Evaluation and Outcomes of Sleep Disordered Breathing in Neonates

University of Sydney

Faculty of Medicine

Discipline of Child and Adolescent Health

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of Doctor of Philosophy, December 2024

Statement of Originality

This thesis is submitted to the University of Sydney in fulfilment of the requirement for the Doctor of Philosophy. This is to certify that the content of this thesis is my own work. The thesis has not previously been submitted for a degree at any university or for other purposes. I certify that the intellectual content of this thesis is the product of my own work and that all the assistance received in preparing this thesis and sources have been acknowledged.

Bhavesh K Mehta

Date: 25th October 2024

ABSTRACT

BACKGROUND

Despite the widespread recognition of sleep disordered breathing (SDB) as a significant health problem in adults and older children, the disorder remains relatively unexplored in neonates where there is a notable lack of research. Multiple factors are responsible for the paucity of research including, but not limited to, lack of established norms, challenges in diagnosing SDB in neonates and limited awareness in physicians. Understanding the prevalence, risk factors, and long-term consequences of SDB in neonates is crucial for developing effective prevention and treatment strategies. The overall aim of this research was to document and explore the impact of SDB in neonates, with a focus on understanding its effects on neurodevelopment, and overall health. The research also aims to identify early indicators, risk factors, and potential interventions that could mitigate the negative consequences of SDB, improving the long-term outcomes for affected children.

METHODS

A range of methods were utilised to accomplish our research objectives. Study 1 (Chapter 2) is a comprehensive review of literature, undertaken to identify any established guidelines or evidence about norms, diagnostic and treatment criteria for SDB in neonates as well as its long-term impact. For Study 2 (chapter 3) a national survey of neonatologists was conducted, investigating their awareness, knowledge and practices around SDB in neonates in Australia and New Zealand. For studies 3 and 4, 80 neonates were enrolled and followed into early childhood in a prospective cohort study. Study 3

(chapter 4) provides comprehensive analysis of key risk factors as well as presenting features, investigations, management and hospital outcomes of moderate-severe SDB in neonates by doing a cross-sectional retrospective cohort study. Study 4 (chapter 5) explores the trajectory of SDB over time and its impact on the medium-term respiratory and neurodevelopmental outcomes at 3 years of age in a prospective cohort study.

RESULTS

Study 1 highlights the absence of established norms, standardised diagnostic and treatment criteria for SDB in neonates, and lack of long-term outcome data. Study 2 demonstrates considerable variation in awareness and practices amongst neonatologists around SDB in neonates and identified lack of management guidelines. Study 3 identifies key risk factors for SDB in neonates and provides a comprehensive overview of the effectiveness of various diagnostic methods and management strategies that can be employed for management of neonates with SDB in the hospital setting. Study 4 demonstrates the long-term trajectory of SDB in neonates and the associated respiratory and developmental outcomes.

CONCLUSION

Our research demonstrates that SDB in neonates is a serious condition with potential for long-term consequences. However, with a specialised multidisciplinary team, the diagnosis and treatment can be implemented in a timely manner, potentially improving long-term outcomes. Our research highlights an urgent need for developing norms and consensus-based diagnostic and treatment thresholds to standardise practices in this vulnerable population. Longitudinal studies that track the development of neonates with SDB over time are crucial for determining causal links with these outcomes.

Authorship attribution statement

I was the lead and corresponding author on all papers. I made substantial contributions to the conception and design of the studies, patient recruitment, the acquisition of data, and the interpretation and analysis of data. I was responsible for drafting and editing all manuscripts. Supervisors were involved in critically reviewing/revising the manuscripts and assisting with data interpretation.

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As supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements above are correct.

Primary Supervisor Name: Prof. Karen Waters

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PUBLICATIONS AND PRESENTATIONS DURING DOCTORAL CANDIDATURE

First author publications related to this thesis

Chapter 2

Mehta B, Waters K, Fitzgerald D, Badawi N. Sleep disordered breathing (SDB) in neonates and implications for its long-term impact. Paediatr Respir Rev. 2020 Apr; 34:3-8. doi: 10.1016/j.prrv.2019.10.003. Epub 2019 Oct 30. PMID: 31753754.

I did the literature search, reviewed the articles and drafted the initial manuscript. I was responsible for undertaking the publication process and submitting the final accepted version of the manuscript.

Chapter 3

Mehta B, Waters K, Fitzgerald D, Badawi N. Survey of the practices of neonatologists in managing neonates believed to be at high risk of sleep disordered breathing. BMJ Paediatrics Open. 2021;5(1). doi.org/10.1136/bmjpo-2020-000979.

I participated in the study concept and design. I participated in the development of the survey questionnaire and conducted the survey, performed data collection, data analysis and drafted the initial manuscript. I was responsible for undertaking the publication process.

Chapter 4

Mehta B, Waters K, Fitzgerald D, Badawi N. Clinical characteristics, associated comorbidities and hospital outcomes of neonates with sleep disordered breathing: a

retrospective cohort study. BMJ Paediatr Open. 2024 Jun 18;8(1):e002639. doi: 10.1136/bmjpo-2024-002639.

I participated in the design of the study, ethics application, collection of data, performed data analysis and drafted the initial manuscript. I was responsible for undertaking the publication process.

Chapter 5

Mehta B, Waters KA, Fitzgerald DA, Badawi N. Respiratory and Neurodevelopmental Outcomes at 3 Years of Age of Neonates Diagnosed with Sleep-Disordered Breathing. *Journal of Clinical Medicine*. 2024; 13(18):5527. doi.org/10.3390/jcm13185527.

I participated in the design of the study, ethics application, patient recruitment, collection of data, follow-up of patients, data analysis, and drafted the initial manuscript. I was responsible for undertaking the publication process.

POSTER PRESENTATIONS

Mehta B, Waters K, Fitzgerald D, Badawi N. Clinical profile of neonates admitted with sleep disordered breathing in a tertiary newborn intensive care unit in New South Wales Australia. Perinatal Society of Australia and New Zealand Congress: March 2023; Melbourne, VIC.

Mehta B, Waters K, Fitzgerald D, Badawi N. Are We Referring the Right Babies for Sleep Studies? Perinatal Society of Australia and New Zealand Congress: March 2021; Adelaide, SA.

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LIST OF ABBREVIATIONS

AASM	American Academy of Sleep Medicine
AHI	Apnoea-Hypopnoea Index
CO2	Carbon Dioxide
CPAP	Continuous Positive Airway Pressure
CT	Computed Tomography
$EtCO_2$	End Tidal Carbon Dioxide
FDA	Food and Drug Administration
HFNC	High-Flow Nasal Cannula
MOAHI	Mixed Obstructive Apnoea-Hypopnea Index
MDO	Mandibular Distraction Osteogenesis
MRI	Magnetic Resonance Imaging
NICU	Neonatal Intensive Care Unit
OAHI	Obstructive Apnoea-Hypopnea Index
OSA	Obstructive Sleep Apnoea
OSAS	Obstructive Sleep Apnoea Syndrome
$PaCO_2$	Partial Pressure of Carbon Dioxide
PMA	Post Menstrual Age

PSG	Polysomnography
RDI	Respiratory Disturbance Index
REM	Rapid Eye Movement
SpO_2	Saturation of Oxygen
$TcCO_2$	Transcutaneous Carbon Dioxide
TCM	Transcutaneous Monitoring
TST	Total Sleep Time
TPP	Tubingen palatal plate

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Chapter 1 Background and Aims

Overview

Sleep and airway conditions are appreciated as areas in need of further research in the neonatal intensive care. Survival rates of preterm and neonates with complex medical and surgical conditions who are at-risk for Sleep Disordered Breathing (SDB) are increasing.[1,2] With improved survival of preterm infants, chronic neonatal lung disease has become a more prevalent condition.[3] We observed a significant increase in the demand for services to diagnose and manage sleep and airway conditions in neonates, particularly over the last decade. This body of work arose from a need to provide a platform to support clinicians caring for neonates and infants with SDB. In this thesis, the neonatal period is defined as the first 28 days of life of a full-term infant or up to 44 weeks conceptional age (gestational age plus chronological age) of a preterm infant.[4,5] This thesis is presented as a series of papers, with additional text and analyses to provide further context to the work done.

This chapter will discuss the key differences between SDB in newborns compared to older children, providing essential background information on both, highlighting existing gaps in our knowledge about SDB in neonates and young children, explaining the rationale for our research, and describing the study objectives.

Background

Adequate sleep is essential for a wide range of biological functions. It plays an important role in early memory, learning and cognitive development.[6] Sleep disorders are common in young children and may have negative consequences for the child, their parents and

the family units. Sleep disorders can be medical (sleep disordered breathing/obstructive sleep apnoea/central sleep apnoea) or behavioural in origin (difficulty in falling asleep, frequent night waking). The prevalence of sleep disorders, primarily behavioural, in Australian infants is estimated to be between 30% and 46%.[7,8] Another Australian study examined sleep problems across different age groups and reported that sleep problems were most prevalent in infancy (17.1%) and decreased through middle childhood (7.7%).[9] Chronic sleep problems are also common in children and are frequently under reported by parents during general practice consultations, indicating the need for increased awareness of children's sleep problems in the community.[10] Despite growing clinical and research interest in paediatric sleep problems in recent years, neonates have been frequently overlooked in research studies, resulting in a knowledge gap. This thesis focuses on sleep-related breathing disorders (SDB) in neonates.

Sleep disordered breathing – key findings and literature in neonatal and paediatric populations

Guilleminault et al. first described obstructive sleep apnoea (OSA) in children in 1976.[11] However, it took another 20 years to recognise the significance and impact of SDB in children.[12]

1.1 ***What is Sleep Disordered Breathing (SDB)***

(a) SDB in children

In children, SDB is described as a spectrum of conditions characterised by the obstruction of the upper airway during sleep which can lead to disruption of normal respiratory patterns, ventilation and sleep quality.[13] It includes primary snoring (mild upper-airway obstruction with no isolated obstructive events or apparent sequelae), upper airway resistance syndrome (associated with frequent arousals, but no blood gas

changes as sequelae of the events), obstructive hypoventilation (associated with gas exchange abnormality without recognisable obstructive events) and obstructive sleep apnoea (OSA) (encompassing all of the sequelae noted above; that is distinct obstructive events, with an associated increased frequency of arousals and disturbances to both oxygen [desaturation] and carbon dioxide [retention]). Three major components of OSA are intermittent hypoxia, hypercapnia and sleep fragmentation.[14]

(b) SDB in neonates

SDB in neonates is distinct from SDB in older children. While upper airway obstruction is the primary characteristic of SDB in children, due to immaturity of respiratory and neurological systems, newborns often experience a combination of upper airway obstruction and central respiratory events (Central apnoea). In neonates, the terms primary snoring, upper airway resistance syndrome and obstructive hypoventilation do not describe the pathophysiological abnormalities observed and so they are rarely used in the literature.

Neonates have distinctive anatomical and physiological characteristics that predispose them to SDB. These include small midface, obligate nasal breathing, compliant chest wall, immature respiratory centres making them prone to central apnoea and predominance of rapid eye movement (REM) sleep state, which exacerbates airway obstruction due to the associated loss of muscle tone.

As many of these factors improve with development during infancy, interpreting polysomnography (PSG) findings and differentiating pathology from normal physiology is challenging in this population. It is the dynamic nature of the evolution of sleep breathing through infancy that provides one of the most perplexing issues for clinicians:

distinguishing physiology from pathology and thereby agreeing upon the clinical threshold for intervention for SDB.

In summary, neonatal SDB is characterised by a combination of both central apnoea and obstructive respiratory events. With age, neurological and respiratory systems mature, and the prevalence of central apnoea typically decreases. Understanding, defining and quantifying the impact of these unique characteristics is crucial for proper diagnosis and management of SDB in neonates.

1.2 ***Clinical Manifestations of SDB***

(a) In Children

The most common presenting symptoms of SDB in children are snoring and mouth breathing during sleep.[15] However, children can present with a variety of symptoms including excessive daytime sleepiness, attention deficit, hyperactivity or behavioural problems, cognitive problems, secondary enuresis, nightmares and restless sleep patterns.[16]

(b) In Neonates

While snoring, mouth breathing, and restless sleep are common presenting symptoms of sleep-disordered breathing (SDB) in children, neonates rarely present with these symptoms. The clinical presentation of SDB is highly variable in neonates and often depends on the severity of airway compromise and the presence of underlying comorbidity. The most common features in neonates are noisy breathing or stridor, increased work of breathing and apnoea. Symptoms reflecting upper airway obstruction are frequently present both during wakefulness and sleep. Neonates who are less severely affected may not have any obvious respiratory symptoms.

In summary, the symptoms of SDB in neonates are distinct from those in older children. This highlights the need for increased awareness and a high degree of clinical suspicion for early detection of SDB in neonates anatomically and neurologically at an increased risk of SDB.

1.3 ***Prevalence of SDB***

(a) What is known in children

It is now well recognised that SDB is a common problem in children. Parental reports suggest a prevalence of habitual snoring between 9%-15% in infants[17, 18] and around 7.5% in children.[19] Previous research has shown a strong association between snoring and OSA in children.[20,21] The majority of SDB in children is obstructive in nature and its reported prevalence varies widely from 0.1-13%.[13] However, most evidence suggests a prevalence of OSA in the range of 1% -5%, making this a relatively common disease in children.[22] The wide range of prevalence described in the literature can be attributed to heterogeneity in the diagnostic methods and criteria used, children's ages at diagnosis, and the presence or absence of co-morbidities. In children with existing comorbidity such as Trisomy 21, the prevalence of SDB may be as high as 80%.[23]

The prevalence of OSA peaks between 2 to 8 years of age, corresponding with the peak prevalence of adenotonsillar hypertrophy.[24] Prevalence of OSA in children is on the rise due to the increasing prevalence of obesity.[25,26] While OSA predominantly affects males in adults, the gender distribution is more balanced between boys and girls in the prepubertal paediatric population.[27]

(b) What is known in neonates

Despite growing recognition of SDB as a significant health issue, the exact prevalence remains unknown in neonates. The lack of clear diagnostic and treatment criteria means that neonates have largely been excluded from previous SDB studies. Previous studies examining SDB in infants (up to 12 months old) have consistently identified a higher prevalence in at-risk populations, including those with craniosynostosis, prematurity, laryngomalacia, neuromuscular disorders, and bronchopulmonary dysplasia.[28,29] Obstructive sleep apnoea (OSA) has been reported to occur more frequently in premature babies.[30-32] Recently, Jaleel et al. reported that prematurity was associated with an almost threefold higher likelihood of developing severe OSA.[33]

In summary, the exact prevalence of SDB remains undetermined in neonates. However, it appears to be higher among at-risk populations such as those born very preterm, with craniofacial abnormalities and hypotonia. The lack of clear consensus on diagnostic criteria and the absence of standardised reference data for respiratory parameters in neonates and infants contribute significantly to the challenges in determining the true prevalence of SDB in this population. Driven by improvements in neonatal intensive care, there is a trend towards resuscitation and intensive care for infants born at 22 and 23 weeks of gestation.[34] With the improved survival of extremely preterm infants and neonates with complex medical problems, there is a possibility that incidence of SDB is on the rise in this population.

1.4 *Aetiology of SDB*

(a) In children

Adenotonsillar hypertrophy is the most common cause of OSA in healthy children, with a peak incidence between 2 and 8 years.[35] The presence of certain comorbid conditions including congenital craniofacial anomalies, genetic syndromes and neuromuscular

diseases can significantly increase the risk of SDB, and these children present earlier in the life.[28,36] Obesity represents a significant risk factor for OSA and the rising rate of obesity is leading to an increased prevalence of OSA.[26,37] The European Respiratory Society (ERS) statement concludes that obesity might be an independent risk factor for obstructive SDB by the age of two years.[13] A recent retrospective study reported high rate of moderate-severe OSA in obese toddlers and preschool children.[38] Finally, genetic factors and a family history of OSA might influence the risk of SDB in children, although a significant interaction effect between these factors was documented only in overweight individuals.[39]

(b) In neonates

The aetiology of SDB in neonates is multifactorial and involves a variety of risk factors. While adenotonsillar hypertrophy is the principal cause of SDB in children, various congenital, syndromic and/or genetic entities are the main causes of SDB in neonates.[28,29] Low muscle tone is also an important predisposing factor, as seen in infants with Down Syndrome, Prader Willi Syndrome or neuromuscular disorders including congenital myasthenia, nemaline myopathy and spinal muscular atrophy. Prematurity is also associated with an increased risk of SDB.[33] Therefore, it is crucial to be aware of the heightened risk of SDB in this vulnerable population to ensure early detection and intervention.

1.5 *Diagnosis of SDB*

(a) Diagnosis in children

Overnight polysomnographic (PSG) testing is considered the gold standard for diagnosing SDB by the American Thoracic Society (ATS),[40] the American Academy of Pediatrics

(AAP),[41] and the American Academy of Sleep Medicine (AASM).[42] Rules for the scoring of sleep and respiratory events in polysomnography are provided in the AASM manual.[43]

The apnoea–hypopnoea index (AHI), defined as the number of mixed, obstructive, and central apnoea and hypopnoea per hour of total sleep time (TST), and the obstructive AHI (central apnoea excluded) are the most commonly used polysomnographic parameters used for classification of SDB severity. Many studies have classified paediatric OSA in to "normal" (AHI <1 event/h), ''mild'' (AHI of 1–5 events/h), ''moderate'' (5–10 events/h), and ''severe'' (>10 events/h).[44] There are very little data to support this classification.[45]

The criteria for diagnosing paediatric OSA is provided by the International Classification of Sleep Disorders, 3rd edition (ICSD-3).[46] Importantly, it requires the presence of both signs or symptoms of SDB and abnormal PSG findings. The PSG criteria for diagnosing OSA include:

(1) ≥1 obstructive events (obstructive or mixed apnoea or obstructive hypopnea) per hour of sleep or

(2) obstructive hypoventilation manifested by $PaCO_2$ >50 mm Hg for >25% of total sleep time (TST) coupled with snoring, paradoxical thoracoabdominal movement, or flattening of the nasal airway pressure waveform.

However, the diagnosis of paediatric OSA in the literature differs according to the different clinical guidelines and cut-off criteria used for defining OSA; especially in younger children <2 years of age.

Difficulty in accessing PSG studies means that alternative screening and diagnostic tests are also described[47] including (in decreasing order of complexity and accuracy) ambulatory PSG, respiratory polygraphy (RP), nocturnal oximetry, and screening questionnaires for example the Paediatric Sleep Questionnaire.[48]

These alternative tests have weaker positive and negative predictive values when compared with PSG. They may be used as a screening tool to identify children at high versus low risk for OSA. The AASM has not recommended home sleep apnoea testing for obstructive sleep apnoea syndrome (OSAS) diagnosis in children.[49]

In conclusion, polysomnography is considered the gold standard test. Diagnostic and treatment thresholds are not well defined in infants and children under the age of 2 years.

(b) Diagnostic challenges in neonates

Currently, there are no universally accepted criteria for diagnosing SDB in neonates and infants. Although the diagnosis may be made based on clinical features in severe cases, PSG is the gold standard test to diagnose and quantify the severity of SDB in neonates.

PSG is not only technically challenging to perform but also difficult to analyse and interpret in neonates due to the immaturity of sleep architecture and lack of normative data to differentiate normal from abnormal parameters. Laboratory based PSG is a highly resource intensive procedure and requires high expertise which can only be performed at a specialised centre with paediatric sleep physicians and expert technicians to ensure the high quality of recording and reporting. The current American Academy of Sleep Medicine (AASM) guidelines recommend different rules for sleep staging for those less than 2 months post term, referred to as infants, and those older than 2 months post term to 18 years of age referred to as children.[50]

The lack of normative data in the neonatal age group has contributed to significant variability in how previous studies have interpreted different parameters recorded in neonatal PSG. The Apnoea-Hypopnoea Index (AHI) is typically used to categorise SDB in adults and older children. However, a variety of criteria have been used in previous studies to categorise SDB in infants including respiratory disturbance index (RDI),[51] mixed

obstructive apnoea-hypopnoea index (MOAHI)[52] and obstructive apnoea-hypopnoea index (OAHI).[53]

The recently published British Thoracic Society guidelines for diagnosing and monitoring paediatric SDB emphasised that AHI values are not validated for intervention in children younger than 2 years of age.[54] In a survey of sleep medicine physicians[55] practising across the world, there was no agreement on the OAHI cut-off values for defining OSA in neonates and infants with OAHI cut-off values ranging from >1 to >20 events per hour. This study also revealed a lack of agreement on the indications for PSG and SDB management in neonates, with a strong consensus on the need for developing evidence-based guidelines, highlighting the importance of further research in this area.

Due to the rapid changes in normal sleep and respiratory physiology during the first year of life, there is a need for different diagnostic criteria and severity classification for neonates and infants. A small study of 30 healthy term newborns demonstrated the presence of higher number of central, obstructive, and mixed apnoea and a significantly higher mean AHI compared to healthy children older than 1 year.[56] A recent study by Stefanovski et al.[57] showed that 39% of the AHI value in 1-month-old infants can be attributed to the central apnoea index (CAI). By the age of 5 months, mean AHI decreased by 75%, mainly due to a reduction in CAI. Another study of 296 infants (< 1 year of age) showed an inverse relationship of both the OAHI and CAI with increasing age, reflecting the changes in respiratory events with age.[58]

These studies highlight that if this age effect is not taken into consideration and PSG criteria similar to those for older children are used, a significant proportion of neonates and infants will be over-diagnosed with SDB, resulting in unnecessary treatment.[59] Severity assessment based on the PSG is very important as it enables the clinician to

stratify risk, plan for appropriate management and consider the importance of alternative methods of treatment in relation to the clinical condition of the infant over time if therapies (e.g. CPAP) are not well tolerated.

Additionally, some of the other diagnostic and screening tools used in older children like paediatric sleep questionnaires[48] and McGill criteria[60] for pulse oximetry study are not validated for use in neonates.

In summary, the lack of universally agreed diagnostic criteria and heterogenicity of PSG parameters cut-off values create challenges for accurate diagnosis and consistent management of SDB in neonates. There is an urgent need to document normative data, develop and use age-adjusted reference values for respiratory PSG parameters for diagnosing SDB and classifying its severity in neonates and infants. Evidence is the best way to generate scientifically valid consensus.

Image 1: A neonate undergoing polysomnography study in our unit (permission for use of the photo given by parents).

1.6 *Management of SDB*

(a) Management in children

Adenotonsillectomy is the first-line treatment for OSA in children over 2 years of age where adenotonsillar hypertrophy is the leading treatable underlying cause. Recent publications have shown variable results of surgery with the efficacy decreasing in children with underlying risk factors. [61-65] In children with persistent disease post adenotonsillectomy or in children with other causes of SDB, positive airway pressure (PAP) therapy is used. Continuous PAP (CPAP) is the most-commonly used modality in children with craniofacial abnormalities and Bilevel PAP (BiPAP) in neuromuscular disorders.[13] Weight management, orthodontic treatment, or medical therapies are offered as alternatives to surgery, especially in children with mild OSA when surgery is not indicated.[66] It is also important to appreciate that SDB can resolve spontaneously,

particularly in children with mild OSA and adenotonsillar hypertrophy. Improvements may be due to the regression of lymphoid tissue and growth of the airway.[62]

(b) Management in neonates

There is no consensus regarding the optimal management options for SDB in neonates, and practice patterns vary widely among sleep providers. While adenotonsillectomy and continuous positive airway pressure (CPAP) are the most frequently used treatment measures in toddlers and preschool aged children, along with interventions targeting specific conditions (e.g. nasal corticosteroids for allergic rhinitis), the lack of agreement for treatment thresholds among healthcare providers contributes to the variability in treatment approaches in neonates.[55]

The optimal management for SDB in neonates depends on the underlying cause and severity, but there is no established stepwise approach. A variety of medical managements including CPAP, nasopharyngeal airway, High Flow Nasal Cannula (HFNC), prone positioning and placement of an orthodontic appliance have been described with varying success.[67] In severe cases, surgery is required including tongue-to-lip adhesion (glossopexy), mandibular distraction osteogenesis (MDO) and tracheostomy.[68-70]

It's important to acknowledge that each treatment approach comes with its own set of advantages and disadvantages. The effectiveness of any given treatment for SDB in neonates can vary depending on the underlying cause and severity, emphasising the importance of individualised treatment approaches.

CPAP is one of the commonly used treatments in newborns with SDB. It prevents the collapse of the upper airway by continuously applying pressure throughout the breathing cycle, thereby preventing airway collapse and resulting in improved gas exchange and

sleep quality. Finding a mask interface with a good fit that ensures comfort and minimises air leakage is crucial for the efficacy, tolerance and compliance of therapy. However, there is a limited commercial market for these interfaces and no defined standards for choosing the right interface making the use of CPAP therapy in neonates challenging, especially in neonates with craniofacial anomalies and genetic syndromes which may have mid-face hypoplasia. After the initiation of CPAP therapy, regular follow-up is necessary to ensure the efficacy of therapy, which is limited by low adherence, often evident after hospital discharge.

Data on the use of CPAP in neonatal OSA are limited and the long-term studies available were undertaken in older children. A single centre retrospective study compared positive airway pressure (PAP) therapy in 41 infants (younger than six months) to 109 school-aged children (5–10 years). They found a median reduction in obstructive apnoea-hypopnea index (OAHI) of 92.1% in infants, which was comparable to the 93.4% reduction observed in school-aged children.[71] One of the largest PAP adherence analyses of paediatric patients with OSA found that only 46.3% of the cohort met the study criteria for adherence requirements after 90 days, highlighting the issue of poor compliance.[72] Other studies have also reported similar findings of poor adherence.[73,74]

Lack of availability of appropriate interfaces, low adherence data and concerns about chronic use causing midface hypoplasia[75] likely contribute to the apparent limited use of CPAP as a first-line treatment in neonates leading to variability in clinical practice. Given the limited long-term data on CPAP therapy in neonates, further research is needed to determine the efficacy and compliance of PAP therapy in neonatal OSA. Like CPAP, other treatment alternatives also have issues and limitations related to their invasiveness and risks of anaesthesia in the case of surgery or effectiveness, adherence, and potential side

effects of non-surgical therapies. Given the limited long-term evidence regarding the efficacy and outcomes of various treatment options, local experience, influenced by the availability of treatment options, plays a crucial role in decision-making, leading to significant variations in practices amongst different centres across the world.

Image 2: An infant on home CPAP device prior to discharge from the NICU.

1.7 ***Impact of SDB***

Evidence in the literature highlights that sleep related breathing disorders in the paediatric population may have significant negative effects on the child's health, as well as on family functioning and parental well-being.

(a) Impact on parents and family

Persistence of SDB in a child can be associated with insecure attachment and a more ambivalent attitude towards the child, increased parental stress, imperfect relationships in the home and maternal depression.[76,77] A large Australian study of almost 5,000 preschool children reported that child sleep problems were associated with

psychological distress in mothers and poor general health in both mothers and fathers.[76] After a comprehensive review of the literature, Meltzer et al.[78] concluded that, children's sleep disruptions can have a significant impact on parental sleep and daytime functioning, including depression, fatigue, parenting stress, and marital satisfaction.

(b) What is known about the impact of SDB in children

SDB in children is linked to various health problems, including growth, behavioural, neurocognitive, cardiovascular, and metabolic issues, negatively affecting the quality of life.

Effect on growth

Studies have demonstrated that OSA can negatively impact a child's growth.[79] The effects of OSA on growth are probably related to increased energy consumption and decreased secretion of growth hormone, which is primarily released during sleep.[80] Studies indicate that these adverse effects on growth can be reversed with appropriate treatment.[80-82] In a systematic review of 12 studies, Lagravère et al.[83] reported that children with OSA have lower levels of insulin-like growth factors, essential for normal growth, compared to healthy controls and tonsillectomy may improve these functions.

Neurocognitive and behavioural consequences

SDB has been associated with different forms of neurocognitive consequences in children. Associations between SDB and cognitive and behavioural disorders, such as attention deficit hyperactivity disorder (ADHD) have been well described in published studies.[13,84-86] In a meta-analysis of 63 studies including children aged 2-18 years, Menzies et al.[87] reported that children with SDB had significant impairment in all cognitive domains with verbal and overall intelligence being the most affected quality. A possible underlying mechanism that might explain the association between SDB and

neurocognitive problems is episodes of intermittent hypoxia.[88,89] However, previous studies have shown that these neurocognitive deficits were not related to the severity of SDB and were also found in children with primary snoring.[90,91] Sleep fragmentation resulting from repeated arousals has been postulated as the other possible mechanism that could be responsible for the neurobehavioral effects associated with SDB.[92]

Identification of children at high risk for SDB and its associated morbidities is particularly important given previous studies showing that treatment can improve quality of life and neurocognitive function.[93-96] However, some of the recent studies have revealed contradictory findings. One study investigated the long-term consequences of SDB on preschool children's cognition and behaviour, showing that irrespective of resolution of SDB, cognitive and behavioural functioning remained significantly worse in children originally diagnosed with SDB compared to the control children.[97] The authors concluded that resolution of SDB in preschool children has little effect on cognitive or behavioural outcomes over the long term. A recent randomized controlled study evaluated the outcome after early adenotonsillectomy compared with no surgery in preschool children with mild OSA; no cognitive gain was found in children after early adenotonsillectomy compared to no surgery group.[61]

In summary, the literature indicates that SDB can have significant long-term negative effects on the neurocognitive development of children. Efforts to identify vulnerable phenotypes and quantify the benefits of early treatment for SDB-related adverse neurodevelopmental outcomes are needed.

Cardiovascular effects

Studies have linked SDB to elevated systolic and diastolic blood pressure, even after accounting for confounding factors.[98] In a recent meta-analysis including 14 studies, Ai

et al.[99] reported that mean systolic blood pressure was higher in children with SDB compared to healthy controls. SDB has also been associated with unfavourable changes in the cardiac health of youth[100] and to a greater prevalence of left ventricular hypertrophy in children.[101,102] Several studies have reported an improvement in cardiovascular function after OSA is adequately treated.[103-105]

Other effects of SDB on children

Studies have shown an increased prevalence of the metabolic syndrome among children with OSA. One study reported six-times increased odds of metabolic syndrome compared to children without SDB.[106] A similar link has been found between nocturnal enuresis and SDB in children.[107] A meta-analysis of 10 studies found that children with OSA have a lower quality of life compared to healthy children.[108]

(b) Impact of SDB in neonates

Despite advancements in neonatal care, there is a scarcity of data on the long-term consequences of SDB in infants. There are very limited, small studies have tried to look at the impact of neonatal SDB on neurodevelopmental outcomes in a specific group of neonates.[109,110] Adverse neurocognitive and other effects of OSA in older children have been well described.[13] However, most paediatric studies looking at the long-term effect, excluded neonates from their cohorts; therefore, making it difficult to understand the sequelae of neonatal SDB. Few infant studies reported that SDB symptoms in early life (snoring, mouth breathing and witnessed apnoea) are associated with lower cognitive development scores and predict behavioural problems at later age.[110-113]

Like children, SDB related respiratory events in neonates are often associated with intermittent hypoxemia, hypercapnia, cortical arousals, and disturbed sleep

architecture. Considering the rapid brain growth in infancy, any correlation of SDB with adverse neurodevelopmental outcomes would be important to understand.

The long-term course of SDB in neonates also remains largely unknown. Understanding the trajectory of SDB in neonates is crucial for informing appropriate management and assessing potential long-term consequences. However, there is a significant lack of research in this area.

In summary, while there is extensive literature on the adverse impact of SDB in children, data on its impact in neonates is extremely limited. Considering the period of rapid growth, SDB has the potential to cause similar adverse effects in neonates. Paediatric studies have shown that early identification and appropriate treatment can potentially improve some of these adverse effects. We hope the same holds true for neonates. However, the lack of robust research in this population makes it difficult to draw definitive conclusions.

1.8 ***Burden of sleep disordered breathing***

Recent evidence shows that children with OSA or SDB require a striking increase in health care utilization however no studies have looked at the health implications and service utilisation in the neonatal population.

What is known in paediatric populations

A cross-sectional paediatric study showed a 226% increase in health care utilisation amongst children with Obstructive Sleep Apnoea Syndrome (OSAS) compared to the control population.[114] The utilisation of heath care services was particularly high in younger children (<5-year-olds). The severity of the OSAS was significantly related to the total annual costs. Tarasiuk et al.[115] reported similar findings of significantly greater

morbidity and health care use in children with OSAS, mainly related to respiratory diseases.

A recent large cohort study of over 16000 children reported higher health care utilisation among children with a chronic medical condition who also have a sleep disorder (OR= 1.83; 95% confidence interval 1.67–2.01), after controlling for comorbid medical conditions and demographics.[116] Those with sleep-disordered breathing were 1.5 times more likely to have increased health care utilization (OR=1.51; 95% confidence interval 1.17–1.95). Sleep-disordered breathing was found in 14.2% of children with medium health care utilisation and 20.6% of those with high utilisation. The authors noted that sleep disorders tend to be underdiagnosed in paediatric populations, so the association between sleep disorders and health care utilisation may be even stronger than the results of this study demonstrate.

In summary, while there are no neonatal studies on this topic, evidence from the adult and paediatric literature clearly points to increased health care utilisation for those with SDB. Effort is needed to improve our understanding about the effects of SDB on neonates. Knowing the clinically significant level of SDB in this at-risk population and their long-term outcome will significantly help to identify the neonates who need to be treated as collective evidence suggests that early diagnosis and prompt intervention may be both effective for the individual and cost effective for the health-care system.

Summary and identified gaps in the literature

SDB is prevalent in children, particularly in those with underlying anatomic and neuromuscular risk factors. It has a significant negative impact on children's health and well-being and leads to increased healthcare utilisation. Despite the negative effects,

effective treatment can reduce many of the adverse consequences associated with this condition.

However, neonatal SDB remains largely unexplored and understudied. There are significant gaps in the literature regarding the SDB in neonates, covering a range of aspects of the disease, highlighting the need for further research. Knowledge gaps are summarised below:

i. There is a lack of established normal sleep breathing parameters in neonates and infants.
ii. Due to varying definitions used for diagnosing SDB, the exact prevalence of neonatal SDB remains unknown.
iii. There is a lack of consensus on standardised treatment thresholds for SDB in neonates.
iv. As neonates may be “asymptomatic” or present with atypical symptoms of SDB (e.g. unexplained hypoxaemia) compared to older children, increased awareness of SDB is needed amongst clinicians to ensure timely diagnosis.
v. PSG is the gold standard for diagnosis of SDB, but it is expensive, resource intensive and has limited availability. As with older children and adults, easily performed and interpreted simpler screening and diagnostic tests on infants at risk of SDB (e.g. Trisomy 21) in maternity hospitals with Level 2 special care units will be needed which may obviate the need for transfer to tertiary NICUs.
vi. There is a lack of consensus guidelines for managing SDB in neonates leading to considerable variation in the management worldwide.
vii. The clinical trajectory of SDB in neonates into early childhood remains poorly understood.

viii. The long-term impact of neonatal SDB is poorly described. Limited small studies suggest a negative association between SDB in neonates and long-term neurodevelopmental outcomes, but additional research is necessary to confirm these findings.

ix. While treatment has been shown to reverse certain deleterious effects of SDB in older children and adults, further investigation is required to understand the equivalent outcomes in neonates and infants.

Hypotheses

Fundamental hypotheses underpinning this thesis:

1. With increased survival of at-risk neonates (very preterm born infants and neonates with congenital anomalies and genetic syndromes), the prevalence of SDB is increasing in the neonatal population. This hypothesis was supported by the increased referrals of infants and neonates for sleep consultation and PSG to our hospital and significant rise in the number of newborns with SDB going home on CPAP from our NICU (Figures 1 & 2).

Figure 1: Numbers of infant PSGs performed in our hospital per year.

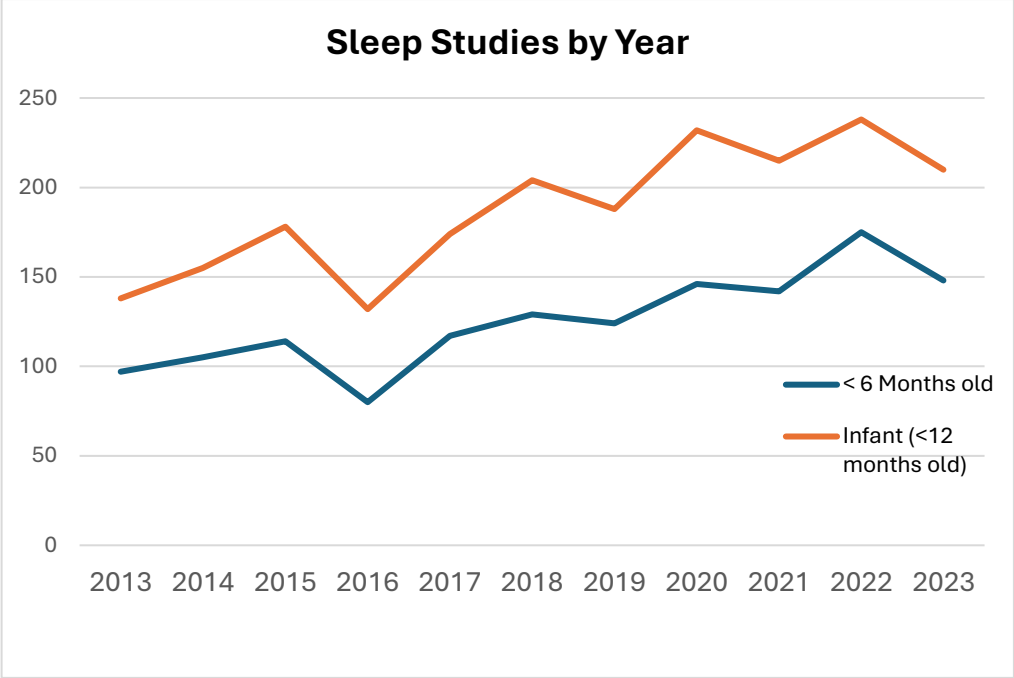
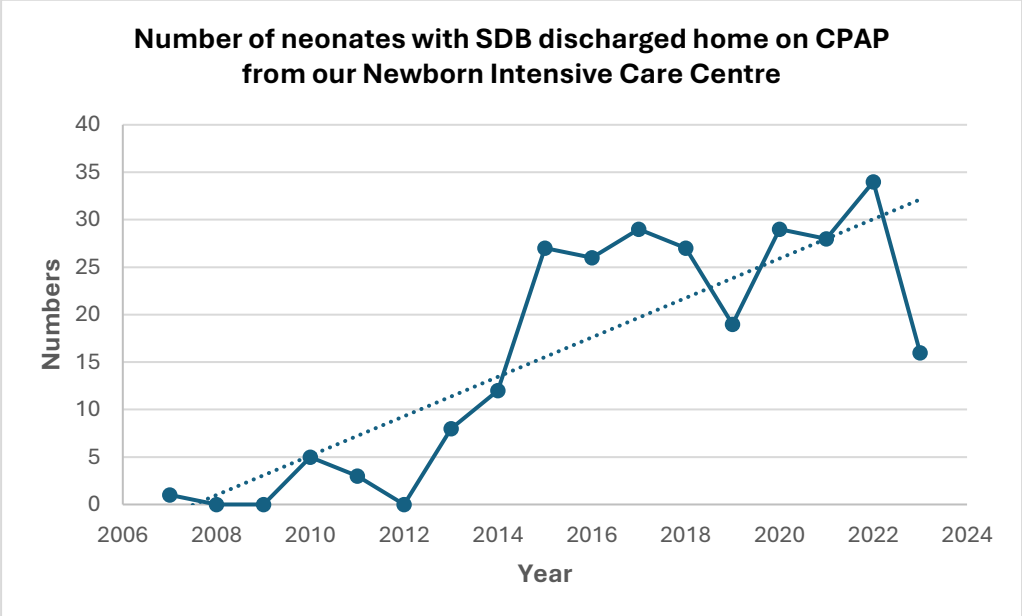


Figure 2: Number of neonates discharged on home CPAP device from Grace Centre for Newborn Intensive Care.



Research aim: A comprehensive profile of these infants is essential for understanding their unique needs and optimising care.

2. We also hypothesised that because of the associated morbidity and potential negative consequences related to SDB, health care utilisation by these infants would be higher. To minimise these effects, early correct diagnosis and management is essential. There is a pressing need for greater clinician awareness, screening tools for neonates at risk of SDB and for clear guidelines on referral thresholds to tertiary care NICUs, diagnostic criteria and treatment indications. New evidence regarding neonatal SDB's long-term impact on neurocognitive outcomes is necessary.

   Research aim: New evidence regarding the short and long-term impact of neonatal SDB is necessary.

AIMS OF RESEARCH

This doctoral program thesis is entitled: ''Evaluation and outcomes of sleep disordered breathing in neonates''. The specific aims are:

1. To summarize the current knowledge and available evidence regarding neonatal sleep, SDB, and their impact on neonates.
2. To investigate neonatologists' knowledge, practices, and awareness of SDB in Australia and New Zealand.
3. To identify risk factors for neonatal SDB and to evaluate diagnostic methods, treatment options, and short-term outcomes for neonatal SDB.
4. To describe the trajectory of SDB from infancy to early childhood and review the impact of SDB in neonates on neurodevelopmental & respiratory outcomes at 3 years of age.

It is our understanding that this is the first thesis to provide a comprehensive account of the practices, profile, short-term outcomes, natural history and medium-term impact of

neonatal SDB on early childhood respiratory and neurodevelopment outcomes. As evidence for the benefits of early treatment continues to build, identifying these neonates most at risk is of utmost importance.

THESIS OUTLINE

This thesis has a focus on optimising the clinical care of neonates with sleep disordered breathing. It is presented as a combination of one published literature review and three published papers. Given the disruptive impact of the COVID-19 pandemic on staffing, research collaboration and research participation that lasted for 3 years, the thesis also includes detailed descriptions of some ancillary work in Chapters 6 and 7 of two studies that were commenced but not completed during this research program and are currently ongoing.

Chapter 2 Provides a comprehensive overview of the available literature on neonatal SDB, identifies the factors that make neonates particularly susceptible to SDB, summarises the current evidence, and discusses the implications for clinical practice. The gaps in existing knowledge on SDB in the neonatal population, research aims, as well as recommendations for future studies were identified from this platform.

Chapter 3 This chapter provides insights into the awareness, knowledge, and practices of neonatologists regarding SDB in Australia and New Zealand. By increasing awareness among neonatologists, we aim to facilitate appropriate, timely referrals and diagnosis of SDB for at-risk neonates, ultimately improving patient outcomes.

Chapter 4 Presents short term outcome findings of a cohort of at-risk neonates with SDB. This study offers a comprehensive overview of the clinical profile of neonates with SDB, highlighting a diverse range of presenting symptoms. It also examines the effectiveness of available diagnostic methods in neonates, describes treatment options, and presents hospital outcomes for affected infants. By investigating these factors, the study aims to enhance understanding of SDB in neonates and provide insights into optimising clinical care for affected infants.

Chapter 5 Discusses the impact of neonatal SDB on neurodevelopmental and respiratory outcomes at age 3 years. It also outlines the trajectory of neonatal SDB, tracing its progression from the neonatal period through early childhood. By providing this information, the chapter aims to enhance physicians' understanding of the consequences of SDB which might help them in better planning and clinical management, leading to improved patient outcomes.

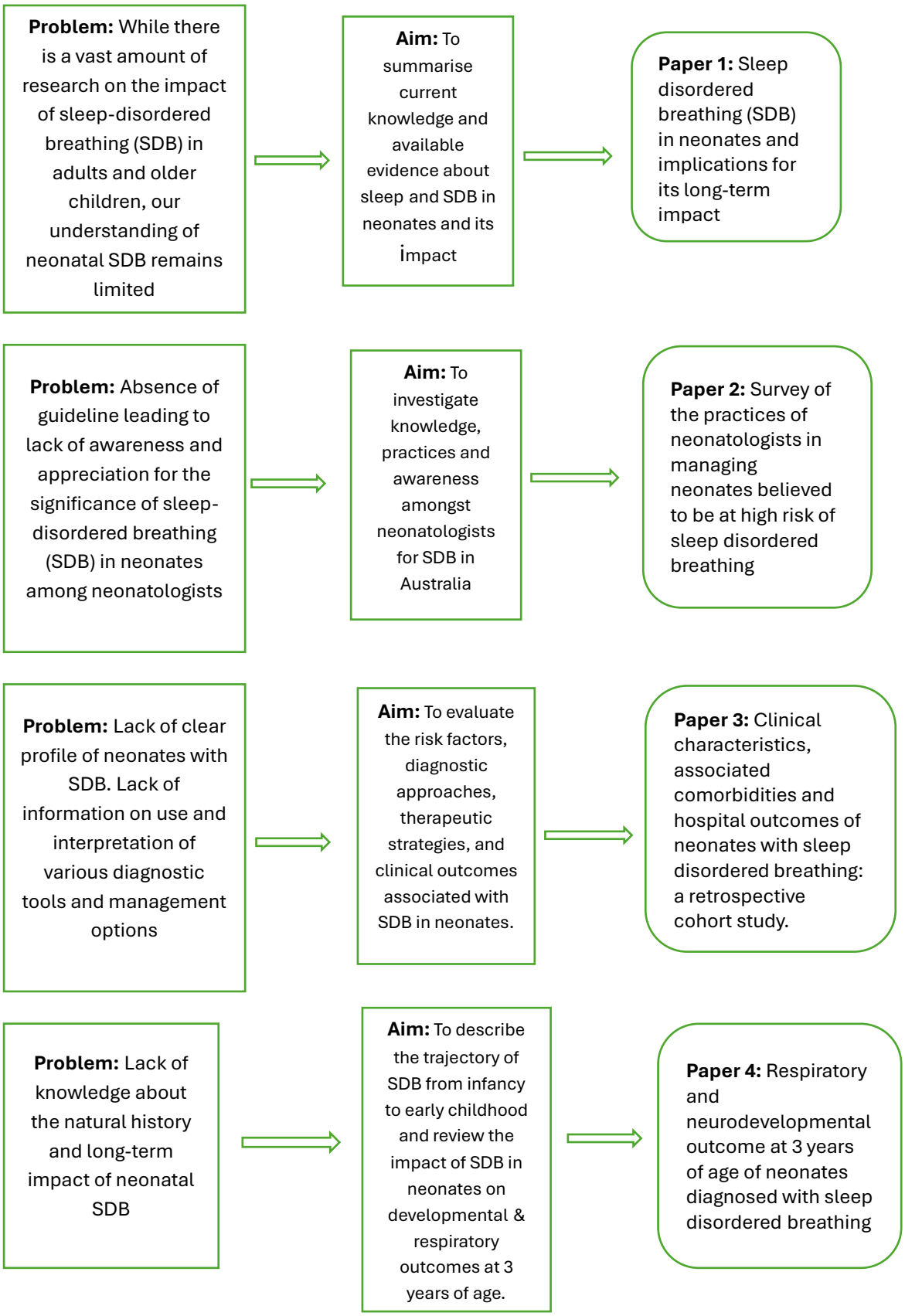
Chapter 6 Outlines the first ancillary work which was started during this thesis and is currently ongoing. The project is entitled: ‘’Evaluation of oxygen saturation and transcutaneous carbon dioxide profile at discharge in neonates post-major surgery.’’ This work was significantly impacted by the COVID-19 pandemic. The progress to date on the project will be presented.

Chapter 7 Outlines the second ancillary project undertaken during this thesis entitled: ‘’Evaluating the use of 3D facial photography in preschool children to investigate a potential association between the facial profile and sleep disordered breathing.’’ This

work was also significantly impacted by the COVID-19 pandemic and is currently ongoing. The progress to date on the project will be presented.

In **Chapter 8**, the key findings are summarised together with recommendations for future research and knowledge translation into clinical practice.

Figure 3: Concept map illustrating the knowledge gaps, the research aims and the publications addressing these aims.



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Chapter 2. Sleep disordered breathing (SDB) in neonates and implications for its long-term impact

Mini-Symposium: Sleep disordered breathing in children: indications, interpretation and implications

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Mini-Symposium: Sleep disordered breathing in children: indications, interpretation and implications

Sleep disordered breathing (SDB) in neonates and implications for its long-term impact

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Educational aims

The reader will come to appreciate

- Characteristics of neonatal sleep and why neonates are more prone to have SDB.
- Neonatal characteristics/conditions associated with SDB.
- How SDB affects neonates and long-term implications.
- Areas that require future research.

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ABSTRACT

Sleep-disordered breathing (SDB) is a significant cause of morbidity in neonates and young infants. SDB occurs more commonly in preterm infants and in neonates with underlying syndromes. Recent evidence shows that infants with obstructive sleep apnoea (OSA) or SDB have greater health care resource utilization, including longer hospital stay. Management of SDB includes non-invasive ventilation or surgical interventions tailored to the patient. Screening high risk newborns should allow for early diagnosis and timely therapeutic intervention for this population. However, the thresholds for diagnosing SDB and for guiding and implementing treatment in neonates remain unclear. A collective effort is required to standardize the practice worldwide. This article will discuss neonatal sleep physiology and characteristics of neonatal sleep, with an emphasis on the epidemiology and diagnosis of SDB in neonates and its implications for long term outcomes.

INTRODUCTION

Sleep disorders are common in infants. In high income countries, sleep problems are reported in approximately 30–46% of infants during the first year of life although these are predominantly behavioural sleep issues [1–5].

SDB is increasingly being recognised as a cause of morbidity in neonates and infants <6 months old. Likely contributors include the increased survival of extremely preterm infants as well as neonates with surgical and complex medical problems [6]. Results from previous studies suggest that infants born at <32 weeks gestation compared to those born at term were 2.7 times (OR 95% CI 2.16–3.49) more likely to be diagnosed with sleep apnoea, and that the diagnosis of SDB is more prevalent in children born preterm [7–9]. The authors emphasise that a high level of clinical awareness is required to identify OSA in the preterm infants. Other research has demonstrated a higher incidence of airway obstruction in infants with disorders such as cleft palate [10] and in neonates with myelomeningocele [11]. However, prevalence rates for sleep disordered breathing are not well defined.

WHAT IS SLEEP DISORDERED BREATHING (SDB)

In children, SDB is described as a spectrum, describing the severities of upper-airway obstruction (Table 1). However, in neo-

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nates the underlying physiology means that central respiratory events (relating to respiratory control) have as much importance as airway obstruction. Thus, sleep disordered breathing (SDB) in neonates is better described as a group of respiratory disorders that occur or are exacerbated during sleep (Table 1).

Accurate identification of SDB in the neonatal population is critical from both clinical and research perspectives. SDB can lead to significant adverse physiological effects that impact on health and development and recent evidence suggests that children with OSA or SDB have a significantly higher level of health care utilization [12,13]. The exact incidence and prevalence of SDB in the neonatal population remains unknown.

SIGNIFICANCE OF SLEEP

A body of literature confirms the importance of healthy sleep for its integral roles in growth and development, metabolism and weight regulation, immune function, learning, consolidation of memory and executive functioning [14–16]. SDB leads to inadequate or unhealthy sleep which is associated with decreased performance or function across these domains.

DEVELOPMENT OF SLEEP PHYSIOLOGY

Studies in pre-term infants and foetuses show that sleep begins as early as 25 weeks gestational age (GA) and it is a distinct behavioural state by 28–32 week GA [17,18]. Identification of different sleep stages is possible by 32 weeks gestation [18]. Towards the end of pregnancy, the percentages of both REM sleep (formerly active sleep) and NREM sleep (formerly quiet sleep) including a small percentage of Indeterminate Sleep (IS), increase [17]. Infants sleep born prematurely tend to have higher percentages of active (REM). These data demonstrate that sleep physiology is well established prior to birth [19,20].

NEONATAL SLEEP CHARACTERISTICS

Like many physiological parameters, sleep changes rapidly in the first two years of life. Sleep architecture evolves rapidly into a mature pattern, with the first twelve weeks of life being a time of particularly rapid change. At birth, REM sleep dominates, accounting for 50–60% of all sleep time, falling rapidly and by 2 years of age where it represents about 25% of sleep time [21]. In neonates, REM sleep differs to that in older children in several ways: there is absence of body paralysis and atonia, its timing differs relative to other sleep elements and it occupies a greater proportion of total sleep time. NREM sleep is also different in neonates where it is not possible to identify the various stages of NREM sleep at birth but these emerge in the first few months of life. Development of spindles, a characteristic of light non-REM (stage 2) sleep occurs from 6 to 8 weeks of age [22]. By three months, bouts of light NREM (stage 2) sleep can be distinguished, and by six months all stages of mature NREM sleep can be identified. Infant sleep staging has traditionally been considered appropriate to the age of 6 months, by which time neuronal maturation is sufficient to reliably distinguish light (stage 2) NREM sleep.

Total sleep time (TST) gradually reduces throughout the infancy from 16-17 hours in the neonatal period to 13–14 h by 6 months of age [23–27]. Circadian rhythm starts to develop around 4–6 weeks of age although it can take several months to establish a regular circadian rhythm [28,29]. By around 10–12 weeks of age, a diurnal pattern begins to emerge with longer bouts of night-time sleep complemented by three or four naps during the day. By age 6–9 months, most infants develop the ability to sleep through the night [30]. Daytime sleeping steadily reduces with sleep occurring in 3 or 4 naps at 6 months of age and in two naps by 9 to 12 months [24].

WHAT HAPPENS TO BREATHING/RESPIRATION DURING SLEEP

A number of factors predispose neonates to SDB. Infants have high nasal resistance and reduced airway stiffness. In addition they are preferential nose-breathers hence OSAS can occur with isolated nasal obstruction. Nasal congestion due to an otherwise mild viral upper-respiratory-tract infection can result in significant respiratory distress in young infants [31].

Neonates have a highly compliant chest wall with reduced functional residual capacity (FRC) resulting in predisposition to desaturation when ventilation is impaired by upper airway obstruction. During REM sleep, inhibition of intercostal muscles means paradoxical movement of the chest and abdomen are typical for infants and during REM sleep, a newborn's FRC decreases further [32,33]. This is made more important by the increased time infants spend in REM sleep and in sleep overall.

Other factors that contribute to breathing control are immaturity of the Central Nervous System and peripheral chemoreceptors. In the neonatal period, central apnoea occurs in all sleep stages [38]. The frequency of central apnoea decreases with age and central apnoeas lasting more than 15 seconds are rare after one month of age [43]. Several factors increase the rate of central apnoea. These include brain stem anomalies (such as Arnold–Chiari Malformation), prematurity, metabolic disorders, anaemia, hypoxia, viral infection, or warm ambient temperature [44,45].

In most preterm and term infants, periodic breathing (PB) is common and generally thought to have no pathological significance [34–36]. The most widely accepted definition of PB is at least 3 cyclical apnoeas of at least 3 seconds duration with less than 20 s of breathing in between [35]. A recent study from Daftary et al [38] showed the presence of PB in 40% of the cohort of healthy neonates (mean 1.16% of total sleep time, range 0–11.3%) while another study [39] reported presence of PB in 90% of neonates studied (95th centile for PB 8.9% of total sleep time). PB is thought to reflect a developmental immaturity in the ventilatory control system and usually occupies less than 10% total sleep time (TST). Its frequency

Table 1
Sleep-disordered breathing in children vs neonates.

Children	Neonates
Primary snoring: mild upper-airway obstruction with no obstructive events or apparent sequelae	**Apnoea of prematurity**
Upper airway resistance syndrome: frequent arousals, but no blood gas changes as consequence of the events	**Central apnoea**
Obstructive hypoventilation: leads to oxygen desaturation and carbon dioxide retention	**Hypoventilation** – central or obstructive
Obstructive sleep apnoea (OSA): includes all of the sequelae noted above i.e. obstructive events with associated increased frequency of arousals and disturbances to both oxygenation and carbon dioxide	**Obstructive sleep apnoea syndrome (OSAS)**: OSAS may present in a mild, moderate or severe form according to the number of respiratory events, severity of gas exchange abnormalities and the amount of sleep disruption

decreases with age, occurring in <3% of TST by 2 months. Healthy infants between 6 and 18 months may exhibit PB during sleep for up to 1–2.5% of TST [40–42]. Preterm infants (32 weeks) with excessive PB were reported to show risk for SIDS [37] although no causative link has been established.

Obstructive apnoeas are more common in neonates during REM (active) sleep [38,46]. The frequency of obstructive and mixed apnoeas (OMA) decreases after 2 week of age [47]. Obstructive apnoeas are rare in older children and preadolescents with an estimated frequency of 0.1 ± 0.5 obstructive apnoeas per hour (range, 0.3–1 episodes) [48].

DIAGNOSIS OF SDB IN NEONATES

Polysomnography (PSG) is the current standard for evaluating OSA. The studies characterize sleep architecture and respiration. Sleep architecture is evaluated using a combination of electroencephalogram (EEG), electro-oculogram (EOG) for eye movements, and sub-mental electromyogram (EMG) for muscle tone with characterization of sleep/wake states and arousals. Respiratory function is assessed using air flow at the nose, movements of the chest and abdomen, oximetry and transcutaneous CO_2. The electrocardiogram (ECG) measures heart rate, and limb movements are monitored using limb EMG sensors. Audio recordings detect sounds such as snoring and video recordings can help characterize movements or behaviours during sleep. Direct observation, or video recording, is important in infants where EEG characteristics may not be so well-defined and body movements are common in REM sleep.

Scoring guidelines are standardized, with criteria for analysis of PSG results in young infants (<6 months old) (American Academy of Sleep Medicine, 2005) [49]. However, diagnosing SDB in neonates remains challenging because there is much variability in how research studies report the different parameters recorded in neonatal PSG and there are no widely accepted norms for defining SDB in this population.

EPIDEMIOLOGY OF SDB

OSA is the most severe form of sleep-related breathing disorder. Its estimated prevalence among the paediatric population is between 1%-4% [50,51] although the prevalence in neonates remains unknown.

A review of literature utilizing PubMed & MEDLINE revealed very few studies utilizing polysomnography for diagnosing SDB among term and near-term newborns in a Neonatal Intensive Care Unit (NICU). Bandopadhyay et al [9] looked at a small group of fifteen preterm infants, mostly with severe bronchopulmonary dysplasia [BPD] who had a PSG performed at term. They reported high levels of sleep apnoea in preterm infants with BPD with elevated levels of apnoea-hypopnoea index (AHI) compared to the published norms for children. However, the AHI did not correlate with developmental scores at 2 years of age. Shellhaas et al [11] reported PSG in 20 neonates with myelomeningocele and compared their PSG results with age matched controls and reported that overall AHI was significantly higher for infants with myelomeningocele than for controls. Meerkov et al [52] studied 48 newborns (>35 week gestation) who were at risk of seizures and found that 50% of the neonates in the study had an AHI > 10/h, with most events being hypopnoeas and central apnoeas, and events more common in REM sleep.

The lack of standard criteria for testing, lack of normative data and a variety of methodological issues, represent significant hurdles to estimating the prevalence of SDB in neonates. Heterogeneity in diagnostic criteria means that the threshold for diagnosing SDB compared to healthy neonates without any obvious risk factors remains unclear [38]. Although AHI is typically the value used to categorise the severity of OSA, study criteria in infants vary with examples including a Respiratory Disturbance Index (RDI) >5/h of sleep [53], a mixed obstructive apnoea-hypopnoea (MOAHI) Index >2/h of sleep [54], an apnoea-hypopnoea index (AHI) >2 unless >25% of events were central [55], or an arousal index of 12 or more and oxygen desaturation of less than 89% for at least 2% of total sleep time [56].

With increasing awareness about SDB in neonates, there is a need for development of reference values in healthy newborns using the latest standardized AASM testing and scoring guidelines [49]. It seems likely that separate AHI criteria are required for neonates and infants for treatment decision making. In PSGs of 30 healthy newborns during their first month of life, Daftary et al [38] reported lower sleep efficiency and significantly higher AHI in neonates compared to infants older than 1 month and a range of obstructive and central respiratory events. As this study indicated, the current severity classifications of sleep apnoea may not apply to newborn infants and there is a risk of overtreatment if paediatric treatment guidelines are used.

AETIOLOGY/RISK FACTORS

The pathophysiology of OSAS is complex with multifactorial aetiology and different phenotypes. High heritability of SDB has been demonstrated in adults and genetic contribution is suggested although no established gene variants conferring risk for OSA have been found [57]. One clear genotype-phenotype correlation for SDB in neonates is the link between PHOX2B and congenital central alveolar hypoventilation syndrome (CCHS) [58]. While other genetic syndromes can predispose to SDB, generally they are classified by the associated physical abnormality that predisposes to the condition, including craniofacial abnormalities [e.g. cleft palate, Pierre Robin sequence], neuromuscular weakness [congenital myopathies, myotonic dystrophy], hypotonia [Prader Willi syndrome] and syndromal diagnoses like Trisomy 21 (Table 2) [59].

COMPLICATIONS OF SDB

In later childhood, SDB has been associated with negative effects on health, growth and development, and behaviour [60–72]. Associations with OSA include acute and chronic changes in blood pressure and heart rate [60–62], with links to hypertension [63], growth failure [64], enuresis [65,66] and impairment of cognition, attention and executive functioning [67–72]. Severe neurobehavioral complications are uncommon although reported associations include developmental delay, poor school performance, hyperactivity, and inattention. Preterm infants are both more likely to develop SDB at school age and more likely to have associated neurocognitive sequelae if they have SDB [73,74].

There is ongoing debate about the origins and reversibility of neurodevelopmental consequences of SDB [75–77]. Possible mechanisms, supported by animal and theoretical models, include sleep fragmentation and sleep loss in addition to intermittent hypoxia precipitating endothelial dysfunction via inflammatory changes [78,79]. Sleep disruption is thought to be responsible for poor neurocognitive outcomes in children with SDB [80,81].

Growth compromise in preterm infants has been studied in association with respiratory rate and altered sleep architecture. In a small cohort of preterm infants with chronic neonatal lung disease (CNLD) reflected by tachypnoea [$N = 16$, average gestation 29 weeks and birth weight 986 g; versus 7 term born controls], Fitzgerald et al. demonstrated a trend toward lower growth velocity in infancy in CNLD group with higher respiratory rate (RR) com-

Table 2
Abnormalities associated with sleep-disordered breathing and obstructive sleep apnoea in infants.

Risk factors for developing SDB in neonates
1. Craniofacial anomalies • Craniosynostosis lncluding Apert, Crouzon & Pfeiffer syndromes, achondroplasia • Choanal atresia/stenosis • Jaw anomalies like micrognathia and/or retrognathia – Pierre Robin Sequence – Stickler syndrome – Treacher-Collins Syndrome • Cleft Palate 2. Neurological problems • Neuromuscular disorders – Nemaline Rod myopathy – Congenital myotonia – Spinal Muscular Atrophy • Arnold-Chiari malformation • Hydrocephalus • Central hypotonia: Praer -Willi syndrome 3. Congenital malformation syndrome – Down Syndrome – Mucopolysaccharidoses – Beckwith-Weideman Syndrome 4. Functional airway anomalies: laryngomalacia, vocal cord paralysis 5. Extreme preterm with chronic lung disease

pared to those with lower RR and controls [82]. This was matched with higher excretion of urinary growth hormone, known to be mainly excreted in SWS. Through infancy, the degree of tachypnoea resolved, urinary growth hormone excretion reduced, and sleep became more consolidated, providing a number of potential mechanisms for impaired growth effects in infants with CNLD including chronic stress, compromised nutrition [GH resistance] or a feedback loop involving a direct effect of GH on lung growth and repair.

LONG-TERM OUTCOME IMPACT OF SDB

The natural course and long-term prognosis of neonatal OSAS is unknown. One study reported a recurrence of OSAS in adolescents who had been successfully treated by adenotonsillectomy during childhood [83], suggesting that children with OSAS may be at risk of recurrence of disease if they acquire additional risk factors such as obesity. Longitudinal studies have documented the persistence of infant onset sleep problems in 30% to 40% of children through 36 months of age [84–86].

There are few published studies of the neurodevelopmental consequences of neonatal SDB. These studies are limited because of the lack of precise means of diagnosing and quantifying OSAS/SDB, and because of uncontrolled treatment interventions. Bandopadhyay [9] reported that despite significantly elevated levels of AHI in a sample of preterm infants with BPD, AHI values were not associated with cognitive, language, or motor scores at 2 years of age. A study by Hunt [87] found that higher numbers of cardiorespiratory events (exceeding conventional threshold criteria) detected by home monitoring during early infancy was associated with lower developmental indices in both term and preterm infants although it was highlighted that this did not equate to a causative role for the cardiorespiratory events. A study from Meerkov et al [52] also found no association between SDB and 18–22 month Bayley-III scores in neonates thought to be at risk of seizures and suggested longer-term follow-up would be required to assess associations between early SDB and subsequent executive function or attentional measures. As thresholds for treatment and approach to management of SDB in neonates remain controversial, studies that compare presence and absence of SDB in neonates to subsequent outcomes of interest could have limited success. No studies have reported on the association between specified levels/severities of infant OSA and adverse outcomes nor on the extent to which treatment for SDB can reduce adverse neurodevelopmental outcomes.

SUMMARY/CONCLUSION

There are significant gaps in the literature regarding the SDB in neonates, covering a range of aspects of the disease and including the incidence of new cases, its prevalence in neonatal populations and its remittance/recurrence with age. Little is also known about the natural history of the disorder from infancy into later childhood. Limited studies show negative links between SDB in neonates and long-term neurodevelopmental outcomes [9,10,52] and while studies have shown reversal of some of the effects of SDB with treatment in children and adults [88,89], more information is required regarding equivalent outcomes for neonates and infants. To improve our understanding about the effects of SDB on neonates, a collective effort is needed to define norms and clinically significant level of SDB in this at-risk population. Knowing the long-term outcome of these children will significantly impact the goal of defining the levels of neonatal SDB that need to be addressed/treated.

DIRECTIONS FOR FUTURE RESEARCH

- Develop consensus for the threshold for diagnosing obstructive sleep apnoea and implementing interventions based on neonatal polysomnography.
- Make neonatologists aware of this condition and develop standard referral criteria for sleep consultation.
- Studies to better understand the relevant causal mechanisms of sleep disordered breathing in neonates.
- Longitudinal studies to evaluate the impact of SDB.

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Chapter 3. Survey of the practices of neonatologists in managing neonates believed to be at high risk of sleep disordered breathing

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Survey of the practices of neonatologists in managing neonates believed to be at high risk of sleep disordered breathing

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ABSTRACT

Objective To determine the practices of neonatologists in managing high-risk neonates believed to be at risk of sleep disordered breathing (SDB).

Design An electronic web-based questionnaire assessing awareness of and current practices for managing neonates predisposed to SDB with conditions like craniofacial anomalies, neuromuscular disorders or airway problems was emailed to 232 neonatologists and neonatal fellows working in Australia and New Zealand (NZ). Additionally, neonatologists were approached directly during the annual Australia and NZ perinatal conference in 2019.

Results 93 neonatologists (40%) responded to the survey. The majority (85%) of the respondents stated that there were no written protocols/criteria for sleep consultation in their unit. We found considerable variations in the threshold for performing tests including oximetry or referring for polysomnography. Most respondents would perform oximetry before referring for a sleep consultation. However, the duration of oximetry varied from 6 to 24 hours and there was no consensus about what is considered abnormal on an oximetry study.

Conclusion Management of SDB is gaining importance in neonatal care because of prolonged length of hospital stay and possible long-term effects of SDB. Responses received suggest a lack of clarity regarding thresholds for referral for treatment of SDB. Likely contributory factors are concerns regarding a lack of long-term outcome data from treatment perceived to be onerous for the family, unsettling to some infants and delaying hospital discharge. To overcome inconsistencies in practice, standardised guidelines for assessing and managing SDB in neonates are needed.

What is known about the subject?

- Sleep disordered breathing (SDB) can have long-term effects in children if not treated.
- There is a lack of clear diagnostic criteria and therapeutic threshold in neonates and young infants.

What this study adds?

- Management practices for neonates with suspected SDB vary considerably.
- There is a lack of guideline for management, and decisions are mostly physician dependent.
- Higher level of evidence is needed to standardise the practices and care of this group of neonates.

BACKGROUND

Sleep disordered breathing (SDB) is increasingly recognised as a cause of morbidity and prolonged hospital stay in neonates and young infants. SDB involves a spectrum of problems in neonates[1]; the most severe form is obstructive sleep apnoea (OSA), which causes obstructive events and associated arousals leading to impaired sleep quality and disturbances in both oxygen saturation and carbon dioxide (CO_2).

Neonates with OSA often suffer recurrent oxygen desaturation and CO_2 retention (type II respiratory failure). Previous studies have demonstrated an association between episodes of hypoxia and poor growth and long-term neurodevelopmental delay.[2] SDB has been linked to several long-term adverse effects in children including hypertension,[3] behavioural problems[4] and impairment of cognition, attention and executive functions.[5 6] Therefore, early identification of high-risk infants is important so that treatment can improve quality of life and neurocognitive function.[7 8] There is a gap in literature regarding SDB in neonates and its long-term outcomes. Piteo *et al*[9] reported that infants who snored had lower cognitive scores compared with controls. In a study of 33 infants with cleft lip/palate, Smith *et al*[10] reported that infants with more obstructive episodes had lower global behaviour scores at 3 years of age. However, a couple of recent studies showed negative links between SDB in neonates and long-term neurodevelopmental outcomes.[11 12]

Neonates are more vulnerable to OSA due to number of reasons including anatomical considerations (small mid-face), obligate nasal breathing, immature respiratory control and predominance of rapid eye movement sleep state, which may exacerbate obstruction due to loss of muscle tone. In young children,

adenotonsillar hypertrophy is the principal cause of OSA. However, in infants, anatomical anomalies are the predominant cause like laryngomalacia, macroglossia, craniofacial disorders such as craniosynostosis (Crouzon's disease, Apert syndrome and Pfeiffer syndrome), cleft palate and Pierre-Robin sequence, infants with mid-face hypoplasia (eg, Treacher Collins and Goldenhar syndromes) and with choanal atresia (CHARGE association).[13–17] Low muscle tone is also an important predisposing factor, for example, in infants with Down syndrome, Prader-Willi syndrome or neuromuscular disorders.[14]

Polysomnography (PSG) remains the gold standard test to diagnose and quantify the severity of SDB. It uses a combination of measurements including electroencephalogram, electro-oculogram for eye movements and submental electromyogram for muscle tone to characterise the sleep architecture. Respiratory function is assessed by nasal air flow, chest and abdomen movements, oximetry and transcutaneous CO_2 level. In addition to that, heart rate, limb movements, audio sounds to detect snoring and video recordings are also monitored.

However, PSGs in infants can only be performed at specialised paediatric centre in consultation with a paediatric sleep physician. There is usually a prolonged wait time for admission in the accepting centre due to a combination of bed constraints and availability of sleep technicians to perform polysomnograms in the neonatal intensive care unit (NICU) which leads to longer hospital stay.

Overnight oximetry study has been used as a screening tool in children and adults; however, there are limited data in young infants. An oximetry study includes monitoring of heart rate, respiratory rate and oxygen saturation. However, its sensitivity depends on the severity of SDB and the presence of more significant oxygen desaturation. Normal oximetry does not rule out SDB and therefore does not replace PSG. A high prevalence of movement artefacts also makes data interpretation challenging. A recent study showed good correlation between the desaturation index obtained from an overnight oximetry study to the Apnoea–Hypopnoea Index (AHI) obtained from PSG in young infants (<6 months) at risk of SDB.[18]

The exact prevalence of SDB in neonates is unknown. However, its recognition seems to be increasing.[12 19 20] Currently, in the absence of clinical guidelines, our experience in the largest surgical neonatal unit in New South Wales is that the approach to assessing a newborn with suspected SDB in both regional and tertiary settings varies significantly and in effect is largely driven by the experience of individual clinician.

Consequently, the aim of our study was to assess the knowledge and awareness of SDB in neonatologists and neonatal fellows working across Australia and New Zealand (NZ), and to determine their practices and referral criteria for sleep consultation.

METHODS

A questionnaire (online supplemental appendix 1) was devised in consultation with paediatric sleep physicians, with questions tailored to suit the clinical picture of neonates seen in our practice. A pilot survey was first sent for feedback to four neonatologists, experienced in managing neonates with SDB who were excluded from the final survey. The final questionnaire had 17 multiple choice questions and respondents could pick one or more answers as necessary (free text was available for additional comments).

In the survey, we asked a series of questions to explore knowledge and practices of neonatologists regarding the management of neonates predisposed to SDB in various conditions including craniofacial anomalies, syndromes like Down and Beckwith-Wiedemann syndromes, neuromuscular disorders, functional anomalies of airway and in preterm infants with moderate–severe chronic lung disease. Symptoms were arranged in a Likert-type scale and respondents were asked to choose a level/symptom at which they would recommend oximetry or initiate referral for PSG. By asking about timing for referral for PSG, we were trying to ascertain timing for sleep consultations as the PSG needs to be conducted and interpreted in specialised centres by the sleep physicians.

Patient and public involvement

Patients or members of the public were not involved in the design or conduct of the study.

Participants

This study was conducted in two phases. In the first phase, a web-based questionnaire was emailed to 232 neonatologists and neonatal fellows working across Australia and NZ (contact information was taken from Australia and NZ Neonatal Network Directory 2017). The survey was created using the online software Survey Monkey. The email contained a paragraph explaining the study with a link to the survey. The survey was open for 8 weeks and two reminder emails were sent in this period. In the second phase, we approached neonatologists at the annual perinatal conference of Australia and NZ in 2019 to complete the survey. The identity of physicians answering the questionnaire was kept confidential throughout the data collection, analysis and presentation of results.

No financial incentive was offered for taking part in the survey. Descriptive analysis was performed using Microsoft Excel, and data are presented as a number or percentage.

RESULTS

Seventy-three responses were received from the online survey, with a further 20 more responses in phase 2, making a total of 93 responses (40% response rate). The majority of responses (80%) were from neonatologists working in a major NICU (centres providing care for

Table 1 Neonatologists' practices about SDB in neonates

Responses	N	%
1. How many neonates have you referred for sleep consultation in the last 12 months?		
a. 0	18	19
b. 1–3	38	41
c. 4–6	6	7
d. >6	31	33
2. Clinical features suggestive of significant SDB in a term newborn (multiple options could be selected):		
a. Bradycardia in the absence of apnoea or desaturation	17	18
b. Apnoea and desaturations	64	69
c. Multiple desaturations on overnight oximetry	62	67
d. Desaturation during feeding	16	17
e. All of the above	26	28

SDB, sleep disordered breathing.

high-risk newborns with complex and critical conditions and providing state-wide specialist services) and majority of them were working in a perinatal unit (67%).

A decision to refer for sleep consultation was taken by the neonatal consultant in almost all cases (96%), however the majority (86%) said that there is no protocol or guideline in the unit, hence this decision is based on an individual consultant's opinion. The majority of respondents (60%) said that they had referred <4 patients for sleep consultation in the last 12 months. Respondents were asked to identify clinical features that concerned them most about the possibility of SDB in a term newborn—obvious apnoea and desaturations after term gestation or multiple episodes of desaturation on overnight oximetry were the most common symptoms determining the referral (table 1).

Responses to the questions regarding management of different groups of high-risk neonates indicated that current practices are very variable. Results are described in figure 1. Practices for the use of oximetry studies also varied, from their use as a screening tool before referring for sleep consultation to how they are performed, and how the result is interpreted (table 2). The most common brand of oximeter used was Masimo. A significant proportion (36%) of the respondents either did not know or did not reply to the question about the type of oximeter used in their unit.

DISCUSSION

In this survey of practices related to management of neonates at high risk for and/or with symptoms of SDB, we found considerable variations in screening, including the performance and interpretation of oximetry, and referral for PSG. In general, there was a shift towards PSG in infants with more severe symptoms. We suggest that there is high need for a standardised approach to the

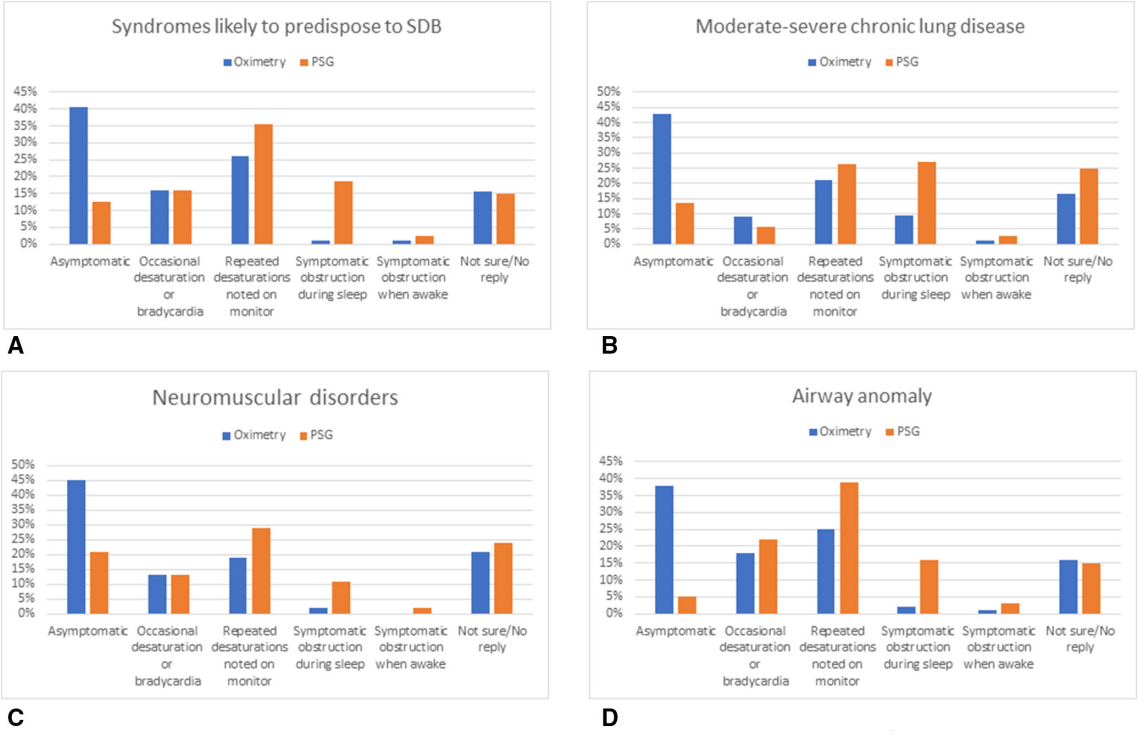

Figure 1 Management practices of neonatologists based on severity of symptoms (Likert scale-type answer option)—graphs showing at which symptom/stage they will first choose doing oximetry or refer for PSG in different conditions predisposing neonates to SDB. PSG, polysomnography; SDB, sleep disordered breathing.

Table 2 Neonatologists' practices about use of oximetry study in neonates

Responses	N	%
1. How often do you use an oxygen download study in your unit before referral to a sleep physician?		
a. Always	42	45
b. Usually	13	14
c. Sometimes	18	19
d. Never	11	12
e. Did not answer	9	10
2. What is the duration of an oxygen download study in your unit?		
a. 6 hours	9	10
b. 8 hours	10	11
c. 12 hours	33	35
d. 24 hours	32	34
e. Did not answer	9	10
3. What device do you use to record oximetry?		
a. Masimo	50	54
b. Nellcor	9	10
c. Not sure	16	17
d. Did not answer	18	19
4. What is considered abnormal oxygen download study in your unit (what features in oximetry would prompt you to refer for sleep study):		
a. Saturation <90% for more than 5% of download	47	74
b. Saturation <85% for more than 2% of download	12	13
c. Saturation <80% for more than 1% of download	12	13
d. Frequent bradycardia and/or desaturation	30	32
e. Clusters of desaturations	26	28

management of infants with conditions associated with a high risk for and/or symptoms of SDB.

Apnoea and desaturations in a term baby were reported as the most common reasons for referral to a sleep physician. These events could be related to central apnoea due to immaturity of the central nervous system and occur commonly in healthy infants in all sleep stages.[21] The frequency of central apnoea decreases with age, and prolonged or significant central apnoea is rare after 1 month of age.[22] We included this question in our study as SDB in neonates is a spectrum of disorders which includes central apnoea.[1] Our aim was to identify the referral pattern/threshold for referral to a sleep physician who can then decide about the need and timing for further investigation and management of apnoea whether central, obstructive or mixed.

Most respondents would perform oximetry before referring for sleep consultation. A large proportion (35%–40%) of neonatologists suggested that they would order an oximetry screening study even in an asymptomatic high-risk neonate. This indicates that extended oximetry recordings are more commonly used in clinical practice to assess infants' respiratory status. However, the duration of oximetry study varied from 6 to 24 hours and there was no consensus about what is considered abnormal on an oximetry study which is consistent with previous studies.[23 24]

Factors contributing to variations in clinical practice

An oximetry study can be used as a surrogate measure of airway obstruction.[25] However, there are limited studies so far comparing oximetry profiles with PSG parameters in neonates.[18] In addition to this, one paediatric study showed that there was variation in clinical interpretation leading to different management plans when the same study report was shown to different paediatricians.[26] We conclude that in addition to the differences in oximeters and analysis software available for use in neonatal units, a major problem with oximetry studies is the lack of consensus guidelines for interpreting neonatal/infant oximetry reports. We think oximetry can play an important role in screening for moderate to severe OSA in high-risk infants and guide referral to a specialist centre for further evaluation. This will also help sleep physician and receiving hospital to prioritise their admission.

The levels for cut-off in various parameters in PSG to indicate pathologically significant OSA in neonates are also still being defined and little is known about the long-term

outcome of the condition. A standardised scoring guideline with criteria for analysis of PSG in young infants (<6 months old) is available from the American Academy of Sleep Medicine (AASM).[27–29] However, diagnosing SDB based on neonatal PSG remains challenging as normative data are not well established. Most of the previous studies of PSG involving infants have excluded neonates and/or used different criteria to define SDB such as, Respiratory Disturbance Index >5/hours of sleep[30]; Mixed Obstructive AHI >2/hours of sleep[31]; and OSA defined as AHI >2 unless >25% of events were central.[32] With many studies performed prior to the publication of AASM guidelines/criteria, the generalisability of their results to the neonatal age group is restricted.[33] Nonetheless, together these studies[30–32] report a much higher incidence of respiratory disturbances in young infants compared with older children. A recent study[21] based on AASM criteria showed that healthy newborns have a wider range of both obstructive and central events and much higher AHI than older infants and children. Thus, applying current AASM paediatric thresholds would likely result in overtreatment of sleep apnoea in neonates. This creates significant clinical dilemmas for neonatologists regarding when intervention is necessary which is further compounded by the uncertainty regarding any causal linkage between SDB and abnormal neurodevelopmental outcomes.[11 12]

LIMITATIONS

The main limitation of this study was low response rate. Despite efforts to improve engagement, the response rate for our survey was only 40% which could indicate selection bias. However, as responses were obtained from individuals rather than a unit-based protocol survey, we believe the result to be reasonably representative of the entire region, especially because responses include representation from across Australia and NZ. We chose to target neonatologists individually as we believed that practices by different neonatologists within a single centre may be different.

Limited feedback suggested that several respondents found this topic too difficult, making them reluctant to complete the questionnaire. Non-respondent neonatologists potentially represent people who chose not to do it due to lack of knowledge or awareness about the condition. Based on the above and considering 80% of the neonatologists who responded were working in a major NICU, we suspected selection bias meaning participation from major centres and experienced neonatologists. Therefore, the results may represent the opinions of a group of neonatologists with a higher level of knowledge than would have been present in the broader community.

Multiple participants from limited number of centres may also bias the survey results. A significant proportion

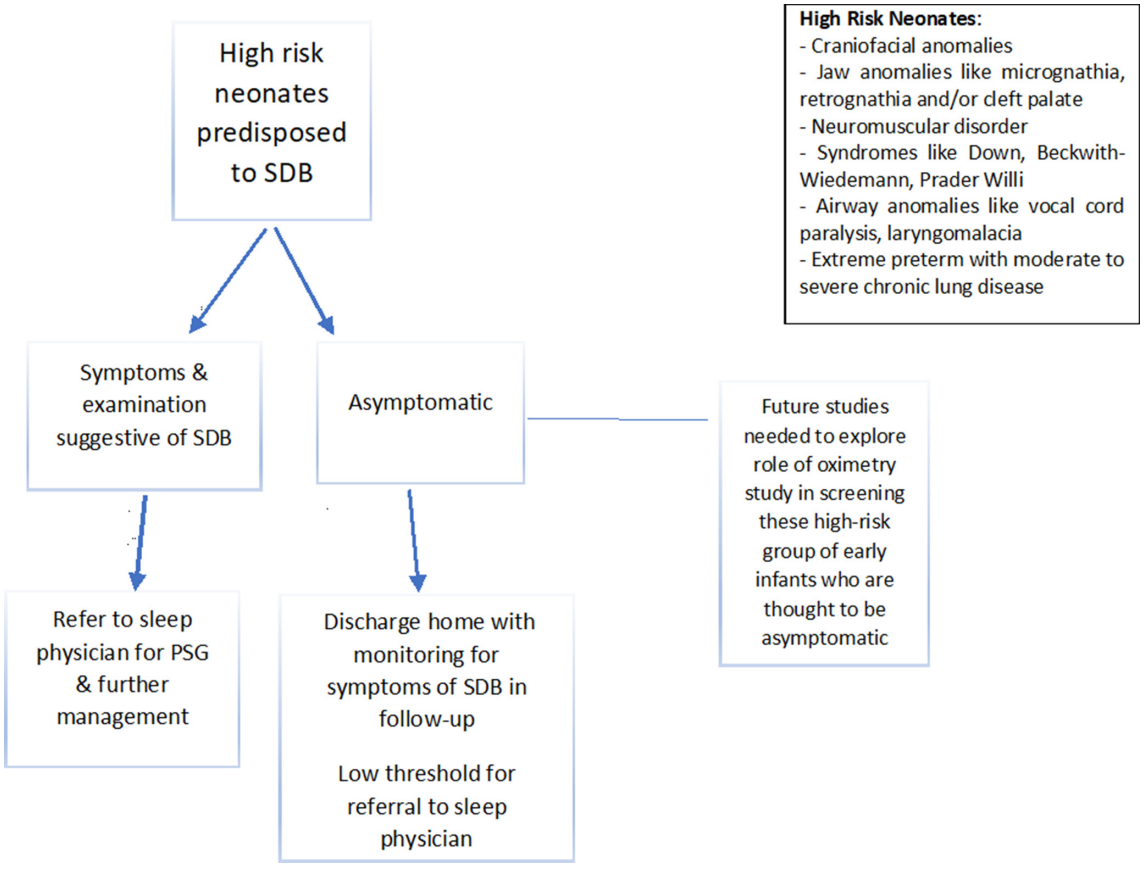

Figure 2 Suggested referral pathway for neonates suspected to have SDB. PSG, polysomnography; SDB, sleep disordered breathing.

(15%–25%) of respondents were either not sure or did not reply to the questions related to the timing of doing oximetry or referring for PSG in different clinical scenarios. Use of structured questions and answers can limit the ability of respondents to express their opinion. Providing more choices to respondents by giving them a free note option with each question can help in addressing this issue in future work. This could be achieved with a qualitative study of neonatologists' opinions on the assessment of SDB in the NICU.

In the present survey, we categorised the clinical features of SDB from being asymptomatic to having severe symptoms. The questions were designed to give the opportunity for clear answers. In reality, patients can present with combination of symptoms and signs such as oxygen desaturations with increased work of breathing which might make decision-making for the need for intervention easier for treating neonatologists.

We did not ask about the oximetry settings in this study. While this information would have been important, it was not a primary aim of the survey to specifically ask about oximetry practices. Furthermore, one-third of neonatologists could not even describe the type of oximeter used in their unit. Asking them about averaging times for data acquisition would have been even more challenging and likely raised further concerns about knowledge in this area.

CONCLUSION

This study has demonstrated a need to develop consensus guideline for screening and referring neonates with high risk for and/or symptoms of SDB. There is a need for a simple guide (figure 2) that would ensure a consistent way these high-risk neonates are managed in neonatal units throughout Australasia in an effort to decrease long-term morbidity and improve neurodevelopmental outcomes. Guidelines also need to take into account the specific condition considering the complexities and inter-related comorbidities of vulnerable infants in the NICU.

Future researchers should focus on:

- Developing a consensus guideline for the practice of neonatal oximetry studies for SDB including appropriate choice of device, settings and reporting format which are critical for interpretation.
- Identifying the prevalence of OSA in extremely low birthweight infants as they approach discharge and whether this is associated with prolonged need for supplemental oxygen.
- Identifying the consequences of SDB by correlating neonatal oximetry profiles and PSG with neurodevelopmental outcomes through early childhood and into the school-aged population.

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Appendix I: Survey questionnaire

Referral Practices for Neonates Suspected to Have Sleep Disordered Breathing (SDB)

1. What level is your neonatal unit classified as?
    a) Level 3
    b) Level 4
    c) Level 5
    d) Level 6

2. Is your nursery in a
    a) Children's hospital
    b) Perinatal centre or maternity hospital

3. How does referral for sleep consultation occur in your unit?
    a. There is a written protocol/criteria for sleep consultation like apnoea/desaturation after term corrected gestational age
    b. No written protocol or instruction – it is based on individual consultant's decision
    c. Other _____

4. Who is responsible for initiating a referral for sleep consultation?
    a. Neonatologist
    b. Fellow
    c. Nurse Practitioner
    d. Others _____

5. How many neonates have you sent for sleep consultation in the last 12 months?
    a. 0
    b. 1-3
    c. 4-6
    d. >6

6. Clinical features suggestive of significant apnoea (requiring sleep study) in a term newborn. You can select multiple:
    a. Bradycardia in the absence of apnoea or desaturation
    b. Apnoea and desaturations
    c. Multiple desaturations on overnight oximetry
    d. Desaturation during feeding
    e. All of the above

7. Enter the level at which you would order oximetry and/or polysomnography (PSG) in a neonate with "CRANIOFACIAL ANOMALIES" like craniosynostosis, cleft palate, Pierre Robin sequence

Management	Asymptomatic	Occasional desaturations or bradycardia noted on monitor	Repeated desaturations noted on nursery monitoring	Symptomatic obstruction on sleep only (e.g. ↑work of breathing)	Symptomatic obstruction when awake	Not applicable/Not sure
Oximetry Study						
Refer for Polysomnography (PSG)						

8. Enter the level at which you would order oximetry and/or polysomnography (PSG) in a neonate with "SYNDROMES likely to affect breathing" like Down, Beckwith-Wiedemann or Prader-Willi syndrome

Management	Asymptomatic	Occasional desaturations or bradycardia noted on monitor	Repeated desaturations noted on nursery monitoring	Symptomatic obstruction on sleep only (e.g. ↑work of breathing)	Symptomatic obstruction when awake	Not applicable/Not sure
Oximetry Study						
Refer for Polysomnography (PSG)						

9. Enter the level at which you would order oximetry and/or polysomnography (PSG) in a neonate with "NEUROMUSCULAR DISORDERS" like SMA, congenital muscular dystrophy

Management	Asymptomatic	Occasional desaturations or bradycardia noted on monitor	Repeated desaturations noted on nursery monitoring	Symptomatic obstruction on sleep only (e.g. ↑work of breathing)	Symptomatic obstruction when awake	Not applicable/Not sure
Oximetry Study						
Refer for Polysomnography (PSG)						

10. Enter the level at which you would order oximetry and/or polysomnography (PSG) in a neonate with "FUNCTIONAL PROBLEM of AIRWAY" e.g. vocal cord paralysis, laryngomalacia

Management	Asymptomatic	Occasional desaturations or bradycardia noted on monitor	Repeated desaturations noted on nursery monitoring	Symptomatic obstruction on sleep only (e.g. ↑work of breathing)	Symptomatic obstruction when awake	Not applicable/Not sure
Oximetry Study						
Refer for Polysomnography (PSG)						

11. Enter the level at which you would order oximetry and/or polysomnography (PSG) in a preterm neonate with "Moderate CHRONIC LUNG DISEASE" [needing <30% O2 after 36 weeks postmenstrual age or at discharge]

Management	Asymptomatic	Occasional desaturations or bradycardia noted on monitor	Repeated desaturations noted on nursery monitoring	Symptomatic obstruction on sleep only (e.g. ↑work of breathing)	Symptomatic obstruction when awake	Not applicable/Not sure

Oximetry Study						
Refer for Polysomnography (PSG)						

12. Enter the level at which you would order oximetry and/or polysomnography (PSG) in a preterm neonate with "Severe CHRONIC LUNG DISEASE" [needing >30% O2 and/or positive pressure after 36 weeks postmenstrual age or at discharge]

Management	Asymptomatic	Occasional desaturations or bradycardia noted on monitor	Repeated desaturations noted on nursery monitoring	Symptomatic obstruction on sleep only (e.g. ↑work of breathing)	Symptomatic obstruction when awake	Not applicable/Not sure
Oximetry Study						
Refer for Polysomnography (PSG)						

13. Enter the level at which you would order oximetry and/or polysomnography (PSG) in a neonate who is "Going Home on oxygen for Other Reason" [e.g. cardiac]

Management	Asymptomatic	Occasional desaturations or bradycardia noted on monitor	Repeated desaturations noted on nursery monitoring	Symptomatic obstruction on sleep only (e.g. ↑work of breathing)	Symptomatic obstruction when awake	Not applicable/Not sure
Oximetry Study						
Refer for Polysomnography (PSG)						

14. How often do you use an oxygen download study in your unit before referral to a sleep physician?
    a. Always
    b. Usually
    c. Sometimes
    d. Never

15. What is the duration of an oxygen download study in your unit?
    a. 6 hours
    b. 8 hours
    c. 12 hours
    d. 24 hours

16. What device do you use to record oximetry? _____

17. What is considered abnormal oxygen download study in your unit (what features in oximetry would prompt you to refer for sleep study):
    a. Saturation <90% for more than 5% of download
    b. Saturation <85% for more than 2% of download
    c. Saturation <80% for more than 1% of download
    d. Frequent bradycardia and/or desaturation
    e. Clusters of desaturations
    f. We do not use oxygen download studies in our unit

18. Any other comments

    _____
    _____
    _____
    _____
    _____

Thank you for completing the survey.

Chapter 4. Clinical characteristics, associated comorbidities and hospital outcomes of neonates with sleep disordered breathing: a retrospective cohort study

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Clinical characteristics, associated comorbidities and hospital outcomes of neonates with sleep disordered breathing: a retrospective cohort study

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ABSTRACT

Objective Awareness of the need for early identification and treatment of sleep disordered breathing (SDB) in neonates is increasing but is challenging. Unrecognised SDB can have negative neurodevelopmental consequences. Our study aims to describe the clinical profile, risk factors, diagnostic modalities and interventions that can be used to manage neonates with SDB to facilitate early recognition and improved management.

Methods A single-centre retrospective study of neonates referred for assessment of suspected SDB to a tertiary newborn intensive care unit in New South Wales Australia over a 2-year period. Electronic records were reviewed. Outcome measures included demographic data, clinical characteristics, comorbidities, reason for referral, polysomnography (PSG) data, interventions targeted to treat SDB and hospital outcome. Descriptive analysis was performed and reported.

Results Eighty neonates were included. Increased work of breathing, or apnoea with oxygen desaturation being the most common reasons (46% and 31%, respectively) for referral. Most neonates had significant comorbidities requiring involvement of multiple specialists (mean 3.3) in management. The majority had moderate to severe SDB based on PSG parameters of very high mean apnoea-hypopnoea index (62.5/hour) with a mean obstructive apnoea index (38.7/hour). Ten per cent of patients required airway surgery. The majority of neonates (70%) were discharged home on non-invasive ventilation.

Conclusion SDB is a serious problem in high-risk neonates and it is associated with significant multisystem comorbidities necessitating a multidisciplinary team approach to optimise management. This study shows that PSG is useful in neonates to diagnose and guide management of SDB.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The profile of neonates with sleep disordered breathing (SDB) has not been adequately described leading to possible delay in recognising this problem. Diagnosis and management of SDB in neonates is challenging due to lack of universally agreed thresholds/criteria.

WHAT THIS STUDY ADDS

⇒ SDB can be a serious problem in neonates, which is usually associated with multisystem comorbidities, especially craniofacial and airway structural abnormalities. It requires coordinated efforts of a multidisciplinary team to ensure comprehensive management of neonates with SDB.

⇒ Timely evaluation and therapeutic intervention can lead to resolution of SDB in this population. Polysomnography as a diagnostic modality is helpful even at this young age.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study highlights the importance of SDB surveillance in high-risk neonatal population. Effort is required to develop clinical guideline and consensus-based recommendation to standardise the management of SDB in neonates.

INTRODUCTION

Sleep disordered breathing (SDB) is a group of conditions characterised by abnormal respiratory patterns during sleep with variable severity. In neonates, it includes periodic breathing, apnoea of prematurity, central sleep apnoea (CSA) and obstructive sleep apnoea (OSA) as opposed to terms used in older children including primary snoring, upper airway resistance syndrome and obstructive hypoventilation.[1] Central apnoea is commonly seen in healthy newborns, is usually benign, and its frequency decreases with age.[2 3] OSA is the most severe form of SDB with an estimated prevalence of 1%–4% among paediatric population.[4 5] SDB has not been thoroughly investigated in young infants and its prevalence remains unknown in neonatal population.

Neonates are anatomically and physiologically prone to have SDB, especially those with certain comorbidities and craniofacial anomalies.[6] If undiagnosed and untreated, OSA can lead to significant growth and neurobehavioural consequences in children.[7–9] This warrants the need for early identification

and timely intervention at a time of rapid brain development, especially as evidence suggests that treatment may improve quality of life and neurocognitive function.[10]

There has been growing recognition of SDB as a concern in neonates and data are slowly emerging about its profile.[6 11 12] However, managing SDB in neonates is challenging due to the complex pathophysiology, lack of normative data and lack of agreement on diagnostic and treatment thresholds. There remain significant variations in knowledge and practices among neonatologists and sleep physicians when treating neonates with suspected SDB.[13 14] A recent survey of paediatric sleep and pulmonology experts from eight different countries showed there was no agreement on the diagnostic threshold for the obstructive apnoea hypopnea index (OAHI) to diagnose OSA in young infants.[14] Our primary aim was to highlight the identifiable risk factors associated with the presence and severity of SDB in neonates. Furthermore, we wanted to describe indications for obtaining a sleep study, use of various diagnostic tools and therapeutic interventions used to manage SDB in neonates as well as their hospital outcome. Collectively, this information will serve to increase awareness and help clinicians manage SDB in neonates.

METHODS

This was a retrospective cohort study conducted at a tertiary level surgical newborn intensive care unit in New South Wales, Australia. We identified all neonates <1 month of postmenstrual age (PMA) who were referred to our institution over the 2-year period from July 2016 to June 2018 for investigation and management of suspected SDB. Patients were identified from the sleep department database and further clinical information was obtained from review of the electronic medical record. The diagnosis of SDB was based on a combination of clinical features (increased work of breathing, noisy breathing, desaturation), oxycapnography study and/or polysomnography (PSG). We collected data about relevant investigations, multidisciplinary teams involved and interventions undertaken to treat SDB to the time of hospital discharge.

PSGs were performed using all standard channels by a certified sleep technician using clinical polysomnography software (Compumedics, Victoria, Australia). All PSGs were performed at term between 37 and 44 weeks PMA. All PSGs included were the first performed studies. All PSGs were reviewed and reported by a paediatric sleep physician using the scoring guidelines of American Academy of Sleep Medicine (AASM) Manual for the Scoring of Sleep and Associated Events.[15–17] Based on previous studies, severity of SDB was classified using the total apnoea-hypopnoea index (AHI): an AHI of <5 was considered normal, AHI of 5 to 9.9 mild, AHI of 10 to 14.9 moderate and AHI of 15.0 or higher was considered severe SDB.[6 12] PSG data related to CSA were also collected and reported.

Table 1 Demographics and reason for referral for sleep consult

Characteristics	Value (N=80)
Mean gestational age (weeks) (mean±SD)	36.7±4.1
Mean birth weight (grams) (mean±SD)	2793.5±882.8
Preterm—N (%)	24(30%)
Male—N (%)	54(67.5%)
Reason for referral for sleep consult	N (%)
Increased respiratory effort/noisy breathing	37 (46.3%)
Apnoea/desaturation	25 (31.3%)
Cyanotic episodes/ALTE/BRUE	4 (5%)
Family history of SIDS	7 (9%)
Chronic lung disease	6 (7.5%)
Other—cardiomyopathy	1 (1%)

ALTE, Apparent Life-Threatening Event; BRUE, Brief Resolved Unresponsive Episode; SIDS, sudden infant death syndrome.

Oxycapnography study was performed using the Radiometer TCM4. It included time matched recording of child's oxygen saturation (SpO_2), transcutaneous carbon dioxide ($TcCO_2$) level and heart rate during sleep. The recorded data were downloaded in a software (Visidownload by Stowood build 080219) and analysed. The mean $TcCO_2$ and SpO_2 level and percentage of SpO_2 readings <90% were recorded. Combinations of abnormalities in respiratory parameters along with clinical symptoms were taken as a indicators of SDB.

Data were analysed using R core team 2023 (www.R-project.org). Data are presented as a number or percentage, mean with SD and median with IQR.

Patient and public involvement

Patients or members of the public were not involved in the design or conduct of the study.

RESULTS

Eighty neonates were included with most (70%) born at term. The majority of newborns were referred due to an abnormal/noisy breathing pattern or unexplained apnoea and oxygen desaturations (table 1).

A wide variety of comorbidities were found in 61 (76.3%) newborns (table 2). Craniofacial malformations and airway anomalies were the most common (30/80) comorbidities including Pierre Robin sequence (17), cleft palate (2) and airway anomalies (11) (vocal cord palsy (5), laryngomalacia (3), tracheomalacia (2) and one case of pyriform aperture stenosis). A high proportion (21/80) of neonates were diagnosed with genetic syndromes including neuromuscular disorders, skeletal dysplasias and chromosomal anomalies. Other comorbidities included chronic lung disease (6) and structural

Table 2 Clinical profile and comorbidities of neonates referred for assessment of SDB

Associated comorbidities and genetic anomalies	Number (N=80)
Craniofacial malformations	
Pierre Robin sequence	17
Isolated cleft palate	2
Neurological	
Stroke	1
Cerebral aqueduct stenosis	1
Dandy Walker variant	1
Neuromuscular	
Nemaline rod myopathy	2
Myotubular myopathy	1
Congenital arthrogryposis	1
Genetic syndromes	
Cri Du Chat syndrome	1
Sotos syndrome	1
Kabuki syndrome	1
Velocardiofacial syndrome	1
Down syndrome	1
Borjeson-Forssman-Lehman syndrome	1
Mathew Wood syndrome	1
CHARGE syndrome	1
Laron dwarfism	1
Other significant chromosomal anomaly	
Chromosome 1p36deletion	1
Unbalanced translocation	1
12p deletion spectrum syndrome	1
Skeletal dysplasia	
Stickler syndrome	1
Larsen syndrome	1
Thoracolumbar scoliosis	1
Camptomelic dysplasia	1
Spondylocostal dysostosis	1
Airway anomaly	
Pyriform aperture stenosis	1
Vocal cord palsy	5
Laryngomalacia	3
Tracheomalacia	2
Chronic lung disease	6
Other	
Cardiomyopathy	1

SDB, sleep disordered breathing.

disorders affecting the neurological system (eg Dandy Walker syndrome) (3) and heart (1).

Table 3 describes investigations undertaken for diagnosis and management. A multidisciplinary approach was used (mean 3.3 teams/patient). PSG studies were performed in 67 (84%) patients. The mean (±SD) PMA at the time of PSG study was 41 (±2.4) weeks. The mean AHI of the study population who underwent PSG was very high (62.5±39). Based on AHI criteria, the majority (53/67) of patients had severe SDB. OSA was the predominant SDB seen in our cohort with a very high mean obstructive apnoea index (OAI) of 38.7 (±34). Mean central apnoea

Table 3 Investigations done to diagnose and manage SDB

Variable	Value (N=80)
Number of teams involved (mean)	3.3
Sleep study—N (%)	80 (100%)
Polysomnography—N (%)	67 (84%)
Oxycapnography—N (%)	13 (16%)
Polysomnography data (N=67)	
Postmenstrual age at the time of PSG (mean±SD)	41±2.4 week
AHI of study population	
Mean (SD)	62.5 (39)
Median (IQR)	49.7 (29.4–88.8)
Obstructive apnoea index (OAI)	
Mean (SD)	38.7 (34)
Median (IQR)	33 (10.3–59.4)
Central apnoea index (CAI)	
Mean (SD)	9.0 (10.8)
Median (IQR)	5.1 (2.2–108)
Central apnoea duration (seconds)	
Mean (SD)	5.5(2.0)
Median (IQR)	5.6(5.2–6.6)
SDB severity (n)	
Normal	7
Mild SDB	7
Moderate SDB	0
Severe SDB	53
Airway assessment—N (%)	38 (47.5%)
Laryngobronchoscopy—N (%)	30 (37.5%)
Fibreoptic nasoendoecopy—N (%)	8 (10%)
Chromosome microarray—N (%)	49 (61.3%)
Normal—N (%)	31 (38.8%)
Abnormal—N (%)	14 (17.5%)
VOUS—N (%)	4 (5%)
Cerebral imaging—N (%)	40 (50%)
MRI brain—N (%)	25 (31.3%)
Abnormal—N	14 (17.5%)
Cranial USG—N (%)	15 (18.9%)
Abnormal—N	3 (4%)

AHI, apnoea-hypopnea index; OSA, obstructive sleep apnoea; SDB, sleep disordered breathing; USG, ultrasonogram; VOUS, variant of unknown significance.

Table 4 Interventions and hospital outcome of neonates referred for assessment of SDB

Variable	Number (%), N=80
Diagnosed with SDB	73 (91.3%)
Based on PSG	60
Based on features of OSA and oxycapnography	13
GORD medication	25 (31.3%)
Patients undergone any surgical procedure	32 (40%)
Airway surgery	8
Surgery done for other anomalies	24
Discharged home on CPAP	56 (70%)
Discharged home on apnoea monitor	11 (13.8%)
Discharged on home oxygen	2
Died in hospital	1

CPAP, continuous positive airway pressure; GORD, gastro-oesophageal reflux disease; SDB, sleep disordered breathing.

index (CAI) was 9(±10.8) and mean duration of CA was 5.5(±2) s. Chromosomal analysis was performed in most patients (61.3%). Half the study patients (40/80) had some form of brain imaging and in 21% (17/80) it was abnormal. MRI abnormalities included diffusion restriction and white matter changes, hydrocephalus, abnormalities of cerebellum and brainstem and myelination abnormalities. About half (47.5%) of the study population had an airway assessment completed by the otolaryngology team.

Table 4 describes the interventions and outcome measures. Most (73/80) neonates were diagnosed with SDB. Interventions included non-invasive respiratory support, home oxygen, home apnoea monitoring and surgery. A substantial proportion (40%) of study patients underwent some form of surgery, however surgical interventions targeted to improve SDB were performed in only 10% of patients. Airway surgical interventions included mandibular distraction osteogenesis (MDO), supraglottoplasty, lip–tongue adhesion and repair of laryngeal cleft. Only one patient underwent a tracheostomy. Almost a third of study patients were started on a proton pump inhibitor. Only one patient died in hospital who had a lethal form of skeletal dysplasia. Most (70%) were discharged home on continuous positive airway pressure (CPAP).

DISCUSSION

The unique characteristic of our study is that it focuses entirely on neonates (aged <1 month). In this retrospective study, we found that SDB can be a serious issue in high-risk neonatal population, occurring in almost 91% (73/80) of the study population. The majority had moderate to severe SDB. OSA was the most predominant SDB seen in our study cohort. This study demonstrates how medically complex these neonates are given the presence of spectrum of risk factors and comorbidities (table 2). However, with involvement of multidisciplinary specialist teams, these neonates were able to be managed appropriately.

The most common presenting symptoms were increased respiratory work of breathing and unexplained apnoea or desaturation highlighting that neonates do not present with the typical symptoms of OSA in older infants and children with snoring and restless sleep. Some infants were referred after a Brief Resolved Unexplained Episode (BRUE). Literature suggests that an apparent life-threatening event (ALTE) or BRUE may be the first clinical sign of SDB and these infants should be further evaluated .[18 19] Guilleminault *et al* observed that ALTE/BRUE were more prevalent in children with micrognathia, retrognathia and anatomic anomalies that increase the risk of SDB.[20] About 9% of the neonates in our study were evaluated due to family history of sudden infant death syndrome (SIDS). In a large cohort study from Denmark,[21] a fourfold higher risk of SIDS was observed among siblings of children who died of SIDS. Other studies also support investigating siblings.[22] Almost a third of our study cohort was born preterm, which is in line with the literature suggesting that premature infants may be at higher risk for SDB secondary to anatomical and physiologic variances.[23 24]

While tonsil and adenoid hypertrophy are the main cause of OSA in older children, literature suggests anomalies of upper airway anatomy, and craniofacial malformations are the main underlying factors in neonates,[6 11 12] which is in keeping with the comorbidities seen in our study. Several genetic syndromes were found to be associated with SDB in our study, similar to what is described in the literature.[6 11 12] These syndromes most likely either lead to increased upper airway obstruction (large tongue, small midface and/or small jaw) or cause hypotonia predisposing neonates to hypoventilation and SDB. Our data emphasise the need to be proactive in neonates with these conditions to the possible diagnosis of SDB. Overall, very high incidence of SDB in our high-risk cohort is supported by the literature showing that children with craniofacial anomalies had an estimated prevalence of SDB in up to 67% patients.[25]

This study underlines the need for multidisciplinary specialist teams in the management of SDB in neonates. In our study, multiple specialists were involved in the care of each patient with sleep physicians, otolaryngologists and geneticists the most frequently involved. Kaditis *et al* underlined the importance of multidisciplinary approach for management of SDB in children aged 1–23 months.[26]

PSG was done in majority (84%) of our study cohort, which is the gold standard to diagnose SDB. Diagnosing SDB based on neonatal PSG remains challenging as normative data are not well established and cut-off levels for various parameters in PSG to categorise pathologically significant SDB in neonates are still being defined.[14]

A recent study from Daftary *et al*[3] showed that healthy newborns have much higher mean AHI (14.9±9.1), OAI (2.3±2.5) and CAI (5.4±6.2) compared with older children. Our study cohort had significantly elevated AHI and OAI, confirming the severity of SDB in our cohort. AHI is calculated by adding central and obstructive apnoea and hypopnoea. The high mean AHI (62.5) of our study cohort was mainly contributed by the OAI, which was significantly higher (38.7±34) than the expected range described in the literature.[2 3 27] Although mean CAI of our study cohort was slightly higher than Daftary *et al*'s study,[3] it was within the expected range for healthy neonates as per the review by Ng and Chan.[2] It is well known that SDB can be a mixture of obstructive or central apnoea, especially in high-risk neonates with certain comorbidities. However, based on the PSG results, it is clear that the most predominant type of SDB in our study cohort was OSA and in majority it was moderate–severe as reflected by very high mean OAI. We decided to choose OAI as a marker of severity of OSA because its scoring criteria is clearly defined by AASM while scoring hypopnoea is difficult and categorising central versus obstructive hypopnoea is even more difficult. Therefore, OAHI can be difficult to replicate with possibility of significant interobserver variability. Despite the lack of universally accepted guideline for diagnosis and severity criteria for SDB in neonates,[12] our data support the usefulness of PSG in medically complex neonates at an early age not only to diagnose SDB but also to guide management.

Thirteen (16%) neonates had compelling clinical signs/symptoms of OSA like increased work of breathing, high CO2 levels and oxygen desaturation. Therefore, treatment was initiated, and diagnosis was based on obvious clinical features and oxycapnography study. The international classification of sleep disorders also supports clinical diagnosis of OSA in paediatric age based on one or more symptoms.[28] Previous studies in children have shown that oxycapnography alone is a reasonable screening tool in a diverse patient cohort with neuromuscular, congenital cardiac and genetic problems.[29 30] However, its sensitivity depends on the severity of SDB; a normal oximetry does not rule out SDB and therefore does not replace PSG. Another limitation is its inability to differentiate between obstructive and central apnoea. A high prevalence of movement artefacts can make data interpretation challenging. A recent study showed good correlation between the desaturation index obtained from an overnight oximetry study to the OAHI obtained from PSG in young infants (<6 months) at risk of SDB.[31] In our study, oxycapnography was only used in very severe cases who had obvious clinical symptoms and physician decided to initiate treatment over waiting for PSG date. We believe that oxycapnography can play an important role in screening for moderate to severe SDB in high-risk infants and help in treatment monitoring once diagnosis is established by PSG.

The clinical intervention was triggered for all but seven neonates (73/80, 91%) in our study based on very high mean AHI, OAI and obvious clinical features of SDB. Clinical factors, such as comorbidities, current symptoms and physical examination findings played equally important role in determining SDB diagnosis and management decisions.

Adeno-tonsillectomy is the first-line treatment in children with OSA, however establishing the specific cause of SDB is critical to selecting the optimal therapy in newborns. Ten per cent neonates in our study underwent surgery to relieve OSA. CPAP was prescribed to neonates with no indication of surgical treatment. All neonates underwent a pressure titration study during PSG to determine the optimal CPAP setting. Efficacy of CPAP was judged by improvement in clinical signs and normalisation of respiratory parameters, which was confirmed by follow-up oxycapnography and blood gases. Majority of our study cohort (70%) were successfully stablished, maintained and discharged on home CPAP therapy. CPAP is reported to be an effective treatment for upper airway obstruction in Pierre Robin sequence and can be used as a first-line treatment in selected patients.[32 33] In a study of sleep apnoea in infants by Robinson *et al*,[34] CPAP showed the highest decrease in AHI for all nonsurgical interventions used. Retrospective studies support the use of CPAP to treat SBD in infants with genetic and muscular problems.[35 36] Midface hypoplasia has been described with the prolonged use of CPAP, but long-term outcome and potential reversibility of this finding are unknown.[37] Long-term compliance and a high dropout rate is a major issue with CPAP use.[38]

Neonates with severe OSA, who did not respond to medical management by CPAP, were evaluated for surgical interventions, including lip–tongue adhesion, MDO and tracheostomy. MDO has been reported to relieve OSA in micrognathic infants and improve feeding and growth. Most of the studies have reported both short-term and long-term near-normalisation of OSA after MDO.[39 40] In our study, only one patient underwent tracheostomy. Literature supports doing tracheostomy only as a last resort when other interventions fail.[26]

Other therapies included anti gastro-oesophageal reflux disease (GORD) treatment was used in 30% of our study population. Literature shows that GORD is commonly seen in infants with SDB, however, it remains unclear whether a causal relationship exists between the two.[41]

Limitations

Our study had several limitations including being a single-centre retrospective study. Being the major referral centre of the state, our cohort represents a highly biased population who were at high risk of SDB. This is a likely explanation for the very high rate of polysomnographic abnormalities among our study cohort. It is possible that infants with severe disease were selectively referred compared with those with milder SDB. Another limitation was that in number of cases diagnosis was based on oxycapnography study and clinical features. The

major reason for this choice of diagnostic test in some cases were obvious signs of SDB and inability to undertake a full sleep study due to the medical fragility of the child while they were in a neonatal intensive care unit. We acknowledge that while oxycapnography has a high diagnostic positive predictive value, a reliable negative predictive value is lacking. The criteria for SDB severity based on AHI cutoffs vary in the literature for newborns and it is possible that we might have under or overestimated the burden of SDB. Another limitation was lack of repeat PSG data prior to discharge to confirm resolution of SDB postintervention. In our cohort, treatment was monitored by serial follow-up oxycapnography, blood gas parameters and clinical improvement of signs and symptoms. Our usual protocol is to do a follow-up PSG in 3–4 months postdischarge.

CONCLUSION

Our data demonstrate that SDB is common in high-risk neonates and are often associated with significant multisystem comorbidity where craniofacial abnormalities and airway malformations (38%) and genetic syndromes were common (26%). It must be identified and treated promptly to avoid negative consequences. However, diagnosis and management of SDB in the neonatal period are complex. This study identifies the critical need to establish normative data for the neonatal population. The establishment of reference values and treatment thresholds for the neonates will help clinicians in making decision based on polysomnographic findings and it will help in standardising the practices. This study also highlights an urgent need for outcome-based research. Longitudinal studies are needed to establish the relationship between SDB in infancy and long-term outcomes.

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Chapter 5. Respiratory and neurodevelopmental outcomes at 3 years of age of neonates diagnosed with sleep disordered breathing (SDB)

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Article

Respiratory and Neurodevelopmental Outcomes at 3 Years of Age of Neonates Diagnosed with Sleep-Disordered Breathing

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Abstract: Objectives: Understanding the long-term consequences of sleep-disordered breathing (SDB) in neonates is crucial. A lack of consensus on diagnostic and treatment thresholds has resulted in limited research in this area. Our study aims to describe the trajectory of SDB in a cohort of high-risk neonates and their respiratory and neurodevelopmental outcomes at 3 years of age, and explore the relationship between SDB during early infancy and neurocognitive outcomes. **Methods**: A retrospectively identified cohort of neonates with moderate–severe SDB were prospectively followed at 3 years of age. Data collected included last polysomnography (PSG) parameters up to the age of 3 years and sleep physician's recommendations, duration of CPAP use, compliance with treatment, timing of SDB resolution, and neurodevelopmental outcomes. Univariate and multivariate logistic regression analyses were performed to evaluate the association between important respiratory and sleep breathing parameters with the developmental outcomes. **Results**: Eighty neonates were included. Respiratory and developmental outcomes were available for 58 (72.5%) and 56 (70%) patients, respectively. In most patients (47/58, 81%), SDB had resolved by 3 years of age. Survival without major developmental delay was seen in 32/56 (57%), but a significant proportion (21/56, 37.5%) demonstrated global developmental delay. Following univariate analysis, primary diagnosis, apnoea–hypopnoea index (AHI) at the time of last PSG and SDB outcome was significantly associated with developmental delay. However, these associations were not seen in multivariate analysis. **Conclusions**: Despite severity at baseline, SDB resolved in the majority of patients with time and treatment. Although statistically insignificant, logistic regression analysis identified some clinically important associations between neonatal SDB and neurodevelopmental outcomes.

Keywords: sleep; newborn; sleep-disordered breathing; obstructive sleep apnoea; neurodevelopmental outcomes

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1. Introduction

Adequate sleep is essential for a range of biological functions including memory consolidation and cognition [1]. Sleep-disordered breathing (SDB) includes a spectrum of disorders, with obstructive sleep apnoea (OSA) being the most severe form [2]. The estimated prevalence of OSA is 1–4% in children [3,4]. In addition to intermittent hypoxia, sleep disruption/fragmentation with SDB is thought to contribute to poor neurocognitive outcomes [5,6]. In children, SDB has been linked to problems with growth [7], cardiac health [8], and impairment of cognition, attention and executive functions [9–13]. Studies have shown a reversal of some of the deleterious consequences of SDB with treatment in children [14]. However, more information is required regarding equivalent outcomes for neonates and infants.

Previous studies have shown that treatment is not always effective in resolving SDB [15], while a proportion of children will have spontaneous resolution of SDB even without treatment [15–17]. Children are also at risk of recurrence of SDB if they develop additional risk factors like adeno-tonsillar hypertrophy or obesity, making it difficult to predict the trajectory of SDB in this population. Although awareness about the risk of SDB and its impact in neonates is increasing [18], its true prevalence remains unknown. The aetiology of SDB in neonates is multifactorial. Maternal OSA during pregnancy can potentially have a negative impact on foetal outcome and neurodevelopment [19]. The management of SDB in neonates is challenging due to the lack of standardised diagnostic criteria, treatment guidelines and normative data. This has led to significant variations in practices worldwide [20,21]. A survey of paediatric sleep medicine physicians [20] from eight different countries revealed a lack of consensus regarding the appropriate cut-off value for defining OSA in neonates and infants with proposed obstructive apnoea–hypopnea index (OAHI) values ranging from 1 to 20 events per hour. Additionally, for infants younger than 2 months, there was no consensus regarding cut-offs used for differentiating mild, moderate, or severe OSA. There was a strong consensus among providers (98%) regarding the need for evidence-based guidelines for infant SDB, underscoring the importance of further research in this area.

There is a lack of information about the natural history of SDB from the neonatal period to early childhood and its impact on the neurodevelopmental outcome. Limited studies have pointed negative links between SDB in neonates and long-term neurodevelopmental outcomes [22,23]. New evidence regarding long-term morbidities associated with residual or untreated SDB in neonates is necessary. The key question is whether the resolution of SDB in infancy improves medium- to long-term neurodevelopmental outcomes.

We hypothesised that the severity of neonatal SDB and/or ongoing residual disease would correlate with worse neurodevelopmental outcomes. The aims of this study were as follows: (1) to demonstrate the trajectory and progression of SDB in a cohort of high-risk neonates through infancy into early childhood, (2) to describe the sleep breathing, respiratory and neurodevelopmental outcomes of this cohort at 3 years of age; and (3) to explore if SDB in neonates is associated with adverse neurodevelopmental outcomes at 3 years of age.

2. Materials and Methods

2.1. Study Design

In this study, a cohort was retrospectively identified and prospectively followed to 3 years of age.

2.2. Setting and Participants

This study consisted of a retrospective review of all neonates <1 month of post-menstrual age (PMA) referred for the management of suspected SDB to a tertiary-level surgical newborn intensive care unit in New South Wales, Australia, between July 2016 and June 2018. Inclusion criteria included neonates >37 weeks post-menstrual age (PMA) and a technically acceptable sleep study. Preterm neonates who were <37 weeks PMA at the time of study were excluded. Eighty neonates were identified from the sleep medicine departmental database and were included in the study. Baseline neonatal data were collected by retrospective chart review, while respiratory and neurodevelopmental outcome data were collected prospectively. A detailed description of the methods, baseline characteristics and hospital outcomes of the study cohort has been previously published [18]. All treatment decisions regarding SDB management were the responsibility of the sleep physician and multidisciplinary team managing the child. All children continued their follow-up as advised by the treating sleep physician. The families of all the children were then approached for a polysomnography (PSG) study and Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III) assessment at 3 years of age. If they could not/did not attend the

3-year assessment, consent was taken to collect outcome data from their medical records. The study protocol was approved by the local ethics committee (LNR/15/SCHN/470).

2.3. Respiratory Outcomes

Respiratory outcomes were assessed by PSG, which is the gold-standard test for diagnosing SDB. All patients with respiratory outcome data had a follow-up PSG performed by 3 years of age. For patients who did not attend the 3-year PSG, the result of their last/latest PSG and clinic report was collected from medical records. Data were also collected about the duration of continuous positive airway pressure (CPAP) use and CPAP tolerance data from the sleep technician or sleep physicians' notes.

All PSGs were attended in hospital and performed using standard channels by a certified sleep technician with standard clinical polysomnography software (Compumedics, Abbotsford, VIC, Australia). All PSGs were reviewed and reported by a paediatric sleep physician using the scoring guidelines of the American Academy of Sleep Medicine (AASM) Manual for the Scoring of Sleep and Associated Events [24–26].

SDB severity was classified using the total apnoea–hypopnoea index (AHI). Clinically significant cut-off or a threshold level for treatment in infants and young children to reduce the consequences of SDB remains unclear and contentious. Considering that several patients in our study had their last PSG before 2 years of age, based on suggestions in recent publications [27,28], we used the following classification to try and identify clinically significant SDB: an AHI of <2 was considered normal, an AHI of 2–5 was considered possibly abnormal, an AHI of >5–10 was considered mild, an AHI of >10–15 was considered moderate, and an AHI of >15.0 was considered severe SDB. Other important PSG parameters were also collected and reported.

The status of SDB was recorded based on the sleep physician's interpretation and recommendation from the last PSG or clinic visit. Respiratory outcome was dichotomised as resolved or unresolved SDB. SDB was considered resolved based on the opinion of the sleep physician, even if it did not match the AHI criteria. The time of resolution of SDB was noted to demonstrate the trajectory of SDB.

2.4. Neurodevelopmental Outcome

Developmental outcome was assessed at 3 years of age using the BSID-III. Assessments were completed by two trained assessors who were not blinded to the history but were blinded to current respiratory status. Neurodevelopmental outcome status was collected from medical records if a patient did not participate in the 3-year BSID-III but had an equivalent formal assessment performed by another specialist such as a developmental paediatrician. If there was a new diagnosis of moderate–severe level autism spectrum disorder (ASD), then it was recorded as global developmental delay.

Bayley-III outcomes were defined based on the composite scores with mean of 100 and SD $\pm$ 15. Mild delay was defined as a score between 1 and 2 standard deviations below the mean for any domains (cognition, language or motor); moderate delay was defined as between 2 and 3 standard deviations below the mean; and severe delay was defined as >3 standard deviations below the mean. Global delay was used to describe infants who had delay across all areas (motor, cognition, and language) or who had received a diagnosis of moderate–severe level ASD.

2.5. Statistical Analysis

Data were analysed using R software for statistical computing (www.R-project.org, accessed on 15 July 2024). Descriptive statistics are presented as a number or percentage, mean with standard deviation (SD) and median with interquartile range (IQR).

Univariate logistic regression analysis was conducted to assess the predictive ability of neonatal clinical parameters and PSG findings on moderate–severe delay (defined as composite score more than 2 SD below the mean) in the three developmental domains or for global delay. A p-value < 0.1 in the univariate analysis was deemed significant

for inclusion in a stepwise backward multivariate logistic regression analysis to identify the most parsimonious multivariate model. This method systematically removed non-significant variables ($p > 0.05$) based on the Akaike Information Criterion (AIC) until the most statistically robust and parsimonious model was identified. The model's goodness-of-fit was evaluated using McFadden's pseudo-R-squared and the Hosmer–Lemeshow tests to assess its adequacy in predicting neurodevelopmental outcomes.

3. Results

3.1. Study Population

Baseline characteristics of eighty neonates whose data formed the basis for this study are shown in Table 1. The majority (61/80) had associated comorbidities. The study population was divided into three diagnostic groups based on their primary diagnosis or comorbidity—craniofacial group, genetic abnormality group and others. The majority of newborns had severe SDB with a very high mean AHI (62.5 ± 39) and OAI (38.7 ± 34). A significant proportion (56/80, 70%) were discharged home on CPAP. Details of their clinical characteristics, management, and hospital outcome have been published previously [18].

Table 1. Baseline demographic, clinical and respiratory parameters of study cohort in the neonatal period.

Study Cohort (n = 80)	Value (N%)
Demographic details	
Gestational age (weeks) (Mean ± SD)	36.7 ± 4.1
Birth weight (grams) (Mean ± SD)	2793.5 ± 882.8
Preterm–N (%)	24 (30%)
Males–N (%)	54 (67.5%)
Diagnostic group based on primary comorbidity	
Craniofacial and airway anomalies group	30 (37.5%)
Genetic syndromes group	21 (26.5%)
Others	29 (36%)
Chronic lung disease	6
Neurological	3
Cardiac	1
No obvious risk factors	19
Abnormal chromosome microarray	14 (17.5%)
Abnormal cerebral imaging	17 (21.5%)
Baseline SDB parameters of neonates	
Number diagnosed with SDB	73 (91%)
AHI of cohort (Mean ± SD)	62.5(39)
OAI of cohort (Mean ± SD)	38.7(34)
Hospital outcome	
Died in hospital	1
Underwent airway surgery	8 (10%)
Discharged home on CPAP	56 (70%)
Discharged home on oxygen	2
Discharged home on apnoea monitor	11 (13.8%)

SDB—sleep-disordered breathing, PSG—polysomnography, CPAP—continuous positive airway pressure, AHI—apnoea–hypopnoea index, OAI—obstructive apnoea index, SD—standard deviation.

3.2. Follow-up Details of Study Cohort

Figure 1 shows the follow-up details of the study cohort. Of the 80 patients who participated in the baseline study, 5 died before 3 years of age, and 11 could not be contacted, leaving 64 patients eligible for follow-up. Six patients did not consent to respiratory follow-up, while eight declined neurodevelopmental follow-up at 3 years of age, thereby leaving 58 and 56 patients, respectively, with respiratory and developmental outcome data. A total of 21/58 [36%] patients returned for PSG at around 3 years of age, while for the remaining subjects, respiratory outcome data were collected from medical records. Forty-five patients [80%] agreed to participate in the BSID-III assessment, while for 11 patients

[20%], outcome data were extracted from medical records. Seven of these patients had their development assessed using the Griffiths Scales of Child Development, while the other four were diagnosed with autism spectrum disorder (ASD).

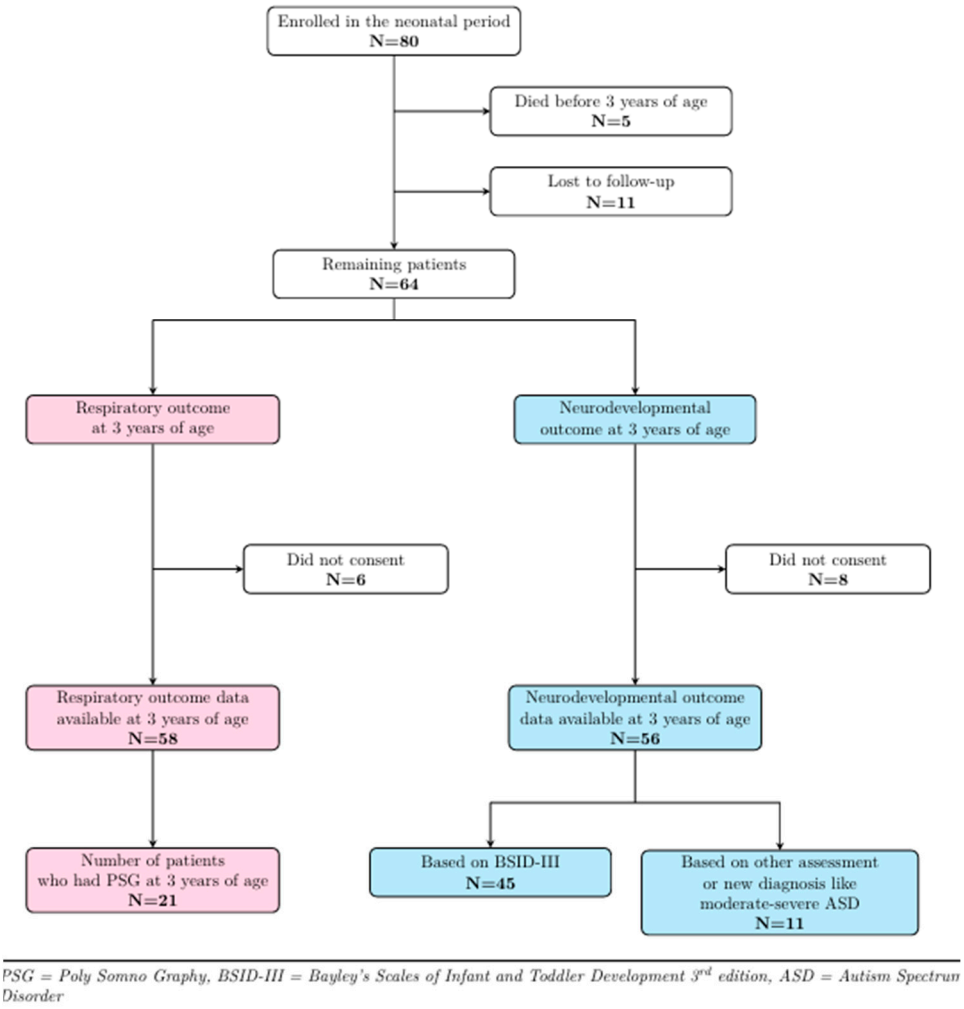

Figure 1. Three-year follow-up details of study cohort.

3.3. Respiratory Outcomes at 3 Years of Age

The median age of the last follow-up PSG was 13 (±11.6) months (Table 2), with an age range of 2 to 42 months. A total of 8/58 (14%) children were <6 months old, 24/58 (41%) were between 6 and 24 months old, and 26/58 (45%) were >24 months old at the time of their last PSG. The mean duration of CPAP use was 12.8 (±11.5) months, with an age range of 1 to 42 months. Follow-up data showed that 9/56 (16%) patients did not tolerate CPAP soon after the discharge, while 17/56 (30%) stopped using it at some point before the recommendation from the sleep physician.

SDB status based on AHI criteria at the time of their last PSG was for the majority (40/58, 69% patients) normal or mildly abnormal, while the remaining 18/58 (31%) showed moderate–severe SDB. Sleep physicians' opinions differed slightly; they interpreted that SDB was resolved in 47/58 (81%) of patients. Out of 11 patients interpreted as having ongoing SDB at 3 years of age, 7 had genetic syndromes, while 2 belonged to each of the craniofacial and other groups. Two patients had an ongoing tracheostomy. Only one patient underwent adenotonsillectomy before the age of three years.

Figure 2 shows Kaplan–Meier curves demonstrating the duration of CPAP use of different diagnostic groups. CPAP use lasted longer in those with genetic abnormalities than others; however, the differences in duration did not reach statistical significance.

Eight children were still on CPAP by three years of age, two had tracheostomy (one with bilateral vocal cord palsy and one with CHARGE syndrome), while the other six patients had genetic syndromes including skeletal dysplasia and chest wall deformity.

Table 2. Respiratory outcome data at 3 years of age.

Age at the time of last follow-up (months) (*n* = 58)	
Mean ± SD	13.02 ± 11.6
Median (IQR)	7 (4–18)
Duration of CPAP use (months)	
Mean ± SD	12.8 ± 11.5
Median (IQR)	7 (4–18.5)
CPAP use/tolerance (*n* = 56)	
Did not tolerate CPAP and stopped soon after the discharge (<3 months of discharge)	9 (16%)
Tolerated CPAP well for several months but stopped before the next scheduled follow-up PSG/before recommendation from sleep physician	17 (30%)
Tolerated CPAP well and stopped after the normal follow-up PSG and sleep physician's recommendation	25 (45%)
Died before 3 years	5 (9%)
Status of SDB according to AHI criteria based on the last PSG (*n* = 58)	
Normal	9 (15.5%)
Possibly normal	16 (27.5%)
Mild SDB	15 (26%)
Moderate SDB	9 (15.5%)
Severe SDB	9 (15.5%)
Status of SDB according to sleep physician's interpretation based on the last PSG (*n* = 58)	
SDB Resolved	47 (81%)
SDB Unresolved	11 (19%)

CPAP—continuous positive airway pressure, PSG—polysomnography, SDB—sleep-disordered breathing, SD—standard deviation, IQR—interquartile range, AHI—apnoea–hypopnea index.

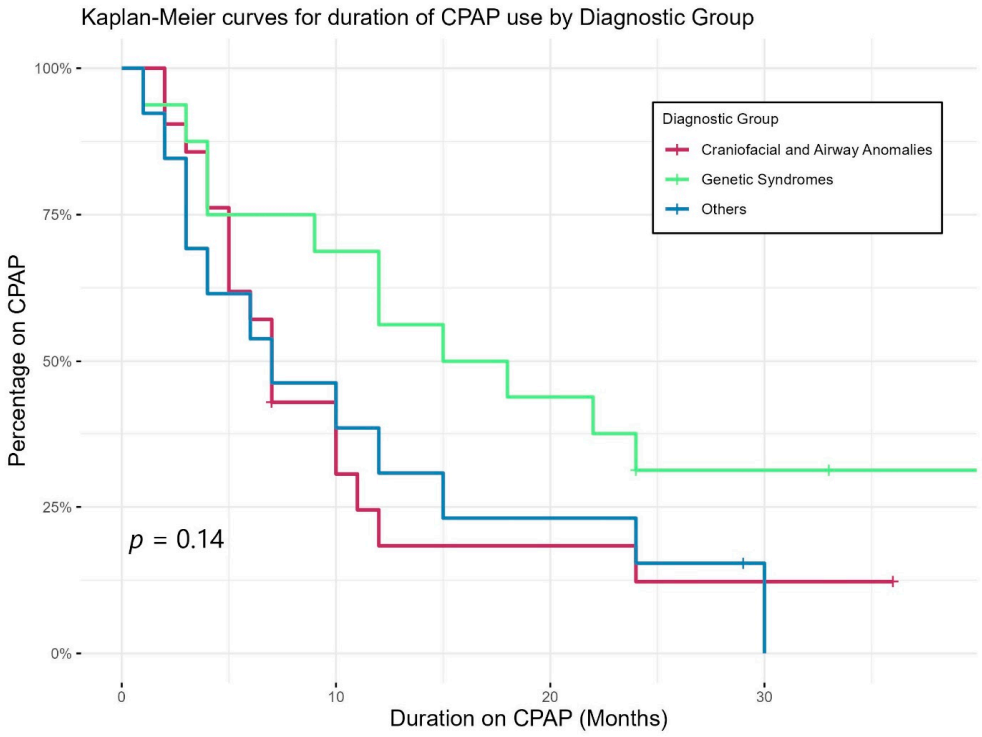

Figure 2. Duration of CPAP use of different diagnostic groups.

Figure 3 shows Kaplan–Meier curves demonstrating the trajectory of SDB by showing the timing of resolution of SDB of the three diagnostic groups. This again shows that SDB persisted longer in the group with genetic abnormalities compared to the rest of the cohort but did not reach statistical significance.

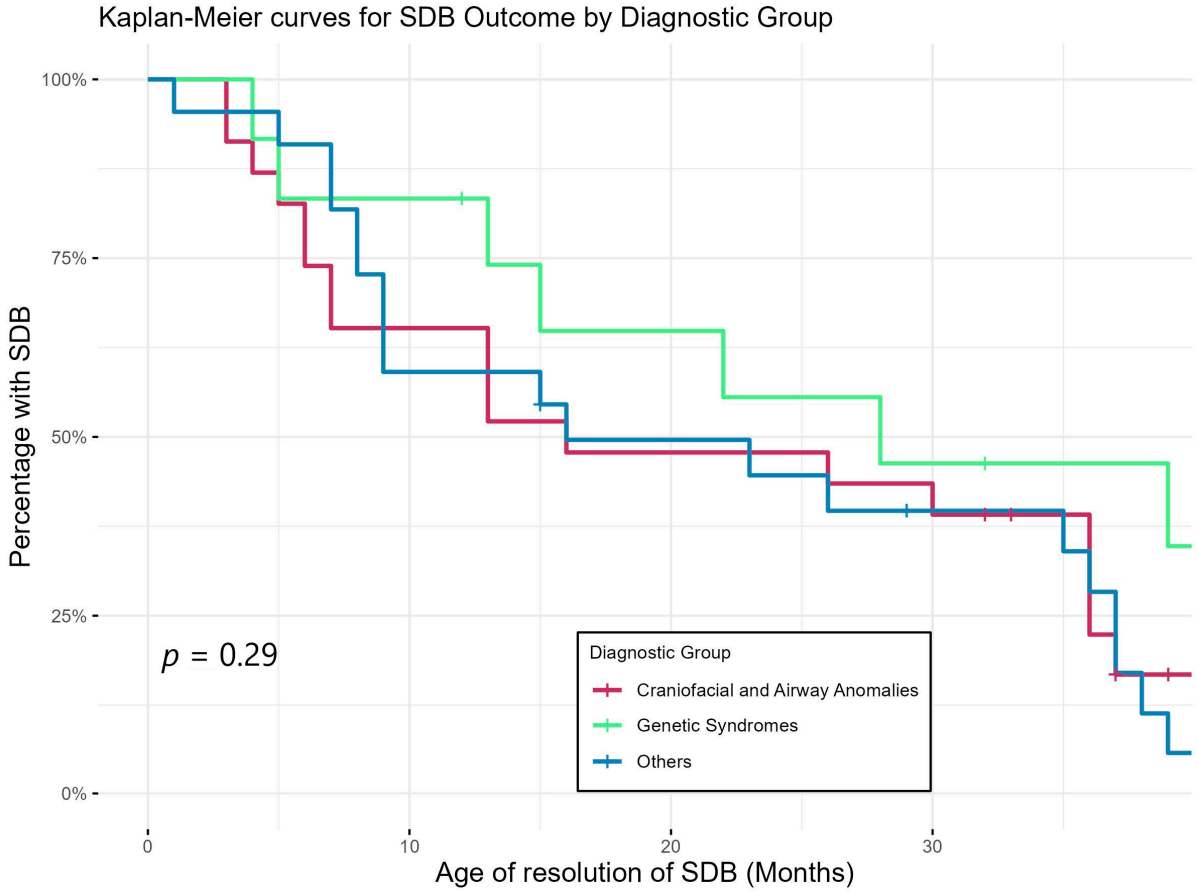

Figure 3. Age of resolution of SDB of different diagnostic groups (based on sleep physicians' interpretation/report of last PSG).

Sleep and respiratory parameters from the last PSG are shown in Table 3. Depending on the timing of PSG, the cohort was divided into three groups: last PSG performed before 6 months of age, between 6 and 24 months of age and after 2 years of age. Baseline neonatal PSG parameters are given for comparison. Follow-up data demonstrated expected changes in sleep parameters with increasing age: sleep efficiency increased, percent of REM sleep decreased, and NREM sleep increased over time. Respiratory parameters also showed progressive improvement with increasing age. Respiratory arousal index was normal in all groups [29]. The desaturation index was higher than the reported norms [29] in the <2 years of age groups; however, mean oxygen saturation (SpO2) and percent of total sleep time (TST) with an SpO2 < 90% and mean TcCO2 (transcutaneous carbon dioxide) remained normal in all groups [30]. The percentage of TST spent with TcCO2 > 45 mm Hg was similar to the norms [29]. TcCO2 time >50 mm Hg was higher in the 3-year group, although it was less than 25% of TST, one of the diagnostic criteria for paediatric OSA [4]. AHI, OAI and CAI all decreased significantly over time, although AHI and OAI remained higher than the norms [29–31].

Table 3. Follow-up sleep and respiratory parameters—data based on the last PSG performed by 3 years of age vs. baseline PSG in the neonatal period.

PSG Parameters	Baseline PSG	Last Follow-up PSG		
	Neonatal Data * *n* = 67	At Less Than 6 Months of Age *n* = 8	At 6–24 Months of Age *n* = 24	At 2–3 Years of Age *n* = 26
TST (minutes)	249.3 ± 55.2	418.9 ± 85.3	420.4 ± 113.8	409.1 ± 103.1
Sleep efficiency (%)	68.9 ± 12.0	75.1 ± 15.8	81.0 ± 10.4	80.6 ± 10.6
REM (% of TST)	54.5 ± 13.2	38.8 ± 11.1	34.3 ± 10.7	22.6 ± 7.2
Stage 2 NREM (% of TST)	38.3 ± 13.2	50.2 ± 10.5	50.6 ± 17.3	54.2 ± 20.3
Arousal Index (n per hour)	28.9 ± 8.4	26.0 ± 9.7	12.3 ± 7.2	13.1 ± 5.5
Respiratory Arousal Index (n per hour)	6.3 ± 4.3	3.1 ± 2.4	1.4 ± 1.2	1.6 ± 1.7
Desaturation Index (n per hour)	38.1 ± 32.1	15.0 ± 12.1	11.8 ± 6.5	3.7 ± 3.4
Mean SpO2%	97.1 ± 3.3	98.0 ± 1.0	96.8 ± 1.5	96.5 ± 1.3
SpO2 < 90 (%TST)	3.7 ± 9.6	0.2 ± 0.3	0.1 ± 0.3	0.1 ± 0.3
Mean TcCO2	46.2 ± 7.1	40.8 ± 4.1	43.2 ± 4.7	45.2 ± 5.8
TcCO2 > 45 mm Hg (% TST)	22.0 ± 25.6	3.3 ± 7.3	20.2 ± 24.7	24.1 ± 26.8
TcCO2 > 50 mm Hg (%TST)	24.8 ± 32.4	0.0 ± 0.0	1.7 ± 3.5	20.4 ± 32.3
AHI (n per hour)	58.1 ± 39.6	19.6 ± 18.6	11.5 ± 11.7	4.8 ± 4.3
OAI (n per hour)	38.3 ± 34.3	5.6 ± 5.5	5.1 ± 8.6	3.1 ± 3.7
CAI (n per hour)	9.1 ± 10.9	10.4 ± 12.3	4.0 ± 2.8	1.3 ± 1.2
Central Apnea (seconds)	5.5 ± 2.0	6.4 ± 0.8	7.2 ± 1.7	9.4 ± 4.3
Hypopnea Index	8.1 ± 7.1	3.5 ± 2.5	1.7 ± 1.5	1.6 ± 4.0

PSG—polysomnography, TST—total sleep time, REM—rapid eye movement, NREM—non-rapid eye movement, $TcCO_2$—transcutaneous carbon dioxide, AHI—apnoea–hypopnea index, SpO2—saturation of oxygen, OAI—obstructive apnoea index, CAI—central apnoea index, Values represent means ± SD. * Neonatal studies were daytime studies, whereas subsequent studies were overnight studies.

3.4. Neurodevelopmental Outcomes at 3 Years of Age

The mean age of BSID assessment was 38.0 ± 2.3 months (Table 4), with an age range of 35 to 42 months. The mean composite score for cognition was at the lower end of the normal range, while mean scores for motor and language domains were just below −1 SD. An outcome without any major developmental delay was seen in 32/56 (57%) children. A significant proportion (21/56, 37.5%) had global developmental delays: four of these children were diagnosed as severe-level ASD, while one patient was diagnosed with optic atresia and blindness. A total of 12/21 (57%) children with global delay had a genetic syndrome.

Table 4. Neurodevelopmental outcome data at 3 years of age.

Bayley Scales of Infant and Toddler Development (3rd Edition) (*n* = 45)	
Age of assessment (months)	
Mean ± SD	38.0 ± 2.3
Median (IQR)	37.0 (36–40.5)
Bayley Scores Summary	
Cognitive composite score (Mean ± SD)	87.8 ± 17.0
Language composite score (Mean ± SD)	84.3 ± 19.6
Motor composite score (Mean ± SD)	82.9 ± 20.9
Neurodevelopmental outcome status at three years of age (*n* = 56):	
Normal	28 (50%)
Mild delay	4 (7.5%)
Moderate–severe delay	3 (5%)
Global DD	21 (37.5%)
Survival without major disability (*n* = 32)	

DD = developmental delay, SD = standard deviation, IQR = interquartile range.

3.5. Regression Analyses

The variables analysed in univariate analysis (Table 5) included baseline neonatal sleep and respiratory parameters, gestational age, gender, birth weight, AHI at the time of

last follow-up PSG, SDB outcome, duration of CPAP use and diagnostic groups (primary diagnosis). In the univariate analysis, the diagnostic group was significantly associated with both cognitive delay ($p = 0.04$) and global developmental delay ($p = 0.01$). Within the same model, the SDB outcome approached borderline significance for predicting cognitive delay ($p = 0.06$) and motor delay ($p = 0.05$). Additionally, AHI at follow-up PSG showed significant association with language delay ($p = 0.04$). However, in multivariate logistic regression, including all variables with $p < 0.1$ in univariate analyses, none of the variables remained statistically significant at $p < 0.05$ for predicting delay. Moreover, there was no significant difference in neurodevelopmental outcome between neonates with an AHI <10 and AHI >10.

Table 5. Factors associated with developmental delay in univariate logistic regression analysis *p*-values.

Variable	Cognitive Delay	Language Delay	Motor Delay	Global DD
Gestation	0.85	0.28	0.56	0.66
Birth Weight	0.88	0.23	0.59	0.94
Gender	0.14	0.47	0.09 *	0.83
AHI	0.55	0.35	0.3	0.17
OAI	0.6	0.47	0.34	0.16
Central AI	0.98	0.32	0.91	0.7
RAI	0.33	0.59	0.5	0.53
T_cCO2 > 45 mm Hg (%TST)	0.19	0.43	0.34	0.38
SpO2 < 90 (%TST)	0.18	0.46	0.31	0.11
Sleep efficiency (%)	0.55	0.3	0.57	0.54
Follow-up AHI (Last PSG) #	0.22	0.04 *	0.4	0.37
SDB Outcome	0.06 *	0.28	0.05 *	0.12
Duration of CPAP use	0.71	0.68	0.97	0.18
Diagnostic group	0.04 *	0.28	0.99	0.01 *

Note: * indicates $p < 0.1$, # except follow-up AHI, all other sleep and respiratory data are from the baseline cohort. DD—developmental delay, SDB—sleep-disordered breathing, AHI—apnoea–hypopnea index, OAI—obstructive apnoea index, RAI—respiratory arousal index, T_cCO2—transcutaneous carbon dioxide, TST—total sleep time, PSG—polysomnography, CPAP—continuous positive airway pressure.

4. Discussion

There are significant gaps in the literature regarding SDB in neonates, covering a range of aspects of the disease and including its trajectory with age. Ours is the first study to report the trajectory of SDB and medium-term outcomes in a group of high-risk neonates and explore the relationship between SDB in the neonatal period and developmental outcomes at 3 years of age. Our data showed that despite having severe SDB at baseline, in the majority of patients, it improved and resolved with treatment and time. Our study demonstrates that patient characteristics or phenotypes are important determinants of both respiratory and neurodevelopmental outcomes. Multivariate regression analysis did not reveal any significant associations between SDB and neurodevelopmental outcomes.

The neonates in our study had significant comorbidities, and the majority had severe SDB, requiring a prolonged period of CPAP support (mean duration 12.8 $\pm$ 11.5 months). CPAP is reported to be an effective treatment for upper-airway obstruction and is widely used to treat SDB in infants with genetic and muscular problems [32–35]. A systemic review by Bedi [36] concluded that the long-term use of non-invasive ventilation (NIV) is both effective and feasible in infants with a wide range of underlying problems. Cielo [32] reported that CPAP is well tolerated in infants compared to the school aged children. In our study, nine (16%) patients stopped using it soon after discharge in early infancy. The most common reason given by parents was intolerance of CPAP, including crying or unsettledness in infants. This is consistent with previous studies showing that compliance and a high dropout rate are major issues with CPAP use [32,37–39]. Other reasons described for poor CPAP adherence include caregiver factors and mechanical factors, including poor mask fitting and irritation to skin or eyes and nasal congestion [32,37,38]. In 17 (30%)

patients, CPAP was well tolerated initially; however, it was electively stopped at some point by the parents before the recommendation of the sleep physician. It is also possible that in these children, improvement in respiratory parameters with time would have led to intolerance of CPAP, as most of these children's SDB was deemed resolved by the sleep physician in the subsequent follow-up PSG. Our study found no correlation between the length of CPAP use and developmental outcomes (Table 5). Children with genetic syndromes used CPAP for longer durations than those of other groups, consistent with the recent literature [32].

Our study showed a discrepancy between the AHI criteria and physician's interpretation of the PSG result, with the physicians recommending fewer patients for ongoing/further treatment. This matches with a previous study [40] showing that physicians are likely to incorporate other factors like age, symptoms, other respiratory parameters, treatment tolerance and family/environmental factors when determining the severity and management of SDB in children, especially under 2 years of age. None of the children whose SDB was thought to be resolved/non-significant by physicians returned with SDB symptoms within the study period. Physicians' global interpretation therefore might be a better predictor of outcomes than strict AHI-based severity alone, considering the holistic view taken by physicians. Based on their interpretation, SDB was resolved in the majority of our patients by the end of the study period. Our resolution rate of 47/58 (81%) is higher than those in previously published studies (20−70%) for older children with mild SDB [41,42]. However, it is similar to the 85% resolution rate reported in a study of infants with OSA [43]. Resolution took longer in the genetic group compared to others (Figure 3), consistent with previous studies showing that genetic conditions, such as Trisomy 21, are usually associated with multi-level anatomic upper-airway obstruction with a higher rate of persistent OSA after treatment [44,45]. Our study results suggest a potential relationship between SDB outcomes and motor and cognitive delays (Table 5). Biggs and colleagues [46] found that preschool children originally diagnosed with SDB, regardless of treatment outcome, had worse cognitive and behavioural functioning than controls.

We chose conservative modified AHI criteria to classify SDB compared to what is commonly used in children [47,48]. A significant proportion of our study cohort had their last PSG performed before 2 years of age. Applying the paediatric classification of SDB to children < 2 years of age would result in a higher severity rating of SDB [40]. Another issue is uncertainty about the benefit of treatment of children who have an AHI $\geq$1 but <5 events per hour of sleep. Previous studies have shown no difference in SDB sequelae between a child that has an AHI < 1 event/h and one who has an AHI between 1 and 5 events/h [49,50]. A recent survey of sleep physicians indicated a lack of agreement amongst them regarding the threshold criteria for treatment [20]. Brooks [28] suggested modifying the current SDB severity classification to make it more useful for treatment outcome with more focus on physiology and outcome. This was also supported by the study from DeHaan [40]. We wanted to clearly identify children with clinically significant SDB who had a therapeutic need. From the literature, an AHI value of at least 5 is considered more suggestive of this need [28]. We therefore decided to use AHI >5 as a cut-off for an abnormal PSG.

We divided the cohort in three groups for the evaluation of follow-up PSG parameters. Infants < 6 months were a distinct subgroup with respect to diagnosis and treatment recommendations, and we wanted to ensure that our analysis reflected the age-related changes in sleep and respiration. This was demonstrated by PSG findings, as sleep parameters differed by age group as expected (Table 3). Younger (<6 months) patients had an increased arousal index as well as slightly poorer sleep efficiency (75–81%) compared to normal children (80% or more) [29–31]. However, these parameters normalised with increasing age. Normative data in infants are important in deciding whether this elevated arousal index is a function of age or a manifestation of SDB. The respiratory arousal and desaturation indices also showed progressive improvement with age. Although AHI, OAI and CAI showed significant improvement with increasing age, they remained higher than the norms [4,27,30].

This may either represent some ongoing residual SDB or show ongoing resolution with time, as baseline AHI was very high to begin with. This study reinforces the view that an experienced sleep physician considers factors outside respiratory parameters when making management decisions. While respiratory events are the primary PSG criteria used to define SDB, further work is needed to determine whether evidence of sleep disruption influences physicians' assessment and management of SDB in younger children.

A significant proportion (24/56, 43%) of the study cohort showed major developmental delay at 3 years of age. Patient-specific factors played a key role in neurodevelopmental outcomes. Although in univariate analysis, we found significant effects of some factors on development, they failed to reach statistical significance in multivariate analysis. It is possible that our small sample size may have limited our ability to detect this association; however, this is no different from limited studies that have also reported negative links between SDB in neonates and neurodevelopmental outcomes [22,23]. However, this is different from the study by Piteo [51], which reported that snoring in the first 6 months of life was associated with lower cognitive scores. Bigg [46] also reported a significant effect of SDB on several neurocognitive and behavioural domains in preschool children. Smith and colleagues [52] reported that infants with cleft lip/palate with more obstructive episodes had lower global behaviour scores at 3 years of age.

Limitations of This Study

We acknowledge that the relatively small sample size reduced the statistical power of our regression model, potentially limiting its ability to accurately predict outcomes. Therefore, these results should be interpreted with caution. Our study comprises a cohort of high-risk infants who had confounding factors/diagnoses that are known predictors of poor neurodevelopmental outcome. Approximately a quarter of patients (21/80, 26%) had genetic syndromes, potentially accounting for the high rate of significant developmental delays in our cohort. The potential for bias towards worse outcomes exists due to the higher rate of associated comorbidities in our cohort.

The data collected were from a single centre, with the cohort representing the severe spectrum of SDB, suggesting a referral bias. Follow-up was completed for about 70% of the original cohort, raising the possibility of selection bias. It is possible that parents who refused to undergo repeat PSG at 3 years might have been under the impression that their child's SDB was resolved. For these patients, parents' view and lack of re-presentation to our sleep department or to another specialist by 3 years of age was taken as a proxy for the resolution of significant SDB. Conversely, families who had concerns about their children may have been motivated to participate in a follow-up. We may have missed surgical intervention in some patients, which might have led to SDB resolution. Repeat PSG data were not available at 3 years of age for all patients prior to BSID-III testing to confirm the persistence or resolution of SDB at that time point. We did not have serial polysomnograms to permit trajectory analyses of sleep data over time for individual patients.

Despite these limitations, our study contributes to a small but growing body of literature aimed at improving our understanding of the history and impact of SBD in neonates leading into the preschool years. This study has several strengths. It demonstrates the trajectory and outcome of SDB in a diverse group of neonates with various conditions, while limited prior studies have focused on single groups [22,23,52]. Additionally, all patients with respiratory data underwent follow-up polysomnography (PSG), the gold standard for SDB diagnosis. Moreover, this study cohort was larger than in comparable studies [22,23,52] and represents the longest follow-up of neonates with SDB to date.

5. Conclusions

Our study suggests that clinically important associations may be present between SDB in the neonatal period and later developmental outcomes (at 3 years of age). Establishing definitive associations may require a larger sample. Additional research is necessary to understand the relationship between SDB severity, treatment effectiveness, and outcomes

in non-syndromic infants. Furthermore, the inconsistency in defining thresholds for SDB in neonates, infants and young children hinders the ability of studies to effectively compare the presence and absence of SDB with outcomes of interest. A coordinated effort to define clinically significant SDB thresholds in this at-risk patient population is required.

Author Contributions: B.M.: participated in the design of the study, ethics application, collection of data, follow-up of patients, data analysis, and drafted the initial manuscript. K.A.W., D.A.F. and N.B.: participated in the conceptualisation and design of the study, reviewed and revised the manuscript, and approved the final manuscript as submitted. All authors have read and agreed to the published version of the manuscript.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on reasonable request from the corresponding author due to privacy concerns.

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CHAPTER 6 – ANCILLARY WORK I

Evaluation of oxygen saturation and transcutaneous carbon dioxide profile at the time of discharge in neonates post-major surgery.

Background

Sleep-Disordered Breathing (SDB) includes a spectrum of abnormal breathing patterns during sleep characterised by increased upper airway resistance and pharyngeal collapsibility, leading to intermittent upper airway obstruction during sleep.[1]

Neonates have several unique anatomical and physiological characteristics that make them more susceptible to SDB such as a highly compliant chest wall, immature respiratory control during sleep, predominance of REM sleep, and narrow craniofacial structures.[2] The combination of these factors makes neonates more vulnerable to hypercarbia associated with hypoventilation or shallower ventilation during sleep after an exposure to anaesthetic agent.[3] The presence of certain congenital or acquired abnormalities can further predispose them to airway obstruction.[2]

Pulse oximetry is widely used in clinical practice to obtain data on oxygen saturation (SpO_2).[4,5] It is a non-invasive technique which provides instantaneous data, which have been shown to correlate well with blood gas measurements. Pulse oximetry devices are non-invasive and carry no serious risks. However, some patients experience minor skin irritation, including redness and sensitivity. Continuous non-invasive monitoring of oxygen saturation (SpO_2) is a routine clinical practice in the neonatal intensive care unit (NICU) and reference values for the saturation profile in preterm and healthy full-term infants from birth through to the first few months of life, during infancy, and childhood has been reported by several longitudinal & cross-sectional studies.[6-13]

Transcutaneous monitoring of carbon dioxide ($TcCO_2$) is also a non-invasive method that provides continuous assessment of a patient's ventilatory status. $TcCO_2$ measurements can be easily used in neonates who are not ventilated or who are on non-invasive ventilation. Its accuracy has been reported as similar to end-tidal carbon dioxide ($EtCO_2$) measurement in preterm infants.[14] Skin oedema, poor tissue perfusion, and acidosis can affect the correlation between $TcCO_2$ and partial pressure of carbon dioxide ($PaCO_2$).[15] Additionally, technical factors such as sensor preparation, positioning, and high humidity can limit the reliability of $TcCO_2$ measurements.[15]

CO_2 measurements are recommended as a marker for airway obstruction and assessment of alveolar hypoventilation in children.[16] Although hypercarbia is relatively common in the NICU,[17,18] routine monitoring of CO_2 levels is not usually performed in neonates who are not on any respiratory support. Alveolar hypoventilation can therefore be missed/ go unnoticed in high-risk neonates. Depending upon the definition used, the incidence of hypercarbia varies from 17% to 31% in NICUs.[17,18] Hypoventilation is defined by the American Academy of Sleep Medicine (AASM) when PCO_2 is >50 mmHg for >25% of the total sleep time.[19]

In a NICU in tertiary referral centres, with a high proportion of surgical and cardiac patients, general anaesthesia is commonly required. Anaesthesia can significantly affect the respiratory system leading to adverse events in neonates. These effects include depressed respiratory drive, atelectasis of lungs and ventilation-perfusion (V/Q) mismatch.[3] The highly compliant thoracic cage of infants puts them at a significantly higher risk of de-recruitment and atelectasis. However, there is minimal information about the respiratory profile that might be expected in neonates who have undergone major surgery in the neonatal period. Non-invasive CO_2 monitoring (especially $TcPCO_2$)

can be helpful in assessing recovery of respiratory drive and alveolar hypoventilation after general anaesthesia. This would be of value in these at-risk newborns for the identification and screening for SDB.

We hypothesised that newborns might be more susceptible to both central apnoea and alveolar hypoventilation post-surgery due to the effects of general anaesthesia. In this study, we aimed to demonstrate the respiratory profile of neonates close to discharge after a major surgery by comparing SpO_2 and CO_2 profiles during sleep with those of healthy term neonates, providing insight into the effects of general anaesthesia & surgery on the respiratory profile of neonates.

Aims

To undertake a case-control study to evaluate the impact of surgery and anaesthesia on oxygen saturation (SpO_2) and carbon dioxide (CO_2) profile during sleep in term-equivalent neonates prior to discharge from a surgical NICU compared to healthy term neonates with no surgery or anaesthetic experiences.

Our primary objective is to assess whether neonates considered ready for discharge show any ongoing respiratory effects of anaesthesia on gas exchange during sleep.

Methods

Parents of all patients gave written informed consent for participation in the study. The local human resource ethics committee (HREC) of our hospital approved the study (HREC Reference: 2019/ETH00632).

Cases

Our newborn intensive care is a specialised cardiac and surgical unit that receives referrals from the entire state and internationally. We plan to recruit neonates who have undergone a major surgery (e.g. Oesophageal atresia repair, congenital diaphragmatic

hernia repair, abdominal surgery) requiring general anaesthesia and were term-equivalent (>37 weeks post menstrual age: PMA) at the time of discharge from the unit.

Exclusion criteria for cases

The following patients will be excluded from the study:

- Neonates less than 37 weeks PMA at the time of discharge
- Neonates with complex cyanotic congenital heart disease
- Neonates who had a minor surgery, e.g. repair of inguinal hernia and
- Neonates who are on respiratory support at the of discharge or transfer

Controls

We will recruit healthy term newborns (>37 weeks PMA) from the co-located hospital's post-natal ward who are >48 hours old (to allow for transition of circulation).

Exclusion criteria for controls

Newborns with respiratory distress or any congenital anomalies will be excluded.

Sample size

As this is a descriptive study, we used previous studies[8-12] to guide our sample size calculations and chose to recruit:

50 neonates who underwent a major surgery as cases and 10-20 healthy newborn infants from the post-natal ward as controls.

Oxycapnography

Oxycapnography study will be performed using the Radiometer TCM4. This portable bedside monitor includes time matched recording of child's oxygen saturation (SpO_2), transcutaneous carbon dioxide ($TcCO_2$) level and heart rate during sleep. The recorded

data is downloaded in a software (Visi- download by Stowood build 080219) and analysed.

Nurses will record sleep times, feeding and care times, and any procedures during the study period. This information will be used to identify periods of wakefulness or handling, allowing for the exclusion of artifact-affected data from the final analysis.

Data Collection

The demographic data will be collected from medical records including birth details, clinical status, reason for referral, primary diagnosis and procedures/surgeries done. Recording of each neonate from the Radiometer TCM4 oximetry machine will be downloaded in a computer software for analysis. Data will be then transferred to excel for collation and analysis. The following variables will be collected to describe the respiratory profile:

- Mean (baseline) oxygen saturation with SD
- Proportion of sleep time spent at saturation <90%
- Number of desaturations per hour (Oxygen desaturation indices or ODI for drops of 3 & 4% below baseline)
- Mean (SD) and Maximum $TcCO_2$ level
- Duration of $TcCO_2$ levels of ≥50 mmHg (hypercarbia time) during sleep
- Median (IQR) respiratory rate and heart rate

Progress and difficulties

Patient recruited but data had to be discarded due to equipment problems:

- 10 study patients (cases)
- 5 Healthy newborns (controls)

We have so far successfully recruited:

- 38 study patients (cases)
- 0 healthy newborns (controls)

We have collected a range of demographic and clinical characteristics data of study cohort (see table 1 below).

TABLE 1: Baseline demographic and clinical parameters of study cohort.

Study cohort (N=38)	**Value**
Demographic details	
Gestational age (weeks) (Mean±SD)	36.2±2.8
Birth Weight (grams) (Mean±SD)	2671.6±27.5
Low birth weight – N (%)	15 (39.5%)
Preterm – N (%)	19 (50%)
Male – N (%)	21 (55.3%)
Primary diagnoses leading to surgical intervention	
Craniofacial & airway anomalies group	1
Gastrointestinal anomalies	26
Gastroschisis	5
Anorectal malformation	4
Oesophageal atresia	6
Small intestinal atresia	2
Malrotation/Volvulus	3
Others	6
Respiratory (CDH)	3
Cardiac	8
Coarctation of aorta	4
Transposition of great arteries	3
Total anomalous pulmonary venous return	1
Syndromic diagnosis/ Abnormal chromosome microarray	4
VACTERL association	3
Duplication of Chromosome 17q12	1

Number of general anaesthesia procedures (Mean±SD**)**	1.8±1.2
Number of days on mechanical ventilation (Mean±SD**)**	5.7±4.9
Time interval between last general anesthesia and oximetry Study (Mean±SD**)**	11.9±9.5
Age (PMA) at the time of oximetry study	40±2.1

SD – Standard Deviation, PMA- post menstrual age, CDH -congenital diaphragmatic hernia, VACTERL – vertebral defect, anal atresia, cardiac defect, trachea-oesophageal atresia, renal anomalies, limb abnormalities

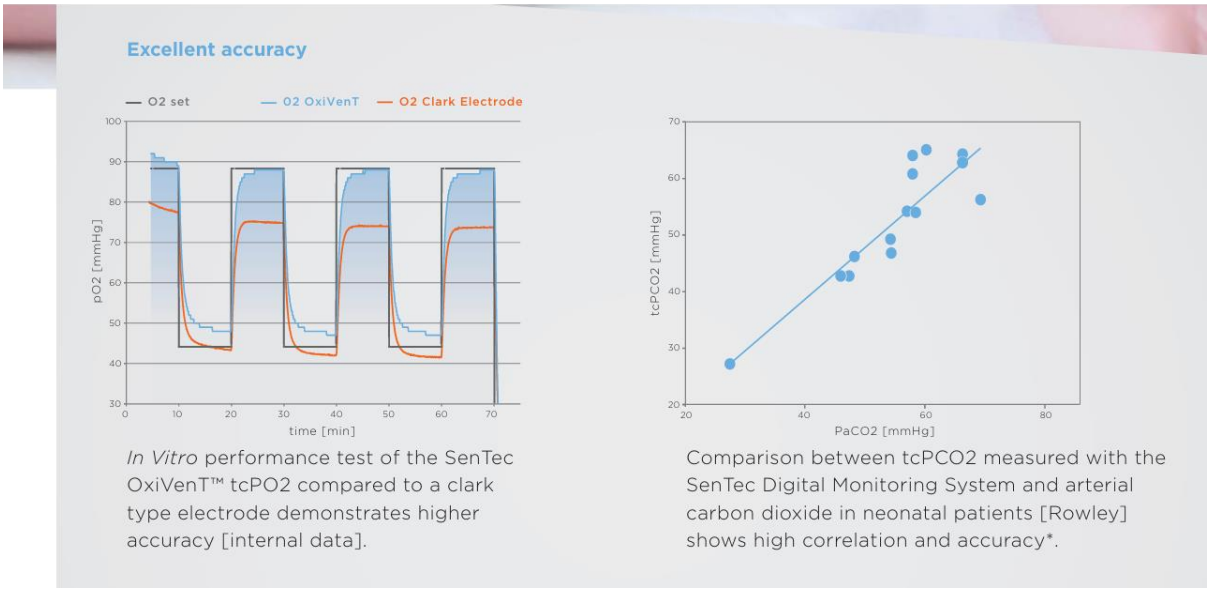
Challenges/difficulties faced with the project

a**.** Challenges with recruitment

The study start was initially delayed by the onset of the COVID-19 pandemic. Following the pandemic, recruitment proceeded at slower pace. During this period, a number of other studies were going on simultaneously in our unit which may have contributed to the slower recruitment rate. Additionally, since our study involved recruiting newborns towards the end of their hospital stay, it is possible that parents might have experienced study and NICU fatigue by that time. Other factors that likely impacted recruitment included changes in clinical scenarios leading to earlier-than-expected discharge or transfer, limited availability of monitors, and technical and patient related issues like insufficient sleep duration during recordings.

b. Challenges related to the equipment

In our original protocol, which was approved by the ethics committee, we selected the SENTEC monitor (SenTec OxiVenT™) for performing oxycapnography. It has been advertised to measure both tcPO2 and tcPCO2 in neonates:



Using the SENTEC monitor, we recruited 15 patients (including 10 cases and 5 controls), over a period of 10 months. However, significant technical issues were encountered with the device's probe, resulting in unreliable and inaccurate oxygen saturation recordings. The data collected was considered uninterpretable.

The SENTEC monitor uses a single probe designed to measure both SpO_2 and $TcCO_2$. However, accurate measurement of SpO_2 requires the probe to be positioned over a bony prominence. In older children, the sternum is typically the preferred site for probe placement, but this approach proved ineffective in neonates. After extensive discussion with the company representatives and in their presence, other bony prominences, such as the forehead and shin were also tried but these efforts also yielded limited success. We also explored alternative methods for securing and holding the probe to improve its contact with the bony surface, but we were unable to achieve consistent and reliable contact and satisfactory SpO_2 readings. Consequently, we were forced to exclude all the studies conducted using the SENTEC monitor, significantly impacting our initial study cohort and requiring adjustments to our approach moving forward.

Image 3: Showing SENTEC monitor and probe

Based on our previous clinical experience in the unit, we then switched to the Radiometer TCM4 monitors for oxycapnography. After the ethics amendment was approved, recruitment was restarted and so far, we have recruited 38 cases. The unavailability

of TCM4 monitor at the co-located hospital's NICU hindered our ability to recruit control subjects.

We plan to begin recruitment of controls from our co-located perinatal NICU at Westmead adult hospital in the near future by loaning them the TCM4 monitor and subsequently analyse the data.

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CHAPTER 7 – ANCILLARY WORK II

Evaluating the use of 3D facial photography in preschool children to investigate a potential association between the facial profile and sleep disordered breathing.

Background

Obstructive Sleep Apnoea (OSA) is common in preschool children (1.8% -6.4%).[1] Whilst enlarged adenoids and tonsils are the major remediable factors with surgery, facial architecture, such as retrognathia and mid-face hypoplasia, are additional contributary factors.[2] The 'gold standard' test for diagnosing OSA is an overnight polysomnography (PSG).[3] However, PSG is a resource-intensive diagnostic tool that requires specialised equipment, trained personnel, and a clinical setting. These limitations make it challenging to widely implement and utilise. There is a need for simpler, more cost-effective, and accessible methods to screen for OSA in children with a history of upper airway obstruction.

Craniofacial anatomy is recognised as an important predisposing factor for OSA in children. Abnormalities such as retrognathia are recognised as risk factors for OSA.[4] Additionally, mid-face hypoplasia is believed to contribute to OSA in children with craniofacial abnormalities, such as trisomy 21.[2,5] Studies have shown that certain facial measurements such as midface width, cervicomental angle and mandibular length, are different between individuals with and without OSA, indicating a potential link between facial features and upper airway obstruction.[6,7]

In a questionnaire-based inquiry, The PANIC study investigated the associations of craniofacial features and body fat with paediatric sleep disordered breathing (SDB) in a

population sample of 491 Finnish children aged 6–8 years. They concluded that abnormal craniofacial morphology, such as convex facial profile had 2.6 times a higher risk of having SDB than those with a normal facial profile.[8] Such differences are more likely to be found in infants with syndromes or chromosomal conditions.[9]

Previous studies have reported decreased mandibular and maxillary lengths, skeletal retrusion, increased facial height, a higher mandibular angle, and an inferiorly positioned hyoid bone as predisposing factors for OSA in children.[10-16] A recent meta-analysis looking at the association between craniofacial features in children and OSA[17] showed that certain craniofacial features such as retrognathia, reduced anteroposterior dimensions of the bony nasopharynx, smaller cranial base angle, narrower intercanine width, and a long facial profile were observed more often in a subgroup of paediatric OSA patients. However, they concluded that given the low to moderate certainty level of the findings, it's inconclusive whether these features are definitively associated with paediatric OSA or not.

Lateral cephalometry, computed tomography (CT), and magnetic resonance imaging (MRI) are used for accurate measurement of maxillofacial anatomical structures and craniofacial evaluations. The limitations of these techniques include their high cost in the case of MRI and potential risks associated with exposure to ionising radiation in the case of cephalometry.

Recent advancements in three-dimensional (3D) facial scanning technology have led to more precise and objective methods of capturing facial morphology.[18] 3D facial photography offers a simple, safe, and accessible method for obtaining information about craniofacial structure. 3D photography can provide novel information regarding

linear distances and angles, as well as on facial contours making it an ideal tool for assessing the role of craniofacial morphology in the development of OSA. Lin et al[19] compared 3D facial photography to 3D CT scans in 36 adult patients with OSA, finding a strong agreement in measurements of craniofacial distances, areas, angles, and volume.

3D facial photography is already used by orthodontists in clinical practice to assess facial parameters, plan treatment, and monitor treatment outcomes. However, few studies have evaluated 3D facial photography for predicting OSA in children.[20]

Data regarding links between 3D photography and OSA comes mainly from the literature on adults. A study of 400 middle-aged adults with OSA in Australia reported that three-dimensional (3D) facial photographs of the face have predictive value for OSA.[21] Using 3D facial photography, the authors measured linear and geodesic (shortest line between points over a curved surface) distances between anatomical landmarks and examined their relationship to the presence and severity of OSA. The results showed that geodesic measurements of craniofacial anatomy improved the ability to identify individuals with and without OSA. A maximum classification accuracy of 91% was achieved when both linear and geodesic craniofacial measurements were combined. The authors concluded that 3D photography can provide a simple and highly accurate method of predicting the presence of OSA. However, the severity of OSA was not able to be determined based on 3D photography.

A meta-analysis of 10 published studies in adults reviewed the diagnostic accuracy and utility of 3D optical devices for predicting OSA. It concluded that although utilisation of 3D optical devices holds considerable promise for OSA diagnosis, further clinical data are essential to assist clinicians in using 3D optical devices.[22]

In this study, we aimed to 1) evaluate the feasibility of using 3D facial photography in preschool children at 3 years of age to assess facial profile and 2) compare the facial profiles of children with and without history of SDB to investigate any potential associations between facial features and SDB.

Methods

This project was approved by the Sydney Children's Hospitals Network Human Research Ethics Committee (LNR/15/SCHN/470). Informed consent was obtained from the parents of all participants prior to their children's inclusion in the study.

Study participants

Study subjects – children who were diagnosed with SDB in the neonatal period, irrespective of their current respiratory status. These children were part of our study cohort. Consent for 3D photography was obtained and image was taken at the time of their scheduled neurodevelopmental follow-up at the age of 3 years.

Control subjects- 3-year-old children with no history of sleep problems and no clinical symptoms of OSA as reported by parents (such as snoring or mouth breathing). We recruited children from our developmental clinic who were enrolled in the clinic for their planned 3-year assessment as a part of the routine practice of unit.

Sample Size

In this pilot study, we planned to enrol up to 50 patients in each group.

Three-dimensional (3D) photogrammetry device

All 3D photographs were obtained using the 3dMD head motion system (3dMD, Atlanta, GA, USA; https://3dmd.com/). To avoid hair covering face and neck region, the head was

covered with a cap (Image 5a). Obtaining the image required the child to sit on a chair between two cameras.

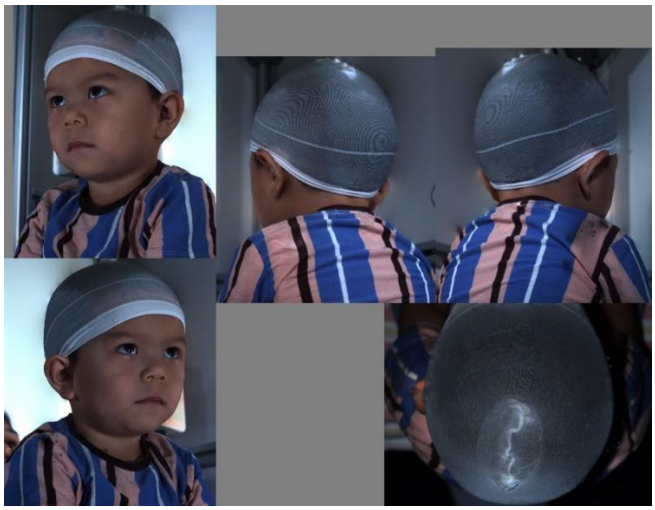
Image 4: 3dMD camera setup.

The children were encouraged to take the natural head position while watching the camera by placing objects of interest in front, if necessary, until their ears were symmetrically visible in the front photo. Children were asked to close their mouth with their lips sealed (Image 5b). However, this was not always feasible with some children, especially in children with developmental delay or challenging behaviours leading to the exclusion of these participants from the study. Once the picture was taken, a 3D image was created.

Image 5: Head cap and positioning of child for 3D photo. The child wears a hair cap and observes towards the screen keeping a natural head position.

(a) Photo included with parental permission

(b) Photos included with parental permission



Landmarks and measurements

Considering the lack of paediatric studies/data, we consulted two experienced paediatric orthodontists working in the University setting to advise on the most appropriate choices for landmarks and measurements.

Following extensive discussion with orthodontists an annotation framework was developed. Previous adult studies had guided the selection of landmarks for facial measurement.[23,24] We identified 17 sets of measurements that would be relevant for assessing the facial profile. These measurements included a combination of linear distances and angles, providing a comprehensive assessment of craniofacial morphology.

TABLE 2: List of names, abbreviations and definitions of the landmarks used for analysis of facial profile.

Landmark	Abbreviation	Definition
Glabella	G	The most prominent midline point between eyebrows
Nasion	N	The point of the deepest concavity of the soft tissue of base the nose in the mid sagittal plane
Subnasale	SN	The point where nasal septum meets the upper lip in the mid sagittal plane
Gnathion	Gn	Most anterior-inferior mid-point of the chin in the mid sagittal plane
Cheilion	Ch	Most distal point located at left and right labial commissure
Exocanthion	Ex	The soft tissue point located at the outer commissure of each eye fissure. The crossing of the lateral ends of the lower and upper eye lid curves
Endocanthion	En	The soft tissue point located at the inner commissure of each eye fissure. The crossing of the medial ends of the lower and upper eye lid curves
Zygoma	Zy	The most laterally positioned point on the zygomatic arches after confirming in two planes frontal and superior inferior view
Alare	Al	The most lateral point on the ala of the nose (right and left)
Otobasion Inferior	OBI	The point of attachment of the ear lobe to the cheek, which determines the lower border of the ear insertion
Menton	Mn	The lowest point of the chin
Jaw Index	JI	by dropping 2D lines from Subnasale (SN) and Gnathion (Gn)

TABLE 3: List of agreed craniofacial measurements derived from facial landmarks.

Craniofacial Landmark	Measurement use/purpose
To Assess Linear (Vertical + Transverse) Measurements	
Nasion (N) to Subnasale (SN)	Facial Height
Subnasale (SN) to Gnathion (Gn)	Facial Height
Left Chelion to Right chelion	Facial width
Left Exocanthus to Right exocanthus	Facial width
Left endocanthus – Right endocanthus - width	Facial width
Left Zygoma – Right Zygoma – width	Facial width
Alar width	Nasal anatomy
Left Otobasion inferior to Right otobasion inferior	Facial width
Otobasion inferior to Nasion (Right)	Antero-Posterior diameter
Otobasion inferior (OBI) to Subnasale -RIGHT	Antero-Posterior diameter
Otobasion inferior to Subnasale - LEFT	Antero-Posterior diameter
Otobasion inferior to Gn -RIGHT	Right Mandibular length
Otobasion inferior to Gn -LEFT	Left Mandibular length
L-OBI to Gn + R-OBI to Gn	Total Mandibular length
To assess angles	
Nasion- Otobasion- Gnathion	Chin protrusion
Nasion, Subnasale, Gnathion	Facial Convexity
Jaw Index as per the mentioned parameter	To assess micrognathia and retrognathia

Figure 4: Positions of anatomical landmarks (see definitions in Table 2).

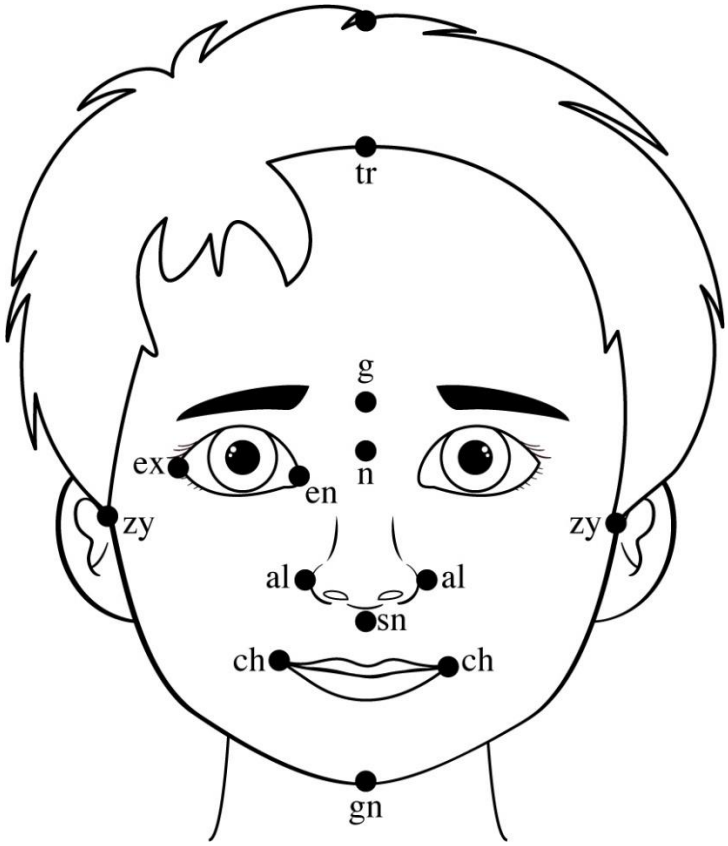


Image courtesy of Belinda Jacmenjak

Based on the linear measurements, ratios for facial height and width and antero-posterior diameters will be calculated. Three operators (1 neonatologist and 2 orthodontists) independently annotated each 3D photograph to assess inter-rater variability. Our first objective of manual annotation was to establish a consistent and reliable standard for marking anatomical landmarks on the 3D facial images, ensuring inter-rater reliability and accuracy in subsequent measurements.

Progress and difficulties

We successfully recruited 44 patients:

- 29 study patients (cases)
- 15 healthy children (controls)

Baseline demographic and clinical characteristics were collected and are summarised in the table below.

TABLE 4: Demographic and clinical profile of 3D facial photo study cohort

Study cohort (N=44)	**Value**
Demographic details of cases (N=29)	
Birth Weight (grams) (Mean±SD)	2684.5±1098.8
Male – N (%)	18 (62%)
Primary diagnoses leading to SDB	
Craniofacial & airway anomaly	12
Skeletal Dysplasia	1
Neuromuscular	1
Neurological	1
Genetic syndrome	5
Chronic Lung Disease	4
Others	5
Initial management in the neonatal period for SDB	
Discharged home on CPAP	22
Discharged home on apnoea monitor	6
Discharged on home oxygen	1
Duration of CPAP use (months) (Mean±SD)	9.3±11.1
Age at the time of 3D Photo (months) (Mean±SD)	38±3.1
Demographic details of controls (N=15)	
Male – N (%)	10 (66%)
Primary reason for their hospital visit	
Cardiac	7
Transposition of great arteries	3
Tetralogy of Fallot	1

Coarctation of aorta	1
Supracardiac TAPVR	1
Critical aortic stenosis	1
Gastrointestinal	6
Jejuanal atresia	2
Exomphalos	1
Anorectal malformation	1
Hirschsprung disease	1
Oesophageal atresia	1
Others	
Congenital diaphragmatic hernia	1
Sacrococcygeal teratoma	1
Age at the time of 3D Photo (months) (Mean±SD)	39.3±2.9

SD – Standard Deviation, SDB – Sleep Disordered Breathing, CPAP- Continuous Positive Airway Pressure, TAPVR -Total Anomalous Pulmonary Venous Return

Challenges/difficulties faced with the project

A. Challenges with recruitment

We initially aimed to recruit an equal number of controls and study patients. This study recruitment was undermined by several issues including the impact of COVID-19 pandemic on face-to-face patient attendance and family concerns about risk of exposure to unwell people in the hospital setting. In addition, there were significant staffing issues in the clinical photography department during the pandemic and the extended shut down of the hospital clinical photography department for maintenance and installation of new equipment.

B. *Challenges related to 3D Facial photography software*

Analysis of facial morphology is based on distances and angles between different facial landmarks. However, it relies on manual annotation of the landmark. Manual annotation of landmarks is known to introduce variability and errors, potentially affecting the accuracy and interpretation of results. This can lead to inter-rater and intra-rater variability. A Danish study on 36 healthy individuals showed that inter-operator variability was primarily influenced by the specific characteristics of landmarks (leniently define landmarks) rather than operator's training or age and gender of the portray. [25]

The 3DMD software we used had several limitations, affecting its functionality and accuracy:

1. Performance lag: The software exhibited significant lag time, resulting in slow responsiveness to commands, which hindered efficient workflow.

2. Annotation accuracy: It lacked precision for annotating finer points, especially involving curves. The software often failed to mark the exact intended points, compromising precision in measurements.

3. Angle measurement: The software did not have the ability to measure some of the angles we intended to measure. Further, there were difficulties with precision annotation, accuracy and reproducibility, contributing to inconsistencies in the results.

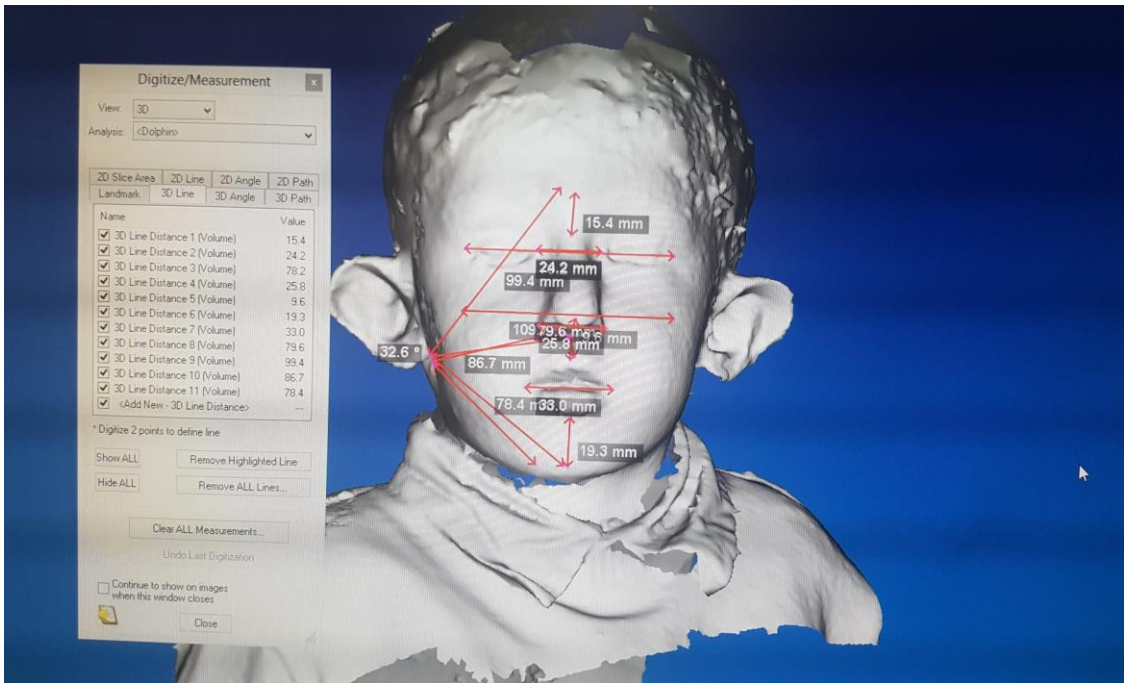
4. Inter-Rater and Intra-Rater variability: Technical issues mentioned above led to significant inter-rater and intra-rater variability, affecting the reliability of the data and overall analysis.

5. There was a problem in saving fully annotated images. Upon reopening the saved images, the marked points would frequently shift, rendering the annotations inaccurate and requiring the work to be repeated.

These limitations posed serious challenges for clinical accuracy and efficiency, necessitating us to look for other software. We reviewed two other software programmes and then decided to try the Dolphin 3D software which is an FDA-cleared Class II medical device (Dolphin Imaging & Management Solutions, a Patterson Technology). This software was used in the clinical practice by paediatric orthodontists involved in this study. Although the Dolphin software solved some of the above-mentioned issues, some problems remained:

- Issue with saving the annotated images
- Unable to measure all the angles intended
- Suboptimal inter-operator reliability

Image 6: An example of 3D-image from Dolphin software.



C. *Lack of stablished norms*

At birth, the face is approximately 40% of the adult size, growing to 65% by 3 years of age. Full facial growth is not completed until after puberty.[26] During this period of rapid facial growth, it is crucial to establish normative data based on gender and ethnicity by studying healthy children without SDB. Without established norms, it is challenging to identify any significant associations between variables. Ethnic differences in OSA risk factors may also affect the accuracy of these facial predictors. Further research is needed in this area to enhance our understanding and improve accuracy in assessments.

Given the significant challenges and limitations outlined above, any data analysis of significance was not feasible for this study.

Summary and Future Directions

The utilisation of 3D optical devices holds considerable promise for the diagnosis of OSA. Introduction of faster, better, and cheaper systems for facial 3D scanning has enabled more accurate (by evaluating geodesic distances and calculating non-linear measurements) and objective methods of capturing differences in facial morphology. Unlike traditional methods such as polysomnography and cephalometry, which can be time-consuming and resource-intensive, 3D optical devices offer a non-invasive, quick, and cost-effective alternative. Moreover, their portability and easy to use design make them well-suited for large-scale screening initiatives.

However, more clinical data are needed/essential to assist clinicians in clinical decision-making, as they are still in the early stages of development. In addition, detection methods must undergo strict standardisation. To reduce operator time and minimise the

variability, there is need for a standardised annotation procedure and an agreed limited set of manually annotated landmarks to ensure consistent and reliable outcomes across diverse populations. Automation of anatomical landmarks would be a vital component in this direction. This standardisation process will be critical in refining the accuracy, reliability and effectiveness of the technology. By establishing clear guidelines and protocols for their use, 3D optical devices have the potential to become more reliable tools in OSA screening and diagnosis.

We are committed to continuing our search for the most suitable 3D software to advance our research with aim to develop model based on craniofacial photographic analysis for the prediction of OSA. To enhance our probability, we plan to collaborate with interdisciplinary experts who have experience in using 3D devices. We will also seek opportunities for national and international collaborations to broaden our access to such innovative resources.

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Chapter 8

Summary and Conclusion, Knowledge Implementation and Future Directions

INTRODUCTION

The multi-dimensional studies included in this thesis were initiated with the aim of exploring common and clinically important aspects of sleep-disordered breathing (SDB) in newborns, as well as their consequences into early childhood. The results address clinical features of their presentation, baseline clinical profile/characteristics, diagnostic and management strategies, natural history, and outcomes into the preschool years. To the best of the candidate's knowledge, this is the first research with its exclusive focus on SDB in newborns, a largely overlooked population in prior studies that have primarily concentrated on older children.

AIMS AND METHODS

In newborns, SDB presents unique challenges in terms of recognition, diagnosis and treatment and may remain unrecognised/unnoticed as it manifests differently to older children who tend to snore loudly, and mouth breathe. Understanding the short, medium and long-term outcomes of SDB in newborns is crucial, as early intervention may have a significant impact on developmental trajectories and overall health. This study, therefore, not only aims to outline the challenges of diagnosing and managing SDB but also to offer valuable insights into its impact on infants' development over time. By focusing on newborns, the research emphasises the importance of addressing their unique needs.

This study describes a range of aspects of SDB in newborns by presenting the short- and medium-term outcomes of a cohort of newborns admitted to a surgical neonatal intensive care unit. The primary research aims of this thesis were:

1. To evaluate the available evidence regarding SDB in neonates
2. To explore the knowledge, awareness, and practices amongst neonatologists about SBD
3. To highlight the risk factors for SDB in neonates and identify challenges associated with their diagnosis and management
4. To describe the respiratory and developmental trajectory of neonates treated for SDB
5. To review the impact of SDB in neonates on their development at age 3 years

To achieve these aims, a combination of methods was employed. To provide an understanding of the current knowledge, a comprehensive literature review summarising the published evidence regarding the SDB in neonates was undertaken. Secondly, a nationwide survey of neonatologists to capture the current knowledge and practices was conducted. Thirdly, a cross-sectional cohort study was conducted to provide a comprehensive analysis of clinical profile, management strategies, and hospital outcomes. Finally, a prospective cohort study of neonates diagnosed with SDB during the neonatal period was undertaken. Baseline data was obtained during the neonatal period and a follow-up study was undertaken in early childhood.

This final chapter presents a summary of main findings in this thesis, addressing the research questions posed. In addition, directions for future research are discussed.

SUMMARY OF MAIN FINDINGS

I. Aim 1

To summarise the current knowledge and available evidence regarding neonatal sleep, SDB, and their impact on neonates using a comprehensive literature review.

Key Findings

1. There are significant gaps in the literature regarding the SDB in neonates, covering a range of aspects of the disease including its prevalence in neonatal population, the natural history of the disorder from infancy into childhood and its impact on development.

2. Sleep architecture and sleep parameters undergo rapid changes in the first year of life, resulting in normative values changing rapidly with age. Neonates have several unique physiological and developmental characteristics that make them more susceptible to SDB and its potential consequences of altered growth and development.

3. Diagnosing SDB in neonates is challenging as normative data are not well established and there is no clear consensus differentiating normal from mild to moderately abnormal SDB parameters. There is a lack of standard criteria for testing and lack of guidelines for defining SDB in the neonatal population, leading to heterogeneity in the diagnostic criteria used.

4. SDB has been associated with negative effects on health, growth and development, and behaviour in children. However, studies confirming that these consequences also occur in neonates are lacking.

Directions for future research

- Develop a consensus for the threshold for diagnosing and treating SBD based on evidence-based defined normal neonatal polysomnography parameters.
- Increase awareness of SDB among neonatologists and establish standardised referral criteria for sleep consultations to facilitate timely diagnosis and intervention.
- Longitudinal studies to evaluate the impact of SDB and its treatment through childhood.

II. Aim 2

To investigate the knowledge, practices, and awareness of SDB of neonatologists working in Australia and New Zealand (NZ) using an electronic web-based survey and a direct clinical interview during the 2019 Australia and New Zealand perinatal conference.

Key Findings

1. Management practices for neonates with suspected SDB vary considerably. The performance and interpretation of screening tests varies in type and interpretation, with considerable variability in thresholds for referral to a paediatric sleep physician.
2. There is a lack of guidelines for the management of SDB, and decisions are mostly physician dependent.
3. Higher levels of evidence are needed to standardise the practices and care of this group of vulnerable neonates to optimise their outcomes. Factors identified in the literature review (lack of normative data, no universally accepted criteria for diagnosing SDB in neonates and uncertainty regarding any causal linkage between SDB and abnormal neurodevelopmental outcomes) contribute to the variation in

practices and creates significant clinical dilemmas for neonatologists regarding the need for intervention.

4. Participant feedback suggested that several respondents found this topic too difficult, making them reluctant to complete the questionnaire, indicating lack of knowledge or awareness about the condition.

Directions for future research

- Develop consensus guidelines for screening and referring neonates with a high risk of and/or symptoms of SDB. A simple referral/management algorithm would ensure a consistent model of care in neonatal units throughout Australasia.
- Developing an evidence-based, consensus guideline for the practice of neonatal oximetry studies as a screening tool for SDB including appropriate choice of device, settings and reporting format.
- Identifying the consequences of SDB by correlating neonatal polysomnography with neurodevelopmental outcomes through early childhood and into the school- aged population.

III. Aim 3

To describe clinical aspects of SDB in neonates, including risk factors, clinical profile, the use of diagnostic tools, intervention options, and hospital outcomes using a cross-sectional cohort study of newborns with SDB.

Key Findings

1. SDB can be a serious problem in neonates resulting in respiratory compromise, hypoxaemia, hypercarbia and prolong hospital stay, highlighting the importance of SDB surveillance in high-risk neonatal population.
2. Neonates present very differently to the typical symptoms of snoring and restless sleep in older children, underpinning the need for increased awareness, timely identification and optimal management.
3. Craniofacial anomalies and genetic syndromes are the main risk factors contributing to neonatal SDB.
4. In neonates, SDB is usually associated with complex multisystem comorbidities, and requires coordinated efforts of a multidisciplinary team to ensure optimal interdisciplinary management before discharge from the NICU is feasible.
5. Although complex to manage, timely evaluation and targeted therapeutic interventions can lead to resolution of SDB in this population.
6. Despite the lack of normative data and the absence of universally accepted criteria for the diagnosis and classification of SDB severity, PSG provided helpful diagnostic information in neonates and helped to guide management.
7. As opposed to adenotonsillectomy as a first line treatment for SDB in healthy older children, establishing the specific cause of SDB and anatomical factors are critical to selecting the optimal therapy in newborns.
8. Although Continuous Positive Airway Pressure (CPAP) use has been described in infants with craniofacial anomalies and genetic conditions, its use as first line treatment has largely been restricted in neonates and infants due to problems

with mask tolerance and compliance adherence with therapy and high drop-out rates.

The majority of our study cohort (70%) were successfully established, maintained, and discharged from the NICU on home CPAP therapy. Our study demonstrates that with appropriate multidisciplinary support, CPAP can be used as an effective therapy in the neonatal population for management of SDB.

Directions for future research

- The study identifies the critical need to establish normative data for the neonatal population. The establishment of reference values and treatment thresholds for the neonates will help clinicians in making evidence-based, clinically appropriate decisions using PSG findings that will help to standardise clinical practice.
- This study also highlights an urgent need for outcome-based research. Longitudinal studies are needed to establish the relationship between SDB in infancy and medium and long- term outcomes.

IV. Aims 4 and 5

To describe the natural history/trajectory of neonates diagnosed and treated for SDB and review the impact of SDB in neonates on their development. A prospective cohort study was done which included a diverse group of neonates with SDB for whom respiratory and neurodevelopmental outcomes were assessed at 3 years of age.

This is the first study to demonstrates the trajectory and outcome of SDB in a diverse group of neonates with various conditions, while limited prior studies have focused on single groups.[1-3]

Key Findings

1. The study cohort was larger than previous reports[1-3] and represents the longest follow-up of neonates with SDB to date.
2. The Study demonstrates that in spite of issues with compliance and tolerance, CPAP was found to be an effective long term treatment option for OSA in neonates and infants.
3. Despite the severity of SDB at baseline, with appropriate treatment and time, SDB was resolved in the majority of this cohort at 3 years of age.
4. Discrepancies were noted regarding the rate of resolution of SDB between apnoea-hypopnoea index (AHI) based criteria and the opinion/recommendation of treating sleep physicians, suggesting that the physicians' global interpretation might be a better predictor of outcomes than strict AHI-based severity alone indicating the need for re-evaluation of classification of SDB in infants and children with more attention paid to physiology and outcomes.
5. Follow-up PSG data demonstrated expected changes in sleep parameters with increasing age with sleep efficiency increased, percent of REM sleep decreased, and NREM sleep increased over time. As expected, respiratory parameters also showed progressive improvement with increasing age suggesting that clinicians should consider the potential for physiologic improvement with time when deciding about the diagnosis and severity of SDB in infants and young children.
6. Resolution of SDB took longer in infants with genetic syndromes.
7. Approximately a third of neonates with SDB (21/56, 37.5%) had global developmental delays when assessed at age 3 years, reinforcing that patient

phenotype plays an important role in both respiratory and neurodevelopmental outcomes.

8. Univariate analysis showed some clinically important significant associations. Patient diagnosis/phenotype was significantly associated with both cognitive delay (p = 0.04) and global developmental delay (p = 0.01) at age 3 years. The SDB outcome approached borderline significance for predicting cognitive delay (p = 0.06) and motor delay (p = 0.05) while AHI at the time of last follow-up PSG was associated with language delay (p = 0.04). These parameters failed to reach statistical significance in multivariate analysis. We acknowledge that the relatively small sample size reduced the statistical power of our regression model, potentially limiting its ability to accurately predict outcomes.

Directions for future research

- Additional research is necessary to understand the relationship between SDB severity, treatment effectiveness, and outcomes in non-syndromic neonates/infants. Establishing definitive associations will require larger sample sizes.
- There is a need for establishing physiology and outcome-based criteria for diagnosing and classification of SDB in neonates and younger children.

KNOWLEDGE IMPLEMENTATION/CLINICAL PRACTICE IMPLICATION

1. Multidisciplinary Breathing and Airway Team formation

This research has shown that managing neonatal SDB is more complex than in adults and older children, largely due to the diversity of conditions associated with SDB and the

absence of clear diagnostic and management guidelines. Moreover, our study has demonstrated that neonatal SDB is often associated with complex multisystem comorbidities, requiring the involvement of multiple specialists in its management.

The involvement of multiple specialists can lead to differing opinions, creating confusion for both parents and the primary care team (neonatologists). Due to their busy schedule, sub-specialists often visit the NICU at different times and may not be able to co-ordinate nor communicate directly with one another, which can contribute to delays in decision making and prolong the hospital stay. Over the last years, staff in our unit came to the conclusion that our patients could benefit from a regular multidisciplinary team meeting, where all specialists are present at the same time to share views and discuss their opinions on the diagnosis and management of neonates with complex multisystem issues affecting breathing and gas exchange involving the upper and lower airways. With these factors in mind, we established the "**Breathing and Airway Team (BAT),"** with a plan to hold regular meetings every four weeks, along with additional ad hoc or urgent meetings when needed.

Multiple studies have reported the effectiveness of multidisciplinary team approach in reducing costs and improving clinical outcomes in children.[4-8] An aerodigestive team model for paediatric patients has been in place in the United States since 2000 and has been in place at our hospital for ongoing outpatient care since 2014. Its importance has been recognised, and its implementation in various institutions is increasing rapidly.[9-10]

The core members of the BAT consisted of a neonatologist, ENT surgeon, general surgeon, plastic surgeon, paediatric pulmonologist and sleep physician. Depending on the underlying condition and the interventions required, other specialists were also

involved in the meeting, including a cardiologist, cardiothoracic surgeon, geneticist and gastroenterologist. Consultants from our paediatric intensive care unit (PICU) and hospital general paediatricians were also invited as frequently neonates with chronic & complex airway and breathing problems require prolonged hospital admissions and need to be transitioned to PICU or to a children's ward depending upon the clinical condition.

Organisation and coordination of these meetings is undertaken by neonatologist (myself) and the meeting is referred to as the "**Airway Meeting**". A calendar invite is sent for regular every 4-weekly meeting to all the stakeholders. During COVID-19 pandemic, these meetings were held online. Currently however, both online and in-person attendance options are available.

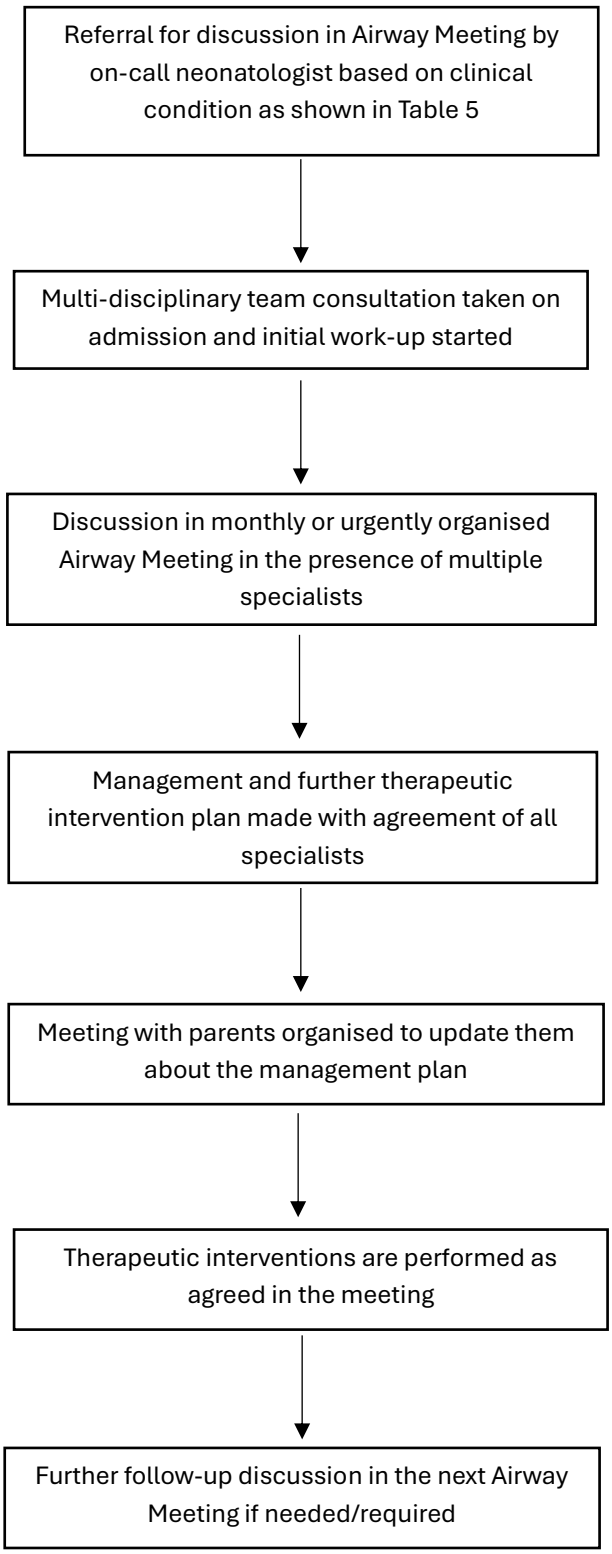
The inclusion criteria for presentation at the meetings includes any newborns referred or admitted to our NICU with complex airway and breathing problems. Our unit is a specialised surgical and cardiac NICU, and it receives referrals from our state of New South Wales and regional international centres. These patients are identified on admission by the on-call neonatologist and neonatal team. Multidisciplinary team consultation is taken and an initial work-up is commenced. The case is then brought to my attention as chair of the BAT for discussion in the Airway Meeting. If urgent care planning is required, an ad hoc meeting is arranged; otherwise, the patient is discussed during the scheduled monthly Airway Meeting. The common conditions and diseases that are included for discussion in the Airway Meeting are shown in Table 5.

TABLE 5: Common risk factors for developing SDB in neonates.

Craniofacial anomalies	Choanal atresia/stenosis Jaw anomalies with micrognathia and/or retrognathia Pierre Robin Sequence Stickler syndrome Treacher-Collins Syndrome Craniosynostosis Apert, Crouzon & Pfeiffer syndromes, achondroplasia Cleft Palate
Genetic Syndromes	Trisomy 21 Beckwith-Weideman Syndrome CHARGE syndrome 22q11 deletion/Velocardiofacial syndrome Prader-Willi syndrome Skeletal dysplasia
Congenital airway anomalies	Laryngomalacia Vocal cord paralysis Tracheomalacia Bronchomalacia Tracheal stenosis Laryngeal Cleft
Neuromuscular disorders	Nemaline Rod myopathy Congenital myotonia Other Myopathies
Neurological problems	Arnold-Chiari malformation Hydrocephalus
Respiratory	Moderate-severe chronic lung disease Sleep disordered breathing – central hypoventilation
Gastric	Oesophageal atresia Tracheo-oesophageal fistula

The workflow of the Airway Meetings is illustrated in Figure 5.

Figure 5: Overview of the Airway Meeting general algorithm.



This model has emerged as a valuable programme to provide coordinated interdisciplinary care for neonates with complex medical and surgical airway and

breathing conditions. It has helped in facilitating communication between different care providers and in coordinating plans to address the complex needs of neonates with aerodigestive conditions. Although we have not yet assessed the impact of this programme it appears to have had a positive impact on both staff (as expressed through staff meetings) and parents anecdotally. As clinicians, we feel this has improved family satisfaction of the care provided. We also believe that this has had a positive effect on the resource utilisation and outcome of these complex patients and intend to assess this formally in future with questionnaires for staff and families.

2. Initiation of new programme through multidisciplinary collaboration for management of SDB in newborns

The background of increased collaboration between sleep medicine, respiratory medicine, neonatology and other teams facilitated the recent introduction of Tübingen Palatal Plate (TPP) programme as a non-surgical treatment approach that can be used in the management of neonates with Pierre-Robin Sequence (PRS). TPP is an orthodontic device that reduces the degree of upper airway obstruction by pushing the base of the tongue forward and opening the upper airway. Data show that the TPP is effective in both mild and severe PRS, results in resolution of OSA, promotes a normal weight gain, and helps to avoid surgery.[11-13] Implementation of this programme required collaboration between multi-disciplinary medical and allied health teams including orthodontist, sleep physician, ENT, neonatologist, speech pathologist and lactation specialist. So far, we have received highly positive feedback from parents and families.

RECOMMENDATIONS FOR FUTURE RESEARCH

The absence of widely accepted guidelines for the diagnosis and treatment of SDB in neonates and infants, along with a lack of established norms for sleep breathing and respiratory parameters in neonates is one of the major challenges clinicians face in diagnosing and managing this condition. Significant variability is therefore seen in how SDB is assessed and treated across different regions leading to inconsistency in clinical practice.[14]

Future studies in this area should focus on recruiting full-term, healthy neonates and following them prospectively, conducting polysomnography (PSG) at regular intervals to document sleep and respiratory parameters during the first year of life. This would provide valuable insights into the rapid changes in sleep physiology during the early months. Such data will be crucial for establishing normative values for sleep and respiratory parameters in newborns and infants. By documenting the natural progression of sleep and respiratory patterns in healthy neonates, these studies could help in establishing guidelines, facilitating accurate diagnoses and uniformity in treatment globally.

Further research should also focus on examining the long-term impact of SDB in non-syndromic neonates by following them into childhood. This type of research with larger sample sizes will help clinicians to understand the impact of early-life SDB on the overall development of children as they grow including cognitive development, growth, behaviour, and quality of life. The data gathered could inform clinicians about the potential long-term risks associated with SDB in this population and guide individualised treatment approaches to minimise adverse effects on childhood development.

To address neonatal SDB as a part of routine care in Australasia (Australia and New Zealand), several key resources and actions are necessary. Here's an overview of the resources required and what needs to be done for their integration into routine care:

1. Specialised medical knowledge and expertise

Our thesis has demonstrated that the characteristics of newborn SDB is distinct compared to SDB in older children and adults. Therefore, care of neonates with SDB requires specialised knowledge and expertise from a multidisciplinary team to ensure early diagnosis and best outcomes. Resources needed are trained neonatologists, paediatricians, sleep medicine experts, nurses, and sleep technicians.

- **What needs to be done:**
    - Establishment of multidisciplinary teams involving neonatologists, paediatricians, sleep specialists, nurses, sleep technicians and social workers.
    - Advocate for specialised fellowship programs or certifications focused on (or that specifically include) neonatal sleep disorders.
    - Ensure that neonatal sleep disorders, including SDB, are included in medical training (especially those of neonatologists) and continuing education programs.

2. Early Screening and Diagnosis Protocols

- **Resources Needed:**
    - Standardised guidelines are needed for screening high risk neonates for sleep-disordered breathing.

- Evidence-based clinical guidelines for the diagnosis and management of neonatal SDB are needed.

- **What needs to be done:**
  - Significant effort and collaboration are needed to establish a universally accepted SDB screening and diagnostic protocols for neonates.
  - Raise awareness of the potential long-term health effects of undiagnosed SDB and the benefits of early intervention.

3. Improved Access to diagnostic tools and equipment

- **Resources Needed:**
  - Access to polysomnography (sleep study) which is a gold standard test to diagnose SDB in neonates.
  - Equipment for treating OSA like home CPAP and mask.
  - Portable monitoring devices to track respiratory status at home like apnoea monitors for high-risk infants.

- **What needs to be done:**
  - Lobby for funding and integration of advanced diagnostic tools for sleep-disordered breathing in neonatal care units.

4. Parent and caregiver Education

- **Resources Needed**:
  - Educational materials for parents regarding the signs and risks of neonatal sleep-disordered breathing.
  - Support programs for parents to understand treatment options and the importance of follow-up care.

- **What needs to be done**:
    - Develop educational resources to raise awareness among parents about neonatal sleep disorders.

5. Collaborative Research and Evidence-Based Practice

- **Resources Needed:**
    - Funding for research on neonatal sleep-disordered breathing, to better define its causes, its long-term impacts and the effectiveness of different treatment options.
    - Databases to track neonatal SDB cases and outcomes.
- **What needs to be done:**
    - Advocate for increased funding for neonatal sleep disorder research and encourage collaboration between paediatric and sleep medicine societies, academic institutions, and healthcare providers.

By addressing these needs, we can ensure that all neonates with SDB in Australasia receive the timely and appropriate care they require.

CONCLUSION

The results presented in this doctoral thesis make an important contribution towards increasing our knowledge about a range of aspects of SDB in newborns and infants. This research sheds light on previously unexplored aspects of SDB in neonates, offering new insights into its manifestations and broader impact on health. By addressing gaps in our understanding about its presentation, management, trajectory, and impact on development in this vulnerable age group which were previously not well described, the

study can help clinicians identify early warning signs and provide coordinated management of SDB in this population.

We hope that our research will encourage further studies in this area as there is an urgent need to establish universally agreed and clinically important thresholds for diagnosis and treatment of SDB in this age group. Standardised treatment guidelines would promote consistency in clinical practice, ensuring that infants receive timely and appropriate care, improving overall outcomes for affected neonates worldwide.

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