coefficient for h/night = 2.4±0.93 at 3 months (after adjusting for PAP mode) (p= 0.01); no effect at 1 month or as univariate analysis (p>0.05)[9]. |

| | | |
|---|---|---|
| | | h/night on nights used = 5.0 (1.4-7.9) vs 4.6 (1.9-7.2) at 3 months (p=0.72)[56]; 6.4(1.8-8.3) vs 5.7 (2.5-7.3) at 6 months (p=0.35)[56]<br>% nights used = 86.7 (33.9-97.9) vs 62.9 (30.8-87.8) at 3 months (p=0.01)[56]; 90.0 (53.3-100) vs 70.7 (29.2-90.8) at 6 months (p<0.01)[56]<br>OR = 2.55 (1.27, 5.13)[12]; 0.82 (0.18, 3.74)[35] |
| | -- | No point estimates reported in two studies (positive association for one study (p=0.08)[45], direction not reported for other study (p>0.05)[36] |
| **Down syndrome** | Down syndrome vs no down syndrome | % adherent = 18 vs 14 (p>0.05)[12] |
| **Genetic syndrome** | Genetic syndrome vs no genetic syndrome | OR = 3.00 (0.87, 10.3)[11]<br>$OR_{adj}$ = 3.36 (0.42, 27.0) (after adjusting for sex, asthma, ventilation mode, and PAP device funding)[11] |
| **Atopic illness** | Atopy vs no atopy | OR = 0.45 (0.20, 1.03)[12] |
| | Asthma vs no asthma | OR = 3.00 (0.87, 10.3)[11]<br>$OR_{adj}$ = 15.9 (2.08, 122.4) (after adjusting for sex, genetic syndrome, ventilation mode, and PAP device funding)[11] |
| | Allergic rhinitis vs no allergic rhinitis | OR = 0.73 (0.22, 2.45)[11] |
| **Type of craniofacial diagnosis** | Orofacial cleft vs craniosynostosis vs branchial arch anomaly | OR = 1.83 (0.75, 4.44) vs 0.70 (0.26, 1.83) vs 1.00 (0.42, 2.39) vs 0.71 (0.28, 1.82)[38] |
| **LeFort classification** | 1, 2, or 3 classification prior to PAP vs no classification | OR = 4.26 (0.46, 39.54)[38] |
| **Mandibular advancement** | Mandibular advancement vs no mandibular advancement | OR = 1.00 (0.19, 5.21)[38]. |
| **Significant comorbidities** | Significant comorbidities vs no significant comorbidities | OR = 0.37 (0.07, 2.00)[35] |
| **PSYCHOSOCIAL FACTORS** | | |
| **Perception of titration** | Perception of 'worse than usual night of sleep' vs not 'worse than usual' | $OR_{adj}$ = 0.20 (0.04, 0.90) after adjusting for insurance status, age, and AHI[52] (univariate analysis showed same relationship (p<0.01)[52]) |

| | | |
|---|---|---|
| **OSA-related quality of life (OSA-18 score)** | Adherent vs non-adherent | Mean score by subscale = 16.2 vs 19.6 for sleep disturbance (p=0.09); 16.5 vs 15.6 for physical symptom (p=0.79); 11.7 vs 11.0 for emotional disturbance (p=0.77); 13.8 vs 14.6 for daytime function (p=0.68); 16.1 vs 21.7 for caregiver concern (p=0.02)[32]<br>Mean total score = 72.2±14.2 vs 82.5±16.0 (p=0.10)[32] |
| | -- | No point estimate reported by one study: positive association between 'level of caregiver concern' subscale and adherence (p<0.05)[51]. |
| **Vigilance** | Adherent vs non-adherent | Vigilance z-score = -1.61±2.59 vs 0.32±0.79 (p=0.08)[46] |
| **Social support** | Medican Outcomes Study Social Support questionnaire | Correlation = 0.50 (p<0.01) for higher level of social support and nights of PAP use at 3 months[9]<br><br>Linear beta coefficient for nights of PAP use per month = 5.47±1.40 at three months (adjusted for PAP mode) (p<0.01)[9] |
| **Parent stress** | Parenting Stress Index Short Form | No effect size reported (p>0.05)[9] |
| **Family member on PAP** | Family member on PAP vs no family member on PAP | h/night = 3.6±0.6 vs 2.3±0.4 (p=0.04) and group X time interaction (p=0.04) at 3 months[10]<br>h/night on nights used = 4.8±0.6 vs 3.8±0.4 (p=0.18) (group-time interaction, p=0.04) at 3 months[10]<br>% nights used = 58.1±6.2 vs 54.7±4.4 (p=0.66) (group-time interaction, p=0.57) at 3 months<br>% nights used >4h = 35.8±7.1 vs 23.3±5.1 (p=0.11) (group-time interaction, p=0.13) at 3 months[10] |
| | -- | No point estimate reported at 1 week or 1 month (p>0.05 for all)[10] |
| **Parent attendance for results morning after PSG** | -- | No point estimate reported: positive correlation between whether the family stayed the following morning and adherence (p< 0.05)[51] |
| **Health cognition factors** | Self-efficacy | Linear beta coefficient for min/night = 48.4 (13.4, 83.4) for caregiver-reported; 38.3 (-5.2, 81.9) for patient-reported[40] |
| | Risk perception | Linear beta coefficient for min/night = 9.8 (-18.1, 37.7) for caregiver-reported;<br>-21.2 (-63.2, 20.8) for patient-reported[40] |
| | Outcome expectations | Linear beta coefficient for min/night = 7.1 (-35.1, 49.3) for caregiver-reported; 30.3 (-28.0, 88.5) for patient-reported[40] |

| | | |
|---|---|---|
| | -- | No point estimates reported for age, sex, race, obesity, and developmental delay interaction terms (all p>0.05 except for caregiver-reported risk perception and sex, p=0.02)[40] |
| **Academic performance** | Adherent vs non-adherent | Self-reported grades (four point system) = 2.0±1.3 vs 2.4±0.9 (p=0.57)[46]<br>school QOL (PedsQL 4.0)= 55.8±28.7 vs 66.7±12.5 for self-reported (p=0.57); 56.7±40.7 vs 56.4±16.8 for caregiver-reported (p=1.00)[46] |
| **School level** | Primary school vs middle/high school | No point estimates reported for two studies, which found a positive association between being in primary school and adherence (p<0.05 for one study[73]; p=0.06 for one study[45] |
| **Psychologist support** | Psychology support vs no psychology support | Median (IQR) h/night = 4.7 (0.9-6.0) vs 4.7 (1.4-7.1) (p>0.05)[36] |

**Abbreviations: AHI** = apnea-hypopnea index; **BPAP** = bi-level positive airway pressure; **CPAP** = continuous positive airway pressure; **IQR =** interquartile range; **OAHI** = obstructive apnea-hypopnea index; **OR =** odds ratio; **$OR_{adj}$** = adjusted odds ratio; **PAP** = positive airway pressure; **PedsQL** = Pediatric Quality of Life Inventory; **PSG** = polysomnography**; QOL =** quality of life; **TST** = total sleep time.

# 3. Clinical predictors of non-adherence to positive airway pressure therapy in children – A retrospective cohort study

## PREFACE

**Objective addressed**: to identify clinical predictors of six-month PAP therapy non-adherence in children with SDB starting PAP therapy through a retrospective cohort study at a pediatric tertiary care centre.

**Author contributions:** Henrietta Blinder developed the protocol, obtained ethics approval, abstracted data, conducted the statistical analysis, and wrote the manuscript. Dr. Sherri Katz and Dr. Franco Momoli provided clinical and methodological expertise on the development of the protocol, supervised all stages of research, and provided guidance on the writing of the manuscript. Mr. Stephen Holland and Ms. Anna Blinder abstracted data. Dr Dhenuka Radhakrishnan provided clinical and methodological expertise on the protocol and guidance throughout the study. All authors reviewed and approved the final manuscript.

**Publication:** This manuscript has not been submitted for publication yet.

**Ethics:** Ethics approval for this study was obtained from the Children's Hospital of Eastern Ontario (CHEO) Research Ethics Board prior to commencement (#16/170X). The initial approval letter is provided in Appendix 1.

## TITLE PAGE

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**Keywords:** Pediatric, sleep-disordered breathing, adherence, positive airway pressure, predictor

**Abbreviations: AHI** – apnea-hypopnea index; **Auto-PAP** – auto-titrating positive airway pressure; **BPAP** – bi-level positive airway pressure; **BMI** – body mass index; **CHEO –** Children's Hospital of Eastern Ontario; **CI** – confidence interval; **CPAP** – continuous positive airway pressure; **CSA** – central sleep apnea; **IQR –** interquartile range; **OSA** – obstructive sleep apnea; **PAP** – positive airway pressure; **PSG** – polysomnography; **RR** – relative risk; **SDB** – sleep-disordered breathing; **SD** – standard deviation.

**Funding**: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

**Declarations of interest:** None.

## ABSTRACT

**Introduction**: Despite the importance of adequate treatment of sleep-disordered breathing (SDB), positive airway pressure (PAP) adherence rates in children are low. Identification of readily available clinical predictors of non-adherence would enable the development of targeted interventions and supports, but literature is limited. Our objective was to identify baseline clinical predictors of six-month PAP therapy non-adherence in children with SDB through a retrospective cohort study.

**Methods**: This study evaluated children prescribed PAP therapy for SDB treatment between 2011-2017 at a single pediatric tertiary hospital. The primary outcome was non-adherence at six months, measured using both machine downloads and self-reports. Candidate baseline predictors included demographics, comorbidities, and SDB characteristics. Relative risks (RR) and 95% confidence intervals (95%CI) were estimated using a modified Poisson regression. Missing data was imputed prior to analysis.

**Results**: The final sample included 104 children. After adjusting for all other predictors, the most promising predictors of non-adherence were older age (RR=1.08 for a one year increase, 95%CI=1.00-1.16), lower arousal index (RR=0.97 for a one event/hour increase, 95%CI=0.95-1.00), less low oxygen saturation nadir (RR=1.03 for a 1% increase, 95%CI=1.00-1.05), and absence of developmental delay (RR=0.58, 95%CI=0.30-1.13) or asthma (RR=0.72, 95%CI=0.44-1.17).

**Discussion**: Overall, children who are older, have less severe SDB, or have less disrupted sleep at baseline are more likely to be non-adherent to PAP therapy, and may benefit from additional supports to acclimatize to therapy. However, these clinical predictors were only weakly associated with non-adherence, suggesting that non-clinical characteristics may play a larger role in predicting adherence.

## 3.1. 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 (CSA), and nocturnal hypoventilation.[1] It affects 1-5% of healthy children, and can lead to high blood pressure, behavioural problems, cognitive impairment, and decreased quality of life in children, if not adequately managed.[2] A common treatment modality for SDB is positive airway pressure (PAP), which is a non-invasive therapy that delivers pressurized air into the lungs through a mask interface to support airway patency and/or ventilation.[1] While highly effective, many studies of PAP use in children report poor adherence of less than four hours of use per night.[3,4]

Identification of predictors of non-adherence in children prior to PAP therapy start would allow clinicians to devote limited resources to those who need the most support to succeed. Our group recently conducted a systematic review to identify predictors of PAP therapy non-adherence in children. The characteristics most consistently associated with greater PAP non-adherence were male sex, older age, non-Caucasian race, lower maternal education, lower baseline apnea-hypopnea index (AHI), and absence of developmental delay.[5–11] However, these findings were limited by several data quality concerns. Many studies consisted of small sample sizes and measured adherence cross-sectionally, which resulted in non-standardized lengths of follow-up within studies. Very few studies conducted adjusted analyses examining the independent associations between the candidate predictors and non-adherence. Furthermore, almost all of these studies excluded participants with missing adherence data from analyses, which may lead to selection bias if non-adherent participants are preferentially not presenting for follow-up.

In order to address this gap in the literature, we undertook a larger cohort study following all children newly prescribed PAP therapy at a single centre pediatric tertiary care hospital. This ensured that identified predictors of non-adherence would be generalizable to *all* children starting PAP therapy, irrespective of whether they obtained a PAP device or had follow-up data available. As such, this study's primary objective was to identify baseline clinical predictors of six-month PAP therapy non-adherence in children with SDB.

## 3.2. Methods

### 3.2.1. Study design and setting

This was a single centre, 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, 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 CHEO Research Ethics Board prior to commencement (#16/170X) (Appendix 1).

Data collection for this study took place between August 18, 2016 and September 31, 2019 by three reviewers (HB, AB, and SH), and data was entered into REDCap, a secure, online database.[12] All data was verified by a single reviewer (HB) prior to analysis. Details regarding the data extraction for each variable are available in section 3.2.5.

### 3.2.2. Study population

Children were identified through a search of our hospital's electronic medical records. We screened all children aged 8-17 years who had a respirology clinic visit between 2011-2017 and had documented PAP use. PAP included both continuous positive airway pressure (CPAP) and bi-level positive airway pressure (BPAP). As all eligible children were included, there was no pre-specified sample size.

Children were included if they were diagnosed with SDB (specifically OSA, CSA, or hypoventilation) by polysomnography (PSG) and newly prescribed PAP therapy at CHEO between January 1, 2011 and December 31, 2017. Children were diagnosed with OSA if they had an obstructive AHI (OAHI) greater than 1 event/hour, CSA if the AHI was greater than 5 events/hour and the OAHI was less than 1 event/hour, hypoventilation if the carbon dioxide level was greater than 50 mmHg for at least 25% of the sleep time, and mixed if the child had more than one type of SDB.[2,13] PAP therapy, which was prescribed by one of two treating sleep physicians at our centre, 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 must have been aged 8-17 years at the time of either PAP therapy prescription or start.

We excluded children who either lived or were prescribed PAP therapy outside of CHEO's catchment area. This ensured that all children in our study received similar clinical care throughout the study duration and were unlikely to have access to another pediatric sleep clinic for follow-up. We also excluded children who did not receive a diagnostic PSG within one year (± one month) prior to PAP

prescription, as we wanted an accurate baseline estimate of SDB severity. Finally, we excluded those who had been previously prescribed PAP, were ventilated invasively through a tracheostomy, were prescribed PAP therapy for a reason besides SDB (such as respiratory failure due to parenchymal lung disease), or whose OSA resolved with adenotonsillectomy within three months of PAP prescription, as these children were considered to represent a different clinical population.

### 3.2.3. Non-adherence

The primary outcome for this study was non-adherence at six months (± three months) post PAP therapy start. In cases where start date was unavailable, or the patient had never obtained a PAP device, we used the date of prescription as a proxy for start date. Six months was chosen as our length of follow-up because it is the typical follow-up interval of children in our clinic, though in practice children are seen anywhere between three to nine months. We defined PAP therapy non-adherence as less than four hours of PAP use per night for at least 30% of nights. In the absence of a validated pediatric definition of non-adherence, this is a commonly used cut-off 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. Children who never obtained the PAP device post-prescription, or who returned it prior to their follow-up visit, were considered to be non-adherent at follow-up. Inclusion of these participants in the analysis minimized possible selection bias by ensuring that all children who had been prescribed PAP therapy were included.

### 3.2.4. Predictors

Baseline characteristics evaluated for associations with six-month adherence status were determined through a search of the literature, as well as expert opinion from a pediatric sleep medicine physician (SK). We evaluated the following baseline characteristics as possible predictors in our study: age, sex, SDB diagnosis, PAP mode, comorbidities (obesity, developmental delay, asthma, mental health disorder, and behavioural disorder), polysomnographic indices (AHI, oxygen saturation nadir, maximum carbon dioxide level, sleep efficiency, and arousal index), and sleep symptoms (daytime somnolescence, daytime energy, and headache frequency). Information on the collection and categorization of these characteristics is described in section 3.2.5 below. We were unable to assess psychosocial characteristics as predictors because these data were not documented in the patient records.

### 3.2.5. Data collection timepoints

***Night of the polysomnography***

All children underwent an in-laboratory nocturnal PSG. PSGs were performed and scored according to the American Association of Sleep Medicine pediatric guidelines.[13] The following data were abstracted from the diagnostic PSG report: SDB diagnosis, sleep efficiency, arousal index, AHI, OAHI, oxygen saturation nadir (i.e. lowest oxygen desaturation), and maximum carbon dioxide level. In cases where children were started on PAP therapy partway through the night of the sleep study, data was only collected from the diagnostic portion of the study.

During the night of the PSG, parents completed a locally-developed sleep symptom questionnaire based on the Pediatric Sleep Questionnaire.[14] Our study collected parents' responses regarding three sleep symptoms of interest: excessive daytime somnolescence (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 subjective sleep symptom were grouped to compare the top two categories (indicating more frequent symptoms) to the lower categories to account for sparseness of data in respective groups.

***Clinic visit***

Children met with a pediatric sleep medicine physician at CHEO to review their diagnosis and receive a PAP therapy prescription. PAP devices were dispensed by local vendors, and families received training either at CHEO or by the local vendor. We collected information on the PAP therapy prescription and start, 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 had stated to a clinician they started using it. Funding for PAP devices was provided through a combination of government-funded programs and private insurance/personal co-pay of up to 25% of the cost of the device.

We also collected data on 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, Trisomy 21, neuromuscular disease, obesity, asthma, mental health disorder (i.e. depression, anxiety, bipolar disorder, or obsessive-compulsive disorder), and behavioural disorder (i.e. 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 (BMI) percentiles, with a BMI $\geq 95^{th}$ percentile defined as obese.[15] In cases where 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 BMI

percentile to account for extreme data skewness, as the median BMI percentile in our data set was greater than the 99$^{th}$ percentile.

***Follow-up***

After PAP prescription, children were followed at the CHEO respirology clinic approximately every six 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, clinician assessments of non-adherence were obtained from the clinic notes and were based on a combination of partial adherence downloads (covering only a portion of the follow-up period), phone calls and follow-up visits.

For our study, we collected non-adherence assessments at the timepoint closest to six months post-PAP therapy start (eligible visit range was 3-9 months), as well as changes in health status and PAP settings. As we anticipated that not all individuals would have six-month adherence data available, we also collected 12-month non-adherence for use in our imputation model of missing data, described in section 3.2.6 below.

### 3.2.6. Statistical Analysis

All statistical analyses were conducted in R version 3.5.0.[16] Baseline demographic data were descriptively reported using frequency tables, with results either reported as mean (standard deviation [SD]) or median (interquartile range [IQR]) for continuous data or n (%) for categorical data. Unadjusted 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 non-adherence at six months as the outcome.[17] We further conducted an adjusted Poisson regression model to estimate the independent RRs for each baseline variable, while simultaneously adjusting for all other evaluated predictors. Interpretation of the associations between the candidate predictors and the outcome was determined based on the magnitude of the relative risk estimate and the width of the confidence interval, rather than the p-value.[18,19]

Given the large number of predictors and risk of overfitting, we included a penalized likelihood analysis (ridge regression) to estimate how well the predictors would perform in future prediction modelling applications. A brief synopsis on penalized regression is provided in Appendix 2. Ridge regression is a method used in prediction modelling that reduces overfitting when there is sparse data or collinearity,

without the need for a variable selection step. It anticipates regression to the mean and shrinks the regression coefficients towards the null in proportion to their variance.[20] The ridge regression model was fit using the *glmnet* package version 2.0-18 in R.[21] The penalization factor was chosen using cross-validation. Associated confidence intervals were not reported as this method was used solely to estimate the value of including the predictors in future adjusted prediction modelling after accounting for sparse data issues.

All missing data were imputed prior to analysis to minimize potential selection bias. Children who had missing outcome data regarding their adherence status were marked as non-adherent if they also had no adherence data within 12 months of PAP therapy prescription or start. CHEO has the only tertiary care pediatric sleep laboratory and the only pediatric sleep clinic in our catchment area; while PSG may be rarely conducted at another institution, adherence to PAP therapy without any clinic follow-up at CHEO is unlikely. The implications of this assumption are described in the discussion. For all other missing data, we conducted multiple imputation. Multiple imputation is a common and methodologically sound technique to preserve study size and address uncertainty due to missing data.[22] Additional details on types of missing data and imputation methods are provided in Appendix 3. Imputations were done using fully conditional specification with predictive mean matching for all variables via the *mice* package version 3.6.0 in R.[23] The imputation model included all predictor variables, as well as non-adherence at 12 months, province, and year of PAP therapy prescription (or start, if it was available). A total of 10 completely imputed datasets were created. An analysis was also conducted among individuals with complete data ('complete case analysis') for the purpose of comparison.

## 3.3. Results

### *Study sample*

A total of 104 children were eligible for our study and included in the final analysis. Reasons for ineligibility are described in Figure 1. The study sample had a mean (SD) age of 13 (3) years, a median (IQR) AHI of 11 (5-23) events/hr, and a mean (SD) lowest oxygen desaturation of 81 (10) %. The majority of the sample was diagnosed with OSA (56%), with the remaining either diagnosed with CSA or hypoventilation (14%), or mixed SDB (31%). Sixty-seven percent of the group were obese. 50% of the study sample was non-adherent. The average (SD) length of follow-up for the 85 children with PAP therapy follow-up visit dates was 168 (58) days. Additional baseline demographics are described in Table

1. Only one child in the study had not picked up their PAP device and was therefore marked as non-adherent.

***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, eight children (7.7%) were missing maximum carbon dioxide levels, one (1.0%) was missing sleep efficiency (outside), and six (5.8%) were missing arousal index. This missingness primarily occurred because the PSGs were conducted at an external institution and the reports were insufficiently detailed, as was the case for eight of the 11 children (73%) with missing PSG data. Forty children (38.5%) were missing information about both daytime somnolescence and daytime energy, and 29 children (27.9%) were missing headache frequency. These subjective symptom questions were missing in cases where children 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 in those who had a PSG earlier in the time frame and therefore would have completed a paper copy of the questionnaire before the hospital fully switched over to an electronic system. Finally, fourteen children (13.4%) were missing the primary outcome of six-month non-adherence status. Two of the 14 children (14%) were further missing 12-month follow-up data and were therefore assumed to be 'non-adherent' at six months, while the remaining 12 had their non-adherence status imputed. In total, 44 children (42%) had complete data for all of the predictors and the outcome. Model checking of the imputed values, including trace line plots and strip plots by iteration number, are presented in Appendix 4 and 5, respectively.

***Unadjusted regressions***

Unadjusted analyses were run on all candidate predictors using the imputed data (see Table 2). Non-adherence was greater in children who were older (RR=1.07 for a one year increase in age, 95%CI=0.99-1.14), had a lower arousal index (RR=0.97 for a one event/hour increase in arousal index, 95%CI=0.95-1.00), and had a less low oxygen saturation nadir (RR=1.03 for a 1% increase in oxygen saturation nadir, 95%CI=1.00-1.05). In terms of diagnoses, non-adherence was lower in children with developmental delay (RR=0.59, 95%CI=0.29-1.22) and asthma (RR=0.66, 95%CI=0.40-1.10), though the confidence intervals were wide. Furthermore, children diagnosed with pure OSA (RR=0.71, 95%CI=0.47-1.07) or a mixed SDB diagnosis (RR=0.67, 95%CI = 0.41-1.10) tended to have lower rates of non-adherence than children diagnosed with only hypoventilation or CSA (the reference group). Due to wide confidence intervals and/or small point estimates, there were no noteworthy associations noted with regards to

sex, PAP mode, presence of obesity, mental health disorders, behavioural disorders, AHI, carbon dioxide levels, sleep efficiency, or sleep symptoms.

***Adjusted regression***

The results of the adjusted analysis, which estimated independent associations after simultaneously adjusting for all other predictors, are reported in Table 2. Similar to the unadjusted estimates, non-adherence was greater in children who were older (RR=1.08 for a one year increase, 95%CI = 1.00-1.16), had a lower arousal index (RR=0.97 for a one event/hour increase, 95%CI=0.95-1.00), and less low oxygen saturation nadir (RR=1.03 for a 1% increase, 95%CI=1.00-1.05). Considering more clinically relevant changes of five units (i.e., a five-year increase in age, five more arousal events/hour, and a 5% increase in oxygen saturation nadir), the relative risks were 1.47, 0.87, and 1.44, respectively. Children with developmental delay or asthma were still less likely to be non-adherent (RR=0.58, 95%CI=0.30-1.13 and RR=0.72, 95%CI=0.44-1.17, respectively). Finally, children with good or excellent baseline daytime energy were less non-adherent than their counterparts (RR=0.77, 95%CI=0.51-1.16). It was unclear whether SDB diagnosis type was predictive of non-adherence in the adjusted estimates due to wide conference intervals. Those with hypoventilation or CSA (combined reference group) were still more likely to be non-adherent than those diagnosed with OSA (RR=0.89, 95%CI=0.42-1.87) or mixed SDB (RR=0.73, 95%CI=0.36-1.50). In contrast to the unadjusted regression which showed only a limited association, there was a greater tendency for children using BPAP (RR=1.62, 95%CI=0.82-3.17) or auto-PAP (RR=1.54, 95%CI=0.92-2.60) to have greater non-adherence than those using CPAP.

***Penalized regression***

In order to estimate how well the predictors might perform in future studies, we applied shrinkage modelling to the adjusted regression analysis (see Table 2). The most promising predictors of non-adherence using the penalized regression estimates were older age (RR=1.03 for a one year increase), having a lower arousal index (RR=0.99 for a one event/hour 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). The utility of daytime energy, SDB diagnosis, and PAP mode as predictors was substantially lower than that estimated in the adjusted regression. A scatterplot of the relative risks estimated by ridge regression in comparison to the those estimated in the full adjusted analysis is displayed in Appendix 6. As expected, relative risks were shrunk towards the null for all estimates.

***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 non-adherence in the complete case adjusted analysis due to wide confidence intervals. Furthermore, absence of obesity was a predictor of non-adherence in both the complete case unadjusted (RR=0.67, 95%CI=0.40-1.10) and adjusted analyses (RR=0.52, 95%CI=0.22-1.25).

### 3.4. Discussion

Predictors of PAP non-adherence 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 and cross-sectional assessments of adherence.[3] To the best of our knowledge, this larger cohort study is the first to estimate the adjusted relative risks for a large set of baseline characteristics of children prescribed PAP therapy and PAP non-adherence at six months. Our study found that, after adjusting for all other variables and considering potential for overfitting, the characteristics most likely to be independently associated with PAP therapy non-adherence were older age, lower arousal index, less low oxygen saturation nadir (i.e. less severe oxygen desaturation), and absence of developmental delay or asthma.

Despite the generally small point estimates and wide confidence intervals 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. Several studies have found associations between non-adherence and older age,[5,24,25] not having asthma,[6] not having developmental delay,[5,7,26] and lower arousal index.[27] However, oxygen saturation (either mean or nadir) was not associated with non-adherence in any other study besides ours,[7,27,28] and other studies have reported either contradictory or ambiguous findings for the other predictors.[6,7,27–30] These differences in findings between the literature and our study can be explained by several factors, including differences in the eligible clinical population, sample size, and the definition of adherence used in the analyses, among others. Unfortunately, direct comparisons of estimates between our study and others were not feasible due to different analysis types, as we were the only study to estimate relative risks.

While our study did not find an association between AHI and non-adherence, our findings suggest that SDB severity may still play a role in pediatric PAP therapy non-adherence. Our study found that children with less severe oxygen desaturations, a measure of SDB severity, were more likely to be non-adherent.

We also found that lower arousal index, an indicator of higher quality sleep, was associated with greater non-adherence. It is possible that children who sleep poorly at baseline may perceive the benefits of PAP therapy more strongly than those who feel otherwise healthy. Similarly, children in our study who did not have asthma were more likely to be non-adherent. As there is a known bi-directional 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.[31]

After conducting a penalized ridge regression to estimate how the predictors would perform in future prediction modelling applications, we found that many of our predictors were generally weakly associated with non-adherence. This suggests that clinical characteristics may play a smaller role in non-adherence compared to non-clinical factors. This has been supported by recent research. 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.[32–34] Quantitative studies have further identified maternal social support,[5] having a family member on PAP,[11] and caregiver-reported self-efficacy,[9] as associated with a clinically meaningful increase in pediatric adherence. It is therefore vital that future studies of predictors of PAP therapy non-adherence collect information on psychosocial factors and family environment, as these factors may ultimately prove to be more strongly associated with non-adherence than the clinical factors evaluated in our study.

Besides one study published in 2006 by Marcus et al of 29 children,[35] this cohort study is the first to consider the impact of excluding participants with missing data from an analysis. 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 towards 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, we addressed selection bias due to characteristics measured in this study through the use of multiple imputation. Furthermore, we attempted to address bias due to characteristics not measured in this study by using an expanded imputation model that included additional factors which may have been associated with missingness and loss to follow-up, such as year of PAP therapy start and non-adherence at 12 months. The inclusion of a proxy outcome assessment in an imputation model has been shown to substantially reduce bias in epidemiological studies.[36] Based on the differences in results, 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.

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 non-clinical predictors of non-adherence such as socio-economic status and psychosocial factors. Furthermore, we used a combination of downloaded adherence reports and clinician summary assessments to evaluate non-adherence. Although this increased the robustness of our outcome measurement in terms of the breadth of data eligible for inclusion, this may have resulted in misclassification bias if the clinician summary assessments were inaccurate. Using clinician summary assessments also limited our ability to evaluate non-adherence continuously, which may have masked more complex relationships between predictors and non-adherence. Finally, our study had some missing data, though this was mainly limited to subjective daytime symptoms and was robustly handled. All data was multiply imputed with the exception of two children who had no follow-up adherence data for over one year following prescription and were therefore assumed to be non-adherent. 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.

**Conclusion**

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

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## Figures, Tables, and Appendices

**Figures:**



**Tables:**



**Appendices:**

**Figure 1.** Participant flow diagram

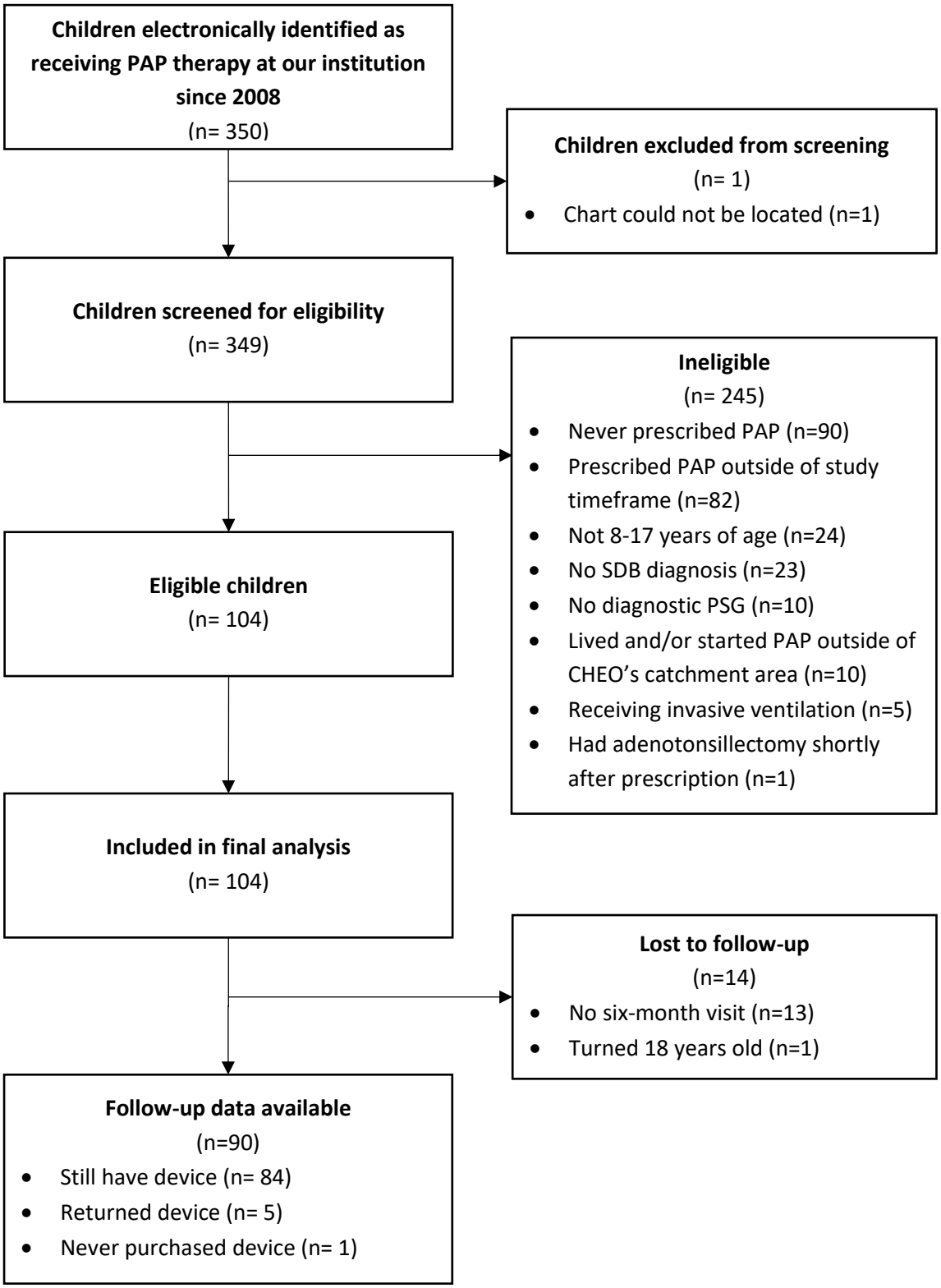


**Table 1.** Baseline demographics.

| Variable | Entire study sample (n=104)[a] | Subset with complete data (n=44)[b] | Imputed sample (n=104)[c] |
|---|---|---|---|
| **Demographics** | | | |
| **Age (years)**, *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) |
| **Behavioural disorder**, *n (%)* | 19 (18) | 7 (16) | 19 (18) |
| **PSG indices** | | | |
| **AHI (events/hour)**, *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/hr)**, *median (IQR)* | 11 (8-18) | 11 (9-19) | 11 (8-17) |
| **Subjective sleep symptoms** | | | |
| **Daytime somnolescence (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+ days per week)**, *n (%)* | 13 (17) | 8 (18) | 20 (19) |

[a]Baseline demographics for the entire study sample. Missing data was present for $CO_2$ (n=8), sleep efficiency (n=1), arousal index (n=6), daytime somnolescence (n=40), daytime energy (n=40), and headache frequency (n=29).

[b]Baseline demographics for the subset of children not missing any predictor or outcome data. Of the 14 children missing data on non-adherence, six were already excluded for missing predictor data.

[c] Baseline demographics for one imputed dataset.

Continuous results were presented as mean (SD) for normally distributed variables and median (IQR) for non-normally distributed variables.

**Acronyms**: **AHI** – apnea-hypopnea index; **auto-PAP** – auto-titrating positive airway pressure; **BPAP** – bi-level positive airway pressure; **CPAP** – continuous positive airway pressure; **CSA** – central sleep apnea; **OSA** – obstructive sleep apnea; **PAP** – positive airway pressure; **PSG –** polysomnography; **SDB** – sleep-disordered breathing.

**Table 2.** Poisson regression estimates evaluating the association between non-adherence at six months and patient and treatment characteristics (imputed data analysis, n=104).

| | Unadjusted analysis | | Adjusted analysis[a] | | Ridge regression[a] |
|---|---|---|---|---|---|
| **Predictor** | **RR** | **95% CI** | **RR** | **95% CI** | **RR** |
| **Demographics** | | | | | |
| **Age** (years) | 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 |
| **Behavioural disorder** | 1.08 | 0.68-1.70 | 1.03 | 0.68-1.56 | 1.02 |
| **PSG indices** | | | | | |
| **AHI** (events/hr) | 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 $CO_2$** (mmHg) | 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/hr) | 0.97 | 0.95-1.00 | 0.97 | 0.95-1.00 | 0.99 |
| **Subjective sleep symptoms** | | | | | |
| **Daytime somnolescence** (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+ days per week) | 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.

**Acronyms**: **AHI** – apnea-hypopnea index; **auto-PAP** – auto-titrating positive airway pressure; **BPAP** – bi-level 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.

**Table 3.** Poisson regression estimates evaluating the association between non-adherence at six months and patient and treatment characteristics (complete case analysis, n=44)

| | Unadjusted analysis | | Adjusted analysis[a] | | Ridge regression[a] |
|---|---|---|---|---|---|
| **Predictor** | **RR** | **95% CI** | **RR** | **95% CI** | **RR** |
| **Demographics** | | | | | |
| **Age** (years) | 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 | 0.50-3.74 | 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 |
| **Behavioural disorder** | 1.06 | 0.52-2.14 | 0.91 | 0.47-1.73 | 0.99 |
| **PSG indices** | | | | | |
| **AHI** (events/hr) | 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 $CO_2$** (mmHg) | 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/hour) | 0.99 | 0.95-1.03 | 0.97 | 0.94-1.02 | 1.00 |
| **Subjective sleep symptoms** | | | | | |
| **Daytime somnolescence** (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+ days per week) | 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.

**Acronyms**: **AHI** – apnea-hypopnea index; **auto-PAP** – auto-titrating positive airway pressure; **BPAP** – bi-level 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.

**Appendix 1.** Ethics approval letter to conduct the study.

# CHEO Research Ethics Board
# Approval - Delegated Review

**Principal Investigator:** Dr. Sherri Katz
**REB Protocol No:** 16/107X
**Romeo File No:** 20160372
**Project Title:** CHEOREB# 16/107X - Clinical predictors of adherence to positive airway pressure therapy in children
**Primary Affiliation:** Clinical Research\Respirology
**Protocol Status:** Active
**Approval Date*:** August 11, 2016
**Valid Until**:** July 15, 2017
**Annual Renewal Submission Deadline: June 15, 2017**

**Documents Reviewed & Approved:**

| Document Name | Comments | Version Date |
|---|---|---|
| Protocol | Protocol | 2016/07/21 |
| Case Report Form | Case Report Form Version 1.0 28-07-16 | 2016/07/28 |

This is to notify you that the Children's Hospital of Eastern Ontario Research Ethics Board has granted approval to the above named research study on the date noted above. Your project was reviewed under the delegated review stream, which is reserved for projects that involve no more than minimal risk to human subjects.

In respect to this study, my signature below certifies, that as a representative of this Research Ethics Board:

1. The membership of this Research Ethics Board complies to the Tri-Council Policy Statement on Ethical Conduct for Research involving Humans;
2. The membership of this Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Part C Division 5 of the *Food and Drug Regulations* **and** Part 4 of the *Natural Health Products Regulations;*
3. This Research Ethics Board carries out its functions in a manner consistent with ICH Good Clinical Practices: consolidated guidelines and applicable laws and regulations of Ontario and Canada; and
4. This Research Ethics Board has reviewed and approved the protocol for this study; which is to be conducted by the qualified investigator named above at the specified site. This approval and the views of this Research Ethics Board have been documented in writing.

Final approval is granted for the above noted study, with the understanding that the investigator agrees to comply with the following requirements:

1. The investigator must conduct the study in compliance with the protocol and any additional conditions set out by the Board.
2. Investigators must submit an annual renewal report to the REB 30 days prior to the expiration date stated above.
3. The investigator must not implement any deviation from, or changes to, the protocol, consents or assents without the approval of the REB.
4. The investigator must, prior to use, submit to the Board changes to the study documentation, e.g., changes to the informed consent letters, recruitment materials.
5. Investigators must provide the Board with French versions of the consent form, unless a waiver has been granted. An interpreter should be offered to participants as required or at the request of the participant throughout the course of research.
6. The investigator must promptly report to the REB all unexpected and untoward occurrences (including the loss or theft of study data and other such privacy breaches).
7. Investigators must notify the REB of any study closures (closed to accrual, temporary, premature or permanent).
8. Investigators must submit a final report at the conclusion of the study.

Should you have any questions or concerns, please do not hesitate to contact the Research Ethics Board Office at 613-737-7600 ext. 3350 or 2128.

Regards,

**Dr. Carole Gentile**
**Chair, Research Ethics Board**
**Présidente, Comité d'éthique de la recherche**
**401 Smyth Road, Ottawa, ON K1H 8L1**

*The final approval date for initial delegated study applications approved with or without modifications will be the date the REB has determined that the conditions of approval have been satisfied.

**The expiry date of REB approval for initial study application that required no modifications will be as follows:
• If the date of review and approval was **on or before** the 15th of the month, the expiry date will be the 15th of the month prior to the date of review and approval by the Chair and/or delegate *in the following year*;
• If the date of review and approval was **after** the 15th the expiry date will be the 15th of the month in which the date of review and approval by the REB *in the following year*.

The expiry date of REB approval for initial study applications that **require modifications** will be as follows:
• If the initial feedback was sent **on or before** the 15th of the month, the expiry date will be the 15th of the month prior to the date the letter of REB feedback is issued to the investigator(s) *in the following year*;
• If the initial feedback was sent **after** the 15th the expiry date will be the 15th of the month in which the feedback was sent *in the following year*.

**Appendix 2.** A synopsis on penalized regression methods.

When a sample size for a regression model is insufficient, either if there are few participants or a low number of events per predictor, the validity of the model can be substantially impacted. This can result in overfitting of the model as it captures both the underlying relationship being considered and spurious relationships particular to the study sample, producing a model that performs poorly in future applications.[18] Overfitting can be addressed using expert knowledge to limit the number of variables being included in a model, but this may be insufficient, particularly in an exploratory study where there is limited literature to draw from. Many studies use stepwise selection to choose variables, but this practice has been widely criticized as producing biased estimates. Furthermore, it is possible that even after incorporating expert opinion and conducting stepwise selection, too many variables would still remain in the conventional model. Shrinkage models provide a robust method to account for overfitting in a model, including those based on datasets with small sample sizes.[18]

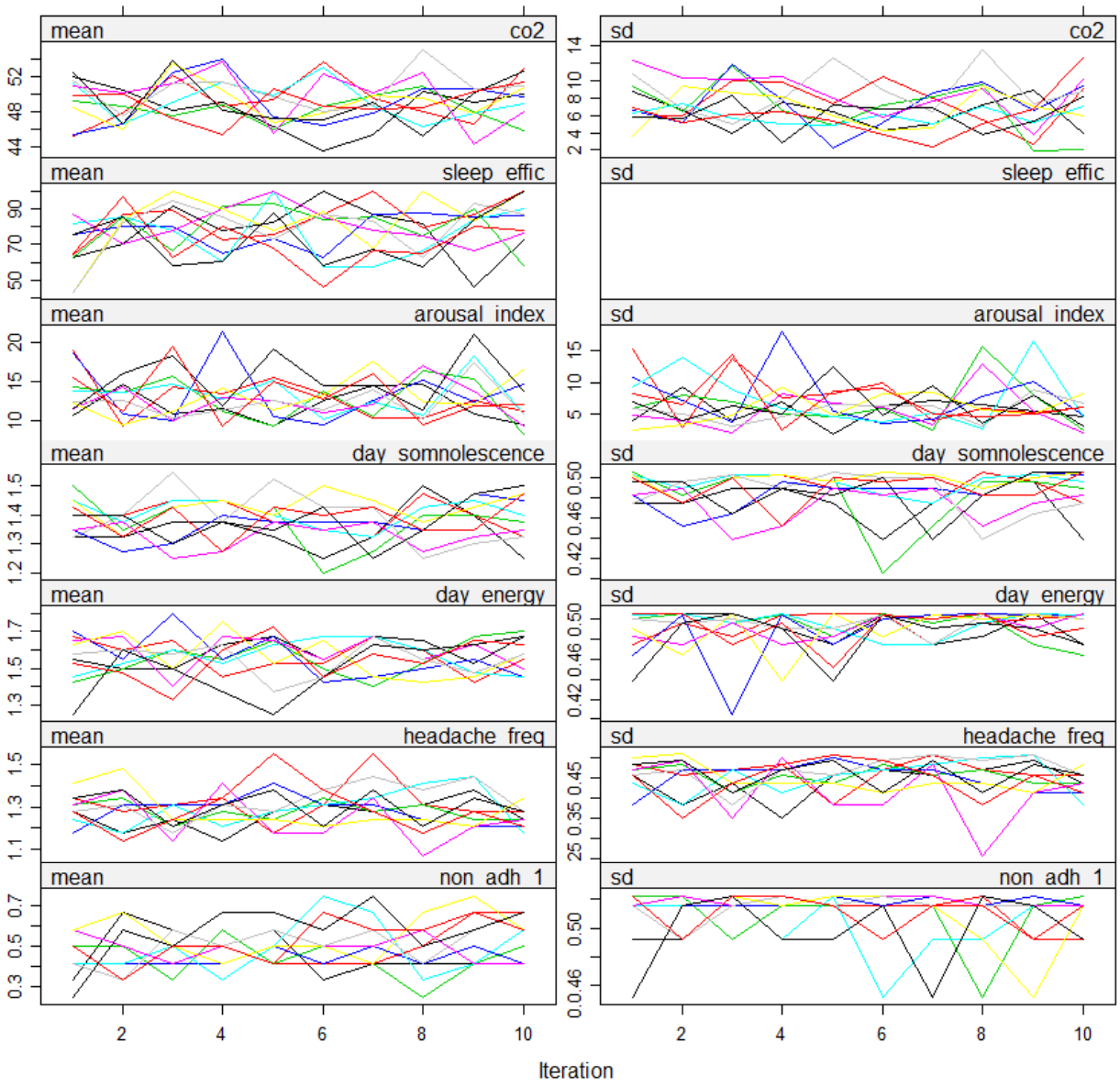
Penalized regression models account for the amount of overfitting in a model by shrinking the regression coefficients and standard errors relative to the amount of overfitting, which tends to produce a small-sample upwards bias in estimates. Shrinking the coefficients is introduced as a bias-variance trade-off, but the set of resulting estimates provide less variability and ideally more accurate predictions when evaluated with new datasets. There are currently two popular penalized regression methods being used. Ridge regression, also called $L_2$ penalization, shrinks the regression coefficients in a model towards zero using a penalty (called 'lambda') that is proportional to the sum of squares of the regression coefficients. Lasso regression, also known as $L_1$ penalization, instead constrains the sum of the absolute value of the regression coefficients. This leads to variable selection, as it sets some coefficients to exactly zero, effectively excluding them from evaluation. Ridge regression is preferred over lasso regression when predictors are correlated, as lasso can choose a different predictor in different iterations due to the instability of the model. Specific to PAP adherence research, where many predictors (such as different measures of disease severity and PSG indices) are likely to be correlated, ridge regression is more appropriate.[18]

**Appendix 3.** A synopsis on imputation of missing data.

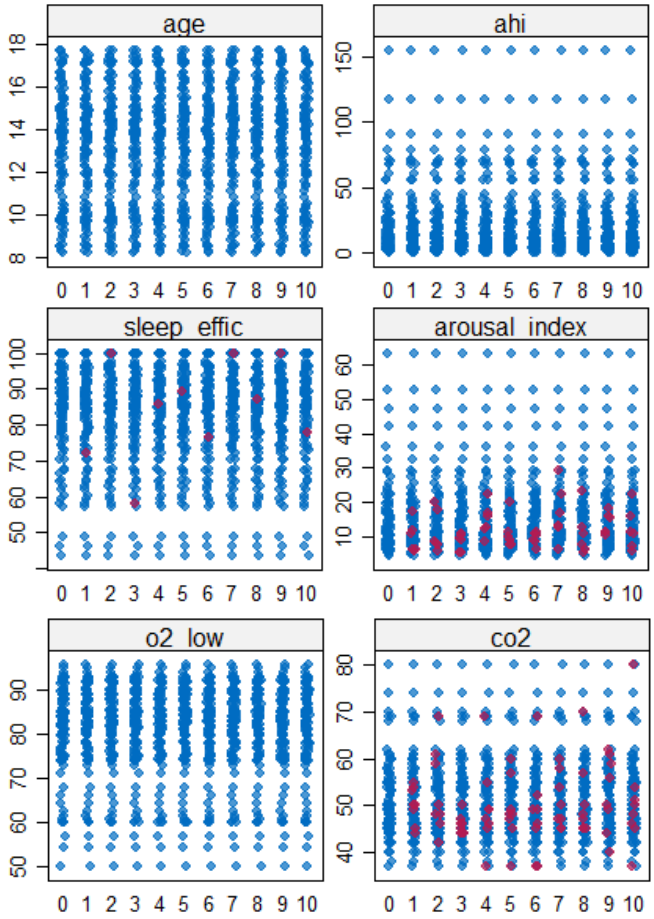
To address any potential sources of bias and ensure the validity of data, it is important to impute missing data. The method of imputation should be determined by the type of missing data. There are three types of missingness:

- **Missing completely at random' (MCAR)**: MCAR means that the reason for missingness is not dependent on any characteristics important for the analysis or on the outcome. If data are truly MCAR, conducting a complete case analysis is reasonable, and excluding participants with missing data will not introduce bias, though it may decrease the efficiency of the analysis by reducing study size. However, it can be difficult to validate such an assumption, particularly with retrospective data.[20]
- **Missing at random (MAR):** MAR, also referred to as covariate-dependent missingness, means that the missingness depends on information that is already observed in the dataset. MAR data *must* be imputed as excluding these participants can bias the analysis. The standard method to impute data that are MAR is with multiple imputation.[20]
- **Missing not at random: (MNAR):** MNAR means that the reason for missingness is related to unobserved characteristics that have not been collected in the dataset. Data that are MNAR need to be imputed carefully, as standard multiple imputation methods alone will result in a biased imputation.[20] Imputation with auxiliary information – extra data not being used directly in the analysis for the study objectives – has been argued to make MNAR problems more MAR-like and the use of standard software approaches possibly acceptable. In epidemiological studies requiring participant follow-up, the use of proxy outcome data in an imputation model has been shown to substantially reduce bias.[32]

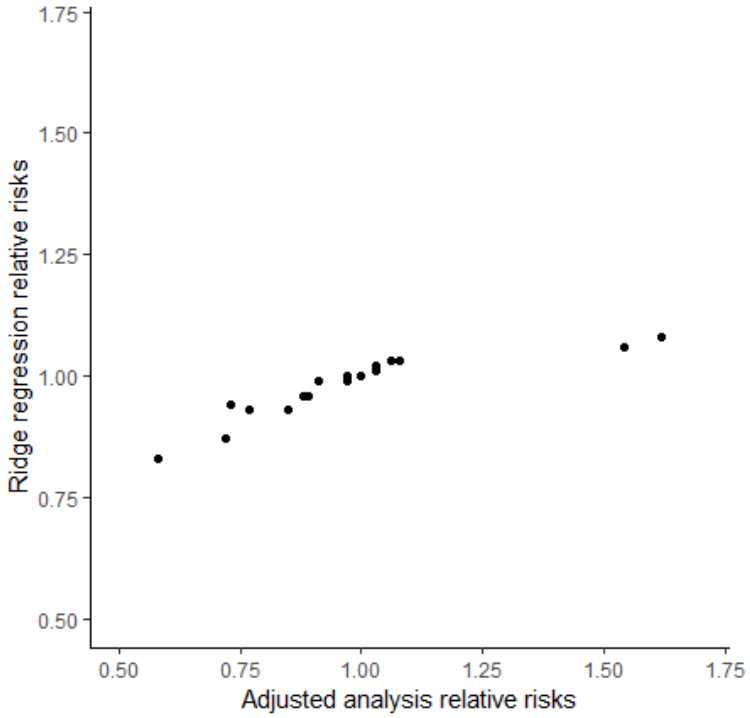
**Appendix 4.** Trace line plots of the variable estimate means and standard deviations against the multiple imputation iteration number.



**Appendix 5.** Strip plots of the continuous variables by multiple imputation iteration number. Imputed values are in red; unimputed numbers are in blue.



**Appendix 6.** A scatterplot comparing the adjusted relative risk estimates from the full model to the ridge regression estimates.



# 4. Discussion

## 4.1. Summary of findings

While literature on predictors of PAP therapy adherence and non-adherence in children exists, its interpretation is challenging, due to a lack of evidence synthesis, variability in factors assessed and methodology used. This thesis aimed to address the dearth of information on predictors of non-adherence to PAP therapy in children with SDB through both a systematic review and a retrospective cohort study. Our systematic review identified greater PAP therapy non-adherence among children with male sex, older age, non-Caucasian race, lower maternal education, lower baseline AHI, and lack of developmental delay. There was also low-quality evidence to suggest that psychosocial factors predict non-adherence. However, the quality of the evidence of the majority of predictors we identified was considered to be low to very low, due to methodological concerns such as small sample size, cross-sectional assessments of adherence, and risk of selection bias. These results were used to inform the development of a cohort study. The cohort study found that the strongest clinical predictors of PAP non-adherence at six months were older age, lack of developmental delay, lack of asthma, less low oxygen saturation nadir, and lower arousal index. However, many of these clinical predictors were only weakly associated with non-adherence, suggesting that non-clinical factors may play a larger role. Together, the systematic review and cohort study provide up-to-date information for clinicians on predictors of non-adherence in children starting PAP therapy. Information on the characteristics that were found to be most predictive of non-adherence in our research are described below.

## 4.2. Predictors of PAP non-adherence

### *Age*

Older age was found to be predictive of PAP non-adherence in both our cohort study and previous literature identified in the systematic review.[1–3] In particular, all studies which evaluated age on a continuous or ordinal scale, including our cohort study, reported a relationship whereby non-adherence increased with increasing age.[1,2] This relationship between older age and non-adherence has been shown in other pediatric adherence literature, and is likely largely explained by the mantle of responsibility shifting from the parent to the child as they gain autonomy.[4] Unfortunately, adolescents may not perceive the benefits of therapy, may not want to feel different from their peers, or may simply be testing the boundaries for making their own decisions, resulting in decreased adherence rates.[2]

### *Developmental delay*

Lack of developmental delay was also predictive of PAP therapy non-adherence in both the cohort study and prior literature. Along with our study, the studies of DiFeo et al, Hawkins et al, and Kang et al reported higher rates of non-adherence in children who did not have developmental delay compared to those who did.[5,2,6] There are several possible reasons for this association. Children with developmental delay may receive closer caregiver supervision and limited autonomy regarding therapy adherence compared to typically developing children. Parents may also have a greater perception of the necessity of treatment if their child has developmental delay, as neurocognitive impairment is a frequent complication of OSA.[6] It is also possible that children with developmental delay undergo more intensive PAP initiation sessions to habituate to therapy compared to children without developmental delay, which may result in less barriers to maintaining adherence over time.[5] However, it should be noted that these results reflect the experiences of a self-selected population of families who believe their child may acclimatize to PAP therapy and were willing to trial it. PAP therapy is not appropriate for all children with developmental delay, particularly in cases where there is fear of aspiration if the child cannot autonomously remove their interface.[7]

### *Asthma*

Lack of asthma, which was predictive of non-adherence in our cohort study, has only been evaluated in two previous studies of PAP non-adherence. One study by Nathan et al reported similar findings to ours.[8] While the Hawkins study found no association between asthma diagnosis and PAP non-adherence, they grouped children with asthma into a general 'atopy' category which also included eczema and rhinosinusitis.[6] Grouping allergic diseases together may be problematic, as the study by Nathan et al reported the associations between asthma and non-adherence to be the inverse of that seen between allergic rhinitis and non-adherence.[8] Children with comorbid asthma may have better adherence compared to those without asthma, in part because they have greater contact with the healthcare system. As such, they are likely being regularly reminded about the importance of consistent medication use to keep their asthma controlled – making the notion of consistent adherence to therapy more familiar to families.[8] There is also a bi-directional relationship between asthma and sleep-disordered breathing, as airway inflammation is a common pathophysiological mechanism in both conditions. Research has shown that asthma and OSA often co-exist, and that treatment of SDB can improve symptoms of asthma.[9] Families of children with asthma may be more motivated to adhere to PAP therapy if they perceive more benefits from its use in terms of improving their asthma symptoms.

### *AHI, oxygen saturation, and arousal index*

It is unclear which polysomnographic indices are the best predictors of PAP non-adherence. In contrast to our cohort study, which reported no association between AHI and non-adherence, our systematic review identified lower baseline AHI as a predictor of non-adherence based on a meta-analysis of three studies.[6,3,10] A possible reason for this discrepancy in findings may be an underlying difference in populations. All three studies included in the meta-analysis only included children who were prescribed CPAP for OSA, whereas our study also included children on BPAP, which is used to treat children with hypoventilation or very severe OSA, if CPAP is insufficient. Despite not finding an association with AHI, our cohort study did find that children with less low oxygen saturation nadir were more likely to be non-adherent. As oxygen saturation nadir, similar to AHI, reflects severity of sleep-disordered breathing, our findings are somewhat consistent with studies demonstrating associations between disease severity and PAP non-adherence. Of the three previous studies which examined oxygen saturation, one study reported ambiguous findings due to wide confidence intervals,[11] and the other two studies reported no association.[6,10] These latter two studies used a different analytic method than ours, where they only compared the mean differences in oxygen saturation nadir between adherent and non-adherent groups, which may have resulted in these different findings. Our cohort study likewise identified lower arousal index, indicative of better sleep quality, as predictive of PAP non-adherence. This finding was in line with the single other study which evaluated arousal index.[10] Children with less severe disease and overall better sleep quality are less likely to exhibit daytime symptoms of SDB,[12] and may therefore perceive less benefits of using PAP therapy compared to children who experience more arousals and feel less well-rested at baseline. Given the variability in results across studies, it is important to consider several different measures of sleep quality and disease severity in future studies of pediatric SDB.

### *Male sex*

Contrary to the findings from the systematic review, male sex was not predictive of PAP non-adherence in our main cohort study analysis. However, in the studies by Nathan et al, Hawkins et al, and Nixon et al, respectively, 2/32 (6%) , 12/63 (19%), and 162/302 (54%) children were excluded from analyses for having missing data.[6,8,11] Our cohort study did find an association between male sex and non-adherence in the unadjusted analysis once children with missing data were excluded (the 'complete case' analysis). This may indicate that male sex is only a predictor of PAP non-adherence in children who continue to present for follow-up, rather than all children prescribed PAP therapy. Speculations as to why females may be more adherent have included that males have a lower level of motivation and less awareness of

their illness, sex-specific phenotypes of SDB that result in greater PAP tolerance in females, and differing parental behaviour towards their children's adherence behaviours based on gender.[6,8]

### *Psychosocial factors*

While we were unable to evaluate psychosocial factors in our cohort study due to the use of routinely collected data, our systematic review identified low quality evidence that psychosocial factors influence non-adherence. Characteristics associated with non-adherence included lower caregiver-reported self-efficacy, lower social support, and not having a family member on PAP.[13,2,14] In addition, lower maternal education was also identified as a predictor of PAP non-adherence in two studies.[3,2] The impact of family environment, community environment, and socio-economic status on non-adherence has been highlighted in several qualitative studies, which independently evaluated barriers to PAP therapy adherence in children and identified common issues such as technical difficulties, inadequate support from the healthcare team, lack of perceived benefits, and poor family communication styles.[15–17] Connecting families with social support, ensuring adequate access to the clinical team to address technical difficulties, and educating families on the importance of consistent therapy are vital pieces of the puzzle that need to be addressed in families with children struggling with adherence. Given the weakness of the associations between many of the clinical predictors in our cohort study and non-adherence, it is possible that these non-clinical factors will play a larger role in predicting adherence behaviours than the clinical factors studied to date.

## 4.3. Implications for future use

This thesis took an important step forward towards identifying predictors of non-adherence in children, laying the groundwork for the next phase of research – to build a prediction model study aimed at identifying children at greatest risk for non-adherence to PAP therapy. Our research showed that children who are older and have less severe SDB or less disrupted sleep at baseline are more likely to be non-adherent to PAP therapy. This thesis also highlighted the importance of considering additional factors that may contribute to PAP non-adherence, such as psychosocial factors. Clinical predictors in our cohort study were only weakly associated with non-adherence, therefore, combining clinical characteristics with non-clinical characteristics may increase the model's overall predictive ability. As psychosocial factors are rarely collected routinely, development of a prediction model will likely necessitate a prospective cohort study. Missing data will need to be considered and accounted for in the analysis in order to be sure the results are robust and generalizable to all children prescribed PAP therapy. Overall, having a validated prediction model will allow clinicians to identify children most likely

to struggle with PAP adherence. Directing targeted interventions to this population at high risk of non-adherence will enhance overall success of PAP treatment in children.

### 4.4. Final conclusions

SDB is a chronic condition which, if not adequately treated, can result in long-term consequences that extend into adulthood. Given the low adherence rates to PAP therapy in children with SDB, identifying predictors of non-adherence can help clinicians direct their support towards the children who require it most. This thesis summarized available literature on predictors of PAP therapy adherence in children through a systematic review and cohort study to identify baseline clinical characteristics associated with PAP therapy non-adherence at six months. Our results not only identified candidate predictors for consideration in successive studies, but also highlighted methodological concerns unaccounted for thus far, such as the impact of excluding participants with missing adherence data on study outcomes. Ultimately, this thesis provides a foundation to help clinicians prioritize limited resources towards the children who require the most support to be successful with PAP therapy before negative long-term non-adherence habits form. Early success with PAP therapy may ultimately prevent secondary health consequences of SDB in children that carry into adulthood.

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