A pilot study on the assessment of upper airway obstruction in patients undergoing tonsillectomy with or without adenoidectomy

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Master of Philosophy.

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Dedication

To my wife, Rashmi, and my children Sanjana and Shaurya for their unconditional love, sacrifices and support in my endeavour.

To my Parents, for their support and guidance throughout my life

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I would like to thank Professor Ron Eccles for his expert supervision and guidance over the past year. Thank you for allowing me this invaluable opportunity to conduct research at the Common Cold Centre.

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I would like to thank Susu, Martez, Ben and Hannah for all their help in setting up, running and support of this study

DECLARATION

This work has not previously been accepted in substance for any degree and is not being concurrently submitted in candidature for any degree

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This thesis is being submitted in partial fulfillment of the requirements for the degree of M.Phil.

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Summary

Adenotonsillectomy is currently indicated as a treatment for sleep-related breathing disorders in children because removal of the tonsils opens up the airway and lowers airway resistance to breathing. Overnight pulse oximetry and polysomnography are two common investigations used to diagnose sleep-related breathing disorders, but these are overnight and time-consuming procedures. This thesis proposes that a simple non-invasive measurement of peak inspiratory flow rates may help in decision-making towards patient selection for surgical treatment of sleep-related breathing disorders. Since the upper airway cause of any sleep-related breathing disorder is believed to be obstruction of oral and nasal airways due to enlarged tonsils or adenoids, it seems reasonable that patient selection for surgery could be better managed by simple measurements of the severity of airway obstruction rather than the consequences of this obstruction as determined by overnight studies

This thesis investigates the severity of upper airway obstruction in patients undergoing tonsillectomy +/- adenoidectomy by measuring peak nasal and oral inspiratory airflow (PNIF, POIF). The study was conducted in two phases: the first phase on the day of surgery and the second phase approximately one month after surgery. Fifty subjects were recruited for the first phase of the study from a cohort of patients on the waiting list for tonsillectomy with or without adenoidectomy at University Hospital Wales. Twenty-five of these subjects were followed up in the second phase of the study at the Common Cold Centre. All the subjects were instructed to perform three measurements of both peak nasal and oral flow during both visits.

This study demonstrated that a simple non-invasive inspiratory flow meter could be used to measure both POIF and PNIF. Postoperative POIF and PNIF had increased compared to the preoperative POIF and PNIF, and this difference was statistically significant.

Chapter 1

Introduction

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1.1 Epidemiology of Sleep-Related Breathing Disorders (SRBD)

The change in trends for the indication of adenotonsillectomy from infections to obstructive symptoms suggests that the prevalence of sleep-related breathing disorders (SRBD) is either increasing or being more frequently diagnosed. A review of the literature gives an estimated prevalence rate of SRBD between 0.7 % and 13% (Bixler et al., 2009). The prevalence of SRBD varies widely depending on the demographics of the population studied, definitions of the disorder and the method of diagnosis. A review of the literature revealed a multitude of diagnostic methods used to diagnose SRBD, from clinical suspicion and questionnaires to pulse oximetry and the standard Polysomnography. As SRBD is a continuum from simple snoring to upper airway resistance syndrome (UARS) to full blown obstructive sleep apnoea syndrome, this prevalence is for the whole spectrum of SRBD rather than an individual component.

A cross-sectional study of 346 patients aged between two and six years attending a well baby clinic in Brooklyn, using the Paediatric Sleep Questionnaire (PSQ), reported a prevalence of snoring of 13.9% and SRDB of 9.4% (Goldstein et al., 2005). The prevalence of snoring for black children was 2.5 as great as that for white children, and for Hispanic children it was 2.3 as great as that for white children ($p = 0.031$). This study suggests that prevalence of SRBD is multifactorial and it is more common in black and Hispanic races than in Caucasians. Kohler et al. have reviewed 27studies, examining a total of 5588 children (1615 obese). On examining these studies, around half report a significant relationship

between obesity and SRDB (Kohler et al., 2008).

The prevalence of SRBD was assessed by Bixler and colleagues via a random sample survey of elementary school pupils (Bixler et al., 2009). This study was conducted in two phases: the first phase (N=5740) included a sleep-related brief questionnaire and the second phase was on randomly selected children (N=700) who underwent overnight polysomnography. This study concluded that the prevalence of Apnoea Hypopnea index (AHI) ≥ 5 was 1.2% in a representative sample of elementary school children. Risk factors for SRDB included waist circumference, nasal abnormalities (e.g., chronic sinusitis/rhinitis) and ethnic minority. The authors also concluded that a strong linear relationship exists between waist circumference and BMI across all degrees of severity of SRDB and metabolic factors may be among the most important risk factors for SRDB in children.

Goodwin et al. (2010) assessed the incidence and remission of SRBD in children aged 6 to 17. This cross-sectional study involved screening 7055 children with sleep-related questionnaires, of whom 319 children completed two home polysomnograms approximately five years apart. Body mass index percentiles were also calculated with childhood growth charts from the Centers for Disease Control and Prevention, adjusted for sex and age. The mean age at assessment was 8.5 years at baseline and 13.7 years at follow-up, respectively. Incident SRDB was more common in boys (odds ratio [OR] = 3.93, P = .008). Children with prevalent SRDB were more likely to be boys (OR = 2.48, P = .006) and had a greater increase in body mass index percentile change (OR 1.01, P = .034). Children with prevalent SRDB also had 3.41 greater odds for development of obesity from baseline to follow-up. This study concluded that adolescent boys are more likely to have persistent and

incident SRDB than girls. Children with prevalent SRDB are more likely to develop obesity.

Hultcrantz et al. (1995) assessed the incidence of SRBD in a cohort of five hundred four-year-old children having their annual health check in Sweden. Parents were asked to fill in a questionnaire detailing their child's snoring, sleep apnoea, sucking habits and infections. Children with a history of snoring were further evaluated by sleep study, lateral cephalogram and dental casts. This study suggested that 6.2% snore every night by age four and another 18% when infected. Tonsillar infection is three times more common in the snorers and twice as many of their parents have undergone adenoidectomy ± tonsillectomy. The dental casts show a significant difference in width of the maxilla and length of the mandible.

Anuntasree et al. (2001) studied the prevalence of habitual snoring and its associations with tonsillar size, allergic rhinitis, obesity and parental smoking, as well as the prevalence of obstructive sleep apnoea (OSAS), in a sample of 1008 children aged six to thirteen years from seven randomly selected schools in Southern Thailand. 8.5% of the children were habitual snorers and the prevalence was same in boys and girls. Significant and independent association was present between snoring and allergic rhinitis, with an odds ratio of 5.27. The odds ratio was significantly increased to 2.65, 5.72 and 11.06 in children with tonsillar size of 2+, 3+, and 4+, respectively. This study concluded that the prevalence of OSAS among Thai schoolchildren was 7/1008 (0.69%). An association of snoring with tonsillar size and allergic rhinitis was demonstrated.

Brunetti et al. (2010) assessed the prevalence of sleep-related breathing disturbances in a

large cohort of school-aged and preschool-aged children in Southern Italy. This study was conducted in two phases: the first phase was a screening phase, which aimed to identify symptomatic children from a cohort of 1207 via a self-administered questionnaire, and the second was an instrumental phase for the definition of sleep related breathing disorders. In total, 1207 children were screened via a self-administered questionnaire and were classified into three groups based on their answers as non-snorers, occasional snorers or habitual snorers. All habitual snoring children underwent a polysomnographic home evaluation, and those with an oxygen desaturation index> 2 were considered for nocturnal polygraphic monitoring (NPM). Children with an apnoea/hypopnoea index > 3 received a diagnosis of obstructive sleep apnoea syndrome (OSAS). This study demonstrated that the prevalence of snoring in this cohort was 4.9% and OSAS was 1.8%.

Gislason and Benediktsdottir (1995) conducted a cross-sectional epidemiologic study on 555 children aged between six months and six years in a small town in Iceland. This study was conducted in two stages: first by questionnaires and second by overnight investigation of children symptomatic of sleep apnoea syndrome. Snoring was reported as occurring ‘often’ or ‘very often’ among fourteen children (3.2%) and ‘occasionally’ in seventy-three (16.7%). Apnoeic episodes were observed in seven children (1.6%). Kaditis and colleagues (2004) studied the prevalence and clinical factors associated with sleep-disordered breathing in 3680 children and adolescents attending schools in central Greece, who were surveyed using questionnaires distributed to parents. They found a similar prevalence of habitual snoring (present every night) among three different age groups (5.3%, 4%, and 3.8% in 1–6, 7–12, and 13–18 year-old subjects). Seventy randomly selected subjects among 307 snorers without adenoidectomy and/or tonsillectomy underwent polysomnography. The estimated

frequency of obstructive sleep apnoea-hypopnoea among children without adenoidectomy and/or tonsillectomy was 4.3%. Factors associated with snoring were: male gender (odds ratio 1.5 [1.2–1.9]); chronic rhinitis (2.1 [1.6–2.7]); snoring in father (1.5 [1.2–1.9]), mother (1.5 [1.1–2.0]), or siblings (1.7 [1.2–2.4]); adenoidectomy in mother (1.5 [1.0–2.2]); and passive smoking (1.4 [1.1–1.8].

From this review of the literature, it is clearly evident that the prevalence of SRBD is multifactorial. The prevalence is more common in boys and has a strong predilection in the Black and Hispanic race compared to Caucasians. High BMI has a linear relation with the severity of SRBD; similarly, the width of the maxilla and the length of the mandible also determine the severity of SRBD. The size of the tonsil may be the single strongest predicting factor to determine the severity of SRBD. There is a strong association between SRBD and chronic rhinitis, family history of snoring and exposure to cigarette smoke. Table 1 summarises the prevalence of SRBD from the literature.

Author	Study Design	Total No	Age-Range	Sex M;F	Diagnostic Methods	Prevalence
Bixler et al. (2009)	Cross sectional	5740(s) 700(m)	5-12	48.8:52.2	Polysomnography	Snoring-15.5% Mild SDB-25% Mod SDB-1.2%
Goodwin et al. (2010)	Cross sectional	7055(S) 319(m)	6-17	50.5:49.5	Polysomnography	Snoring 4% SDB-
Hultcrantz et al. al.1995)	Cohort	500(s) 325(m)	4-5		Questionnaire	Snoring-6.2% SDB-1.2%
Ali et al. (1993)	Cross-sectional	782	4-5		Questionnaires followed by pulse oximetry	SDB- 7%
Anuntaseree et al. (2001)	Cross-sectional	1142(s) 8(m)	6-13	50:50	Questionnaire followed by Polysomnography	Snoring-8.5% OSA-0.69%
Brunetti L et al. (2010)	Cross-sectional	1207(s) 8(m)	3-11	49:51	Questionnaire followed by Polysomnography	Snoring-4.9% OSA- 1.8%
Gislason et al. (1995))	Cross-sectional	454	.6-6	50.3:49.7	Questionnaire followed by Polysomnography	Snoring19.7% OSA-2.9%
Kaditis et al. (2004)	Cross-sectional	3680(s) 399(m)	2-18	58; 42	Questionnaire followed by Polysomnography	Snoring-34.5% OSA-4.3%

***Table 1**: Prevalence of SRBD by different diagnostic methods*

1.2. Aetiology and pathogenesis

Before discussing in detail the aetiology and pathogenesis of SRBD, it would be prudent to understand the sleep mechanism, as the entity SRBD involves breathing disorder occurring during sleep.

1.2.1 Sleep Physiology

According to the Macmillan Dictionary for Students, sleep is defined as a naturally recurring state characterized by reduced or absent consciousness, relatively suspended sensory activity and inactivity of nearly all voluntary muscles. In mammals and birds, sleep is divided into two broad types: rapid eye movement (REM) and non-rapid eye movement (NREM). A newborn infant spends about sixteen to eighteen hours asleep in a day, 60% of which is REM. This decreases to twelve to fifteen hours at one year and they spend about 30% of total sleep time in the REM stage. The function of the different stages of sleep is unclear, but REM sleep (the predominant state during foetal and early post-natal life) may be a basic activation programme for the central nervous system that increases the functional competence of neurons, circuits and complex patterns (Royal College of Paediatrics and Child Health Guidelines. 2009). The duration of the REM/NREM cycles also changes during sleep from around fifty minutes in early infancy to sixty minutes at six months and to the adult period of ninety minutes during late childhood to early adolescence (Azaz et al., 1992).

The NREM stage of sleep is further divided into four stages. Stage 1 is the lightest stage, and is rather a transitional stage where one drifts off and usually last for five to ten minutes, just enough to allow the body to slow down and muscles to relax. Stage 2 is still considered a light stage, where the brain activity slows down, the heart rate and breathing are regular

and eye movement decreases significantly. Stage 3 is a stage of deep sleep: the brain activity further slows down in this stage, breathing slows and muscle relaxes. Children sometimes wet the bed during this stage of sleep. Stage 4 is the deepest stage of sleep and is characterized by very slow brain waves.

The REM stage is characterized by rapid eye movements even though the eyes are closed, and breathing is rapid, irregular and shallow. The heart rate and blood pressure increase. Arm and leg muscles experience a type of paralysis that keeps people from acting out their dreams.

Obstructive sleep apnoea has been recognized to be more severe in the REM stage of sleep than in the NREM stage because of differences in ventilation patterns during the REM stage. During NREM sleep, breathing is regular, but the tidal volume and respiratory rate are decreased. This results in a decrease in minute ventilation and a decrease in the functional residual capacity. However, during REM sleep, apart from breathing being erratic, with variable respiratory rate and tidal volume, the tone of pharyngeal dilators will be greatly reduced to account for symptoms of OSA.

1.2.2 Definition of SRBD

Sleep related breathing disorder (SRBD) This term is used to describe a spectrum of respiratory disturbances that occur during sleep. The International Classification of Sleep Disorder (ICSD) is a primary diagnostic, epidemiological and coding resource for clinicians and researchers in the field of sleep and sleep medicine in its 2nd edition. ICSD-2 has defined two major categories of SBD: Central Sleep Apnoea Syndrome (CSAS) and Obstructive Sleep

Apnoea Syndrome (OSAS) (Thorphy et al., 2005). The fundamental difference between these two categories is the central respiratory (ventilator) drive. In CSAS, there is no central respiratory drive, but in OSAS there is central respiratory drive, but the chest wall does not ventilate due to upper airway obstruction, causing symptoms of sleep apnoea.

Obstructive sleep apnoea syndrome is often considered as a continuum from primary snoring to upper airway resistance syndrome (UARS) to full-blown Obstructive Sleep Apnoea Syndrome (OSAS).

Snoring- Snoring is noisy breathing caused by turbulent airflow through the upper airway without the sequel of obstructive apnoea, frequent arousals from sleep or disordered gas exchange (Marcus et al., 2002).

Upper airway resistance syndrome (UARS)- UARS was first described in 1992 and is defined as the combination of a clinical complaint of excessive daytime sleepiness with documentation of flow limitation and demonstration of increased respiratory efforts with arousal just following peak negative oesophageal pressure during inspiration (Guilleminault, 1993). One of the characteristic features of UARS, different from snoring, is that there is negative intrathoracic pressure as measured by oesophageal manometry.

Obstructive sleep apnoea syndrome- Obstructive sleep apnoea is defined as a disorder of breathing during sleep that is characterised by prolonged partial upper airway obstruction and/or intermittent complete obstruction that adversely affects ventilation during sleep and disrupts normal sleep patterns (Marcus et al., 2002).

Apnoea- Obstructive apnoea is the absence of oronasal airflow in the presence of continued respiratory effort. The significance of apnoea duration depends on background respiratory frequency (ranging from sixty beats per minute in a premature infant to a rate of twelve beats per minute in adolescents), hence a duration of two respiratory cycle times is a useful measure, which corrects for this (Carroll et al., 1995). The number of such apnoeic episodes per hour is termed the Apnoea Index.

Hypopnoea- is defined as reduction (either qualitative or quantitative) in airflow over two or more respiratory cycles, accompanied by a 3% or 4% fall in oxygen saturation and/or terminated by an arousal (Halbower et al., 2007). The number of such hypopnoeic episodes per hour is termed the Hypopnea Index.

Arousal Index- is a measure of sleep fragmentation and is defined as the number of arousal events occurring during sleep. Respiratory effort related arousals (RERAs) are specific to SRBD.

Apnoea Hypopnea Index (AHI) / Respiratory Disturbance Index (RDI)-The total number of apnoea/hypopnea divided by hours of sleep is termed as AHI or RDI.

1.2.3 Aetiology of SRBD

The causes of SRBD are multifactorial. As described by Marcus (2000), a combination of upper airway narrowing due to anatomical factors, abnormal upper airway tone and other factors such as genetic factors contribute to the spectrum of SRBD. However, the severity of

the spectrum of SRBD varies among individuals.

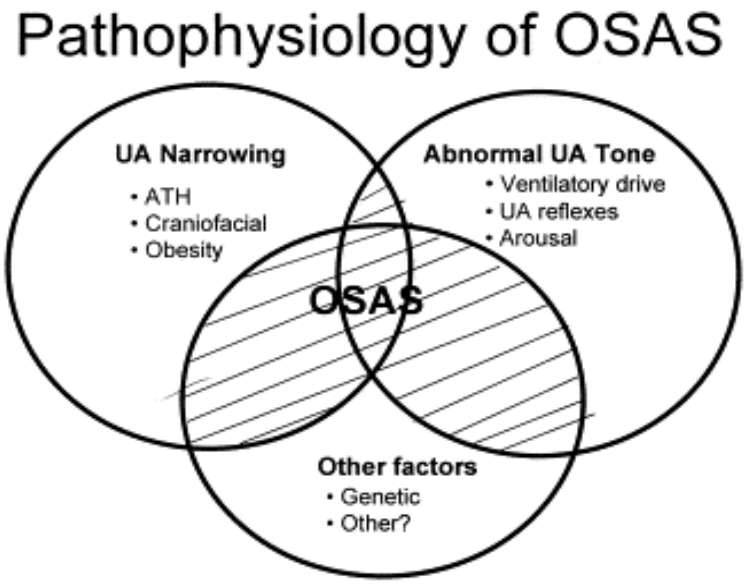

Figure 1: *Adapted from Carroll and Loughlin (1995) Childhood OSAS results from a combination of upper airway (UA) narrowing, abnormal upper airway neuromotor tone and other, poorly understood factors. (ATH- Adenotonsillar Hypertrophy, UA- Upper airway)*

Upper Airway Obstruction-

Upper airway obstruction could be due to obstruction to the airway from the nose to the epiglottis, as described below.

Nose	Deviated nasal septum (Lavie et al., 1982) Hypertrophied inferior turbinates Masses-benign/malignant Mucosal disease- Allergic rhinitis (Brouillette et al., 2001) Nares (Kramer et al., 2004)
Nasophaynx	Adenoid hypertrophy (Brooks et al., 1998) Chonal Atresia
Oropharynx	Tonsillar hypertrophy (Brooks et al., 1998) Macroglossia

	Retrognathia Micrognathia
Systemic iIlness	Cerebral palsy (Kotagal et al., 1994; Magardino et al., 1999) Myotonic dystrophies (Suresh et al., 2005) Obesity (Verhulst et al., 2008; Stepanski et al., 1999; Rosen et al., 1999; Carroll et al., 1995) Sickle cell disease (Samuels et al., 2007) Mucopolysaccharidoses (Mogayzel et al., 1998) Achondroplasia (Mogayzel et al., 1998)
Craniofacial Syndromes	Downs syndrome (Shott et al., 2006; Marcus et al., 1991) Pierre Robin syndrome (Buchenau et al., 2007) Crouzon syndrome (Gonsalez et al., 1998) Aperts syndrome (Gonsalez et al., 1998) Treacher Collins syndrome (Johnston et al., 1981)
Other	Genetic, Familial predisposition

***Table 2**: Etiological factors causing upper airway obstruction*

Role of nasal pathology in SRBD

Historically, even in the Hippocratic era, it was thought that the nose played a role in snoring and caused restless sleep. The nasal airway is the preferred route of respiration during both wakeful and sleep states and the nose is the first port of air entry: thus, the nose and various nasal pathologies can have a significant impact on collapsibility of different segments of the pharyngeal lumen (Olsen, 1991). Nasal congestion is one of the most important predisposing factors for OSAS (Papsidero, 1993). Nasal congestion can be due to structural abnormality in the nose, such as a deviated nasal septum, or mucosal disease

such as allergic rhinitis or NARES (non-allergic rhinitis with eosinophillic syndrome). Lavie et al. (1982) reported that twelve of the fourteen patients with excessive sleepiness and chronic fatigue who underwent septal corrective surgery had subjective improvement in the level of diurnal alertness and quality of nocturnal sleep.

Kramer et al. (2004) conducted a study on twenty-six patients presenting with symptoms of sleep apnoea . Ten of these patients also had symptoms of nasal obstruction and rhinorrhea and were diagnosed as having NARES. These ten NARES patients were compared with sixteen age- and BMI-matched individuals without any nasal inflammation. All the patients underwent overnight polysomnography and the investigators concluded that NARES patients had statistically significant ($p<.01$) impaired polysomnographic parameters compared with patients without any nasal inflammation.

Brouillette et al. (2001) conducted a randomised, triple-blinded, placebo controlled, parallel-group trial of nasal fluticasone propionate versus placebo in twenty-five children aged one to ten years with obstructive sleep apnoea proven on polysomnography and found that the mixed/obstructive apnoea/hypopnea index decreased in twelve of thirteen subjects treated with fluticasone versus six of twelve treated with placebo. They concluded that nasal fluticasone decreased the frequency of mixed and obstructive apnoeas and hypopnoeas, suggesting that topical corticosteroids may be helpful in ameliorating paediatric obstructive sleep apnoea.

From the above studies, it is evident that nasal pathology is an important factor in the aetiology of SRDB, and thorough nasal examination is a critical step in evaluating a patient

with SRBD. Simple measures like avoidance of allergens, treating patients with steroid nasal spray in allergic rhinitis or NARES syndrome and correction of any anatomical structural abnormality in the nose may relieve symptoms of SRBD.

Role of adenoid and tonsillar hypertrophy in SRBD

The anatomical location of the adenoid in the nasopharyngeal isthmus and palatine tonsil in the oropharyngeal isthmus plays an important role in the processing of inhaled and ingested antigens and immunity. Adenotonsillar hypertrophy is an undisputed major contributor to the development of SRBD. Anatomical impingement of the upper airway by enlarged upper airway lymphoid tissues will increase the pharyngeal resistance, and may ultimately result in episodic airway narrowing and collapse that characterize OSAS (Marcus, 2000; Marcus et al., 1994) .The prevalence of OSAS in children peaks at three to seven years of age parallel to the age of adenotonsillar enlargement. Not all children with adenotonsillar hypertrophy suffer from OSAS. Nevertheless, despite contribution from other factors like neuromuscular tone and genetic factors, the severity of OSAS has been associated, at least in part, with tonsillar and adenoidal size (Brooks et al., 1998).

In sedated young children (4.8 ± 2.1 yr; range, 1.9–9.3 yr), there was a positive linear correlation between the tonsil and adenoid volume and the AHI , but there was no such correlation with airway volume (Arens et al., 2001). In unsedated, older children (9.5 ± 1.2 yr; range, 7–12 yr), the tonsil cross-sectional area (CSA), soft palate CSA, oropharyngeal volume and ratio of the retropalatal airway to soft palate CSA were strongly correlated (tonsils and palate) or inversely correlated (ratio of retropalatal airway to soft palate) with the obstructive AHI (Fregosi et al., 2003). A correlation with apnoea severity was observed

with the younger children's combined adenotonsillar volume (Arens et al., 2001), but not with the older children's combined adenotonsillar CSA (Fregosi et al., 2003).

Yagi et al. (2009) assessed the morphological features in 141 patients diagnosed with OSAS, and found that the body mass index, narrowness of the fauces, neck circumference and tonsil size showed significant correlations with the apnoea-hypopnoea index. Brodsky et al. (1989) evaluated sixty children aged between three and eleven intraoperatively to determine variations in nasopharyngeal and orpharyngeal dimensions due to adenotonsillar hypertrophy in OSAS. A significantly larger oropharyngeal diameter was found in children with small non-obstructing tonsils ($p < 0.01$). Children with large non-obstructing tonsils had a similar oropharyngeal diameter to those with large obstructing tonsils. However, tonsil volume, not weight, was increased in the children with large obstructing tonsils as compared to those with large non-obstructing tonsils and small non-obstructing tonsils ($p < 0.04$). A shorter soft palate was associated with larger obstructing tonsils ($p < 0.004$). The length of the hard palate was similar in all patients; however, a trend towards a higher arched palate was seen in patients with larger, obstructing tonsils. The distance from soft palate to posterior pharyngeal wall was greater in obstructed patients with adenotonsillar hypertrophy ($p < 0.003$). In patients requiring adenoidectomy, the nasopharyngeal volume prior to adenoidectomy was significantly smaller in patients with obstructive symptoms ($p < 0.001$). Post-adenoidectomy, no significant difference was found in the nasopharynx volume amongst all subjects. These data indicate that subtle differences in oropharyngeal dimensions exist, which, along with increased lymphoid tissue volume, lead to the development of obstructive symptoms.

Greenfeld et al. (2003) conducted a study on twenty-nine children aged less than eighteen months, who were diagnosed with OSAS by polysomnography, and compared their pre- and post-adenotonsillectomy body weight and developmental assessment by parents. The authors concluded that there was significant weight gain, and improvement in clinical symptoms. Bhattacharjee et al. (2010) assessed the nocturnal polysomnograms of 578 children undergoing adenotonsillectomy for the diagnosis of OSAS at six paediatric sleep centres and found that adenotonsillectomy resulted in a significant AHI reduction from 18.6 to 4.1 /hour total sleep time.

From the above studies, it is clear that adenotonsillar hypertrophy, along with subtle changes in the pharyngeal dimensions, does play a important role in the aetiology of SRBD, and hence the practice guidelines established by the American Academy of Paediatricians recommends adenotonsillectomy as the first line of treatment for childhood OSAS (Marcus et al., 2002) .

Role of Systemic Illness in SRBD

A review of the literature suggests that systemic illness, as mentioned in Table 2, does have a role in the aetiology and pathogenesis of SRBD. There appears to be a clear link between obesity and SRBD in adults, but the association between body mass and SRDB severity amongst children is not straightforward.

Obesity is the presence of excess fat or adipose tissue. The International Obesity Task Force has defined cut-off points for overweight and obesity based on body mass index (BMI: the ratio of weight in kg to the square of height in m), corrected for age and gender (Bellizzi et

al., 1999), and recommended that paediatric growth charts be readily available. Amongst children, a BMI between the 85th and 95th percentile for age is considered overweight and a BMI at or above the 95th percentile is considered obese (McLennan, 2004).

Obesity may influence SRBD predominantly via mass exerted on upper airway structures and/or by the influences of excess adipose tissue on neuromotor physiology. Rosen et al. (1999) retrospectively evaluated the PSG data from 326 children who had been referred for evaluation of snoring and difficulty breathing during the night. Based on a BMI greater than the 95th percentile for age, or an ideal body weight greater than 120% of ideal body weight for height, 28% of the study population were obese. However, obesity did not increase the likelihood for OSAS diagnosis. The authors explain these results in terms of a referral bias based on the adult experience but acknowledge that the role of obesity in childhood SDB remains to be determined. Similarly, Carroll et al. (1995), in an evaluation of symptoms amongst eighty-three children referred for clinical evaluation of snoring and SDB, found that 26% of the total group were defined as obese (weight greater than the 95th percentile for age). However, there was no difference in the proportion of obese children when comparing those diagnosed with OSAS to those who demonstrated primary snoring only. Finally, Stepanski et al. (1999) found that 28% of 198 consecutive patients referred for overnight PSG (97% were specifically to rule out SRDB) were obese; however, the incidence of OSAS did not vary according to weight across the total group. A study reporting on liver function in 518 habitually snoring children showed that while 27% of patients were obese, and that severity of SRDB was greater amongst obese children, BMI z-scores were not different when comparing children later diagnosed with OSAS and those without OSAS (Kheirandish Gozal et al., 2008). Clearly therefore, the association between body mass and SRDB severity

amongst children is not straightforward, and other factors may influence the association.

Verhulst et al. (2008) reviewed some of the evidence for obesity being a significant risk factor for SRDB amongst children. In addition, they explored adenotonsillar hypertrophy as a modulator of this association and effectiveness of adenotonsillectomy in treating SRDB amongst obese children. Their conclusions are justified based on the evidence presented, which, to summarize, suggests that childhood obesity is linked with an increased prevalence of SRDB, and is often mediated by enlarged adenoids and/or tonsils. As such, adenotonsillectomy has been shown to be an effective primary treatment in the majority of cases. Kohler et al. (2008) performed a critical review to see whether there is a clear link between overweight/obesity and SRBD in children and suggested that a greater proportion of studies amongst older children demonstrate a significant association between obesity and SRDB severity compared to those amongst younger children. Developmental changes to neuromuscular control, body fat distribution and/or cephalometric changes may underlie this observation. They also found that significant associations between obesity and SRDB severity appear to be more prevalent amongst children of certain ethnicities, such as Africa American and possibly Asian. Irrespective of these potential moderators, adenotonsillar hypertrophy appears to be a critical consideration when considering SRDB and treatment efficacy amongst obese children compared to normal weight children.

Children with Sickle Cell disease (SCD) experience hypoxemia during wakefulness and sleep, and thus, low baseline values on oximetry or abnormal desaturation during sleep are not unexpected. In a prospective randomized study involving SCD patients (most of whom were referred for suspected SRBD), Samuels et al. (1992) reported that eighteen of fifty-three

subjects (36%) had OSAS; 16% had episodic hypoxemia (SaO2 ≤ 80%) and/or baseline SaO2 < 95.8%. After adenotonsillectomy, PSG was performed on fifteen of the eighteen patients with OSAS. All subjects demonstrated improvement in symptoms and a reduction or abolition of episodic hypoxemia.

Children with Cerebral Palsy (CP) are at high risk for developing OSA (Kotagal et al., 1994). The medulla oblongata is responsible for control of respiration and is also believed to coordinate contractions of the diaphragm and upper airway musculature to maintain a patent airway during inspiration. Asynchronous medullary neural output has been recorded in children with CP. This dysfunctional neuromuscular control is thought to contribute to the collapse of oropharyngeal tissues into the upper airway via the negative pressure generated by an inspiratory effort. Decreased tone of the pharyngeal musculature during sleep further contributes to this potential for upper airway collapse. Children with CP and spastic quadriplegia are unable to effectively move their body during sleep. Therefore they are less able to compensate for upper airway obstruction with repositioning than normal children (Kotagal et al., 1994). Increased oropharyngeal secretions, increased gastrooesophageal reflux and seizure disorders, all of which commonly affect children with CP, have all been shown to contribute to the development of OSA. Magardino et al. (1999) retrospectively reviewed twenty-seven children with cerebral palsy who underwent surgical treatment for obstructive sleep apnoea and recommended that tonsillectomy or adenoidectomy, or both, is indicated for initial surgical management of OSA in CP children if there is evidence of tonsillar and/or adenoidal hyperplasia. Post-operatively, these patients should be closely monitored in an ICU for upper airway obstruction. Aggressive medical management of gastro-oesophageal reflux and seizure disorders is essential to successful treatment of OSA.

With this medical and surgical approach, they found that 84% of their CP children with OSA avoided tracheotomy.

Many neuromuscular dystrophies are associated with SRBD, and respiratory abnormalities occur due to a variety of underlying factors, including primary weakness of the diaphragm and other muscles of respiration, bulbar weakness, restrictive lung disease, impaired central respiratory control, recurrent infection, impaired cough, malnutrition, and obesity (Gozal, 2000). Suresh et al. (2005) reported a bi-modal presentation of SRBD, with OSAS in the first decade of life, followed by sleep related hypoventilation in the second. Ten (31%) of thirty-two Duchenne Muscular Dystrophy patients referred for suspected SRBD had OSAS on overnight PSG (median age eight years, mean AHI 12, median nadir SpO2 87%). Fifteen (47%) were normal (median age ten years, median nadir SpO2 94%), and eleven (32%) had sleep related hypoventilation (median age thirteen years, mean AHI 13, median nadir SpO2 90%). Children or adolescents with mucopolysaccharidoses (MPS) are at risk for OSAS. Santamaria et al. (2007) compared overnight PSG, nasal endoscopy and upper airway CT scans in five children (median age 6.9 years) to six adults (median age twenty-five) with various types of MPS. They found OSAS (mean AI 10.4 and AHI 14.7) in all five children with MPS, but in only one adult (mean AI 2.3 and AHI 7.4). Nasal endoscopy demonstrated adenoidal hypertrophy in all subjects. Mogayzel et al. (1998) studied the prevalence of SRBD in eighty-eight children with achondroplasia, and found that 48% showed respiratory PSG abnormalities, including hypoxemia.

Role of Craniofacial Syndromes in SRBD

The role of craniofacial anatomy cannot be ignored in the aetiology of upper airway obstruction leading to SRBD. The patency of the airway depends on the bony framework and the soft tissue, and any abnormality of the bony framework in the presence or absence of soft tissue abnormality will have an impact on breathing by reducing the patency of the airway. A review of the literature suggests an increased incidence of SRBD in syndromes with abnormal craniofacial anatomy.

Down's Syndrome children are at significant risk for SRBD due to craniofacial anomalies such as midfacial hypoplasia and glossoptosis, as well as hypotonia, increased secretions, tracheal anomalies, obesity, and hypothyroidism. Marcus et al. (1991) reported that all of their overnight polysomnographic studies, performed in sixteen patients with Down's syndrome, were abnormal for the presence of OSAS in 63%, hypoventilation in 81% and oxygen desaturation in 56%. Shott et al. (2006) prospectively studied the incidence of OSAS in sixty-five children aged between two and four years with Down's syndrome using PSG, and also assessed the parents' ability to predict sleep abnormalities in this group of patients. The PSGs revealed that 57% of the children had abnormal results and evidence of obstructive sleep apnoea syndrome. Overall, 69% of parents reported no sleep problems in their children, but in this group, 54% of PSGs had abnormal results. The study concluded that because of the high incidence of obstructive sleep apnoea syndrome in young children with Down's syndrome, and the poor correlation between parental impressions of sleep problems and PSG results, baseline PSG is recommended in all children with Down's syndrome at age three to four years. This recommendation is in keeping with the guidelines of the Working Party on Sleep Physiology and Respiratory Control Disorders in Childhood, which recommends that Down's syndrome children with abnormal screening for SRBD

should have PSG, and if significant SRBD with hypoxia is noted, then appropriate treatment should be offered.

Children with *Pierre Robin syndrome* (PRS) and *Treacher Collin syndrome* usually have poorly formed jaws and tongues that fall back into the throat. These two features will cause upper airway obstruction and lead to SRBD (Johnston et al., 1981). Buchenau et al. (2007) performed cardiorespiratory studies in infants with Pierre Robin syndrome. The primary aim of this study was to evaluate the use of an intra-oral appliance, and thus only infants with an AHI ≥ 3 were included. However, the authors found that sixteen of twenty-one (76%) infants met this criterion. Data presented on eleven subjects who participated in the trial showed a mean AHI of 13.8, suggesting that infants with Pierre Robin sequence have mild-to-moderate OSAS.

Other craniofacial dysostosis syndromes, such as *Crouzon's* and *Apert*'s syndrome, are associated with high risk of SRBD (Gonsalez et al., 1998). The Working Party on Sleep Physiology and Respiratory Control Disorders in Childhood recommends that all children with syndromes involving mid facial hypoplasia or micrognathia should be evaluated for SRBD with a minimum assessment of oximetry, preferably with a measure of CO_2. This should be performed urgently if they have any clinical signs of airway obstruction and within the first four weeks of life in any event. Clinicians should be aware that infants with Pierre Robin syndrome may have worsening airway obstruction between four and eight weeks and ascertain whether symptoms worsen at this age. If so, repeat assessment should be carried out. Reassessment for SRBD in children with syndromes involving midfacial hypoplasia or micrognathia should occur at three- to six-monthly intervals in the first year of life, and

subsequently should be dictated by clinical symptoms and signs.

The role of genetics or familial predisposition in SRBD

Sleep-related breathing disorders are common in some races, including Africo- Americans and Hispanics, when compared to Caucasians. This could be because of associated factors like obesity, socioeconomic status or craniofacial abnormality. However, there is a possibility of familial predisposition, which could perhaps increase the risk of SRBD in some groups of children.

Descriptive reports of families with multiple affected members (Strohl et al., 1978) show that there could be a potential role of inheritance apart from familial influence. Another study (Gislason et al., 2002) calculated the estimated risk ratios for relatives of patients with OSA and found that they were increased. The risk ratio for first-degree relatives was 2.0 for parents and 1.9 for siblings. For second-degree relatives (half-siblings, uncles/ aunts, grandparents) the estimated risk ratios were 1.9, 1.3 and 1.3, respectively, with the first two being significant. The estimated risk ratio for cousins was 1.3, which was also statistically significant. From these studies, it is clear that familial predisposition does have a role to play in the aetiology of SRBD, but the exact gene responsible is still not clear. More research on the genetics of SRBD could pave the way for the role of gene therapy in the management of SRBD.

Abnormal upper airway tone

From the above discussion, it is clear that anatomical narrowing of the upper airway plays a role in the aetiology of SRBD. The collapse of the pharynx, either partial or complete, during OSA is not entirely due to anatomical narrowing of the upper airway, as OSA is not seen in every child with upper airway narrowing, and also most children with OSA can breathe normally and do not desaturate during the wakeful state. This could be due to activity of upper airway dilator muscles, which keep the airway patent during the wakeful state. There appear to be high levels of upper airway dilator muscle activity present during wakefulness in OSA patients (Mezzanotte et al., 1992), thereby compensating for the deficient anatomy. At sleep onset, upper airway dilator muscle activity is reduced in both OSA patients and controls (Fogel et al., 2005) and this likely contributes to airway collapse in patients with OSA and the increase in airway resistance observed in healthy individuals (Trinder, et al., 1994). One can conclude from the above that there appears to be an inverse relation between the level of activity of upper airway dilators and the collapsibility of the upper airway.

1.2.4 Pathophysiology

The upper airway, extending from the nasal chonae to the level of the epiglottis, lacks rigid bony support and hence is a collapsible segment. It serves many functions, including swallowing, speaking and breathing. During the inspiratory phase of breathing, negative pressure is generated in the upper airway, due to activation of the diaphragm and intercostal muscles. Under normal circumstances, this negative pressure is compensated by the activity of pharyngeal dilator muscles, preventing this segment from collapsing (Remmers et al., 1978). Narrowing of the upper airway due to anatomical obstruction, as discussed in the section on aetiology, will increase the upper airway resistance. To maintain

adequate airflow through a narrow lumen, the patient must increase respiratory effort. Because of the Bernoulli effect, there will be further increase in intraluminal negative pressure, forcing the compliant upper airway to collapse and leading to the cessation of airflow.

As in adults (Smith et al., 1998), the upper airway in children has been shown to behave in accordance with the Starling resistor model, when a collapsible pharyngeal segment is situated between two non-collapsible segments with fixed diameters, resistance and pressures (nasal and tracheal), as described in Figure 2:

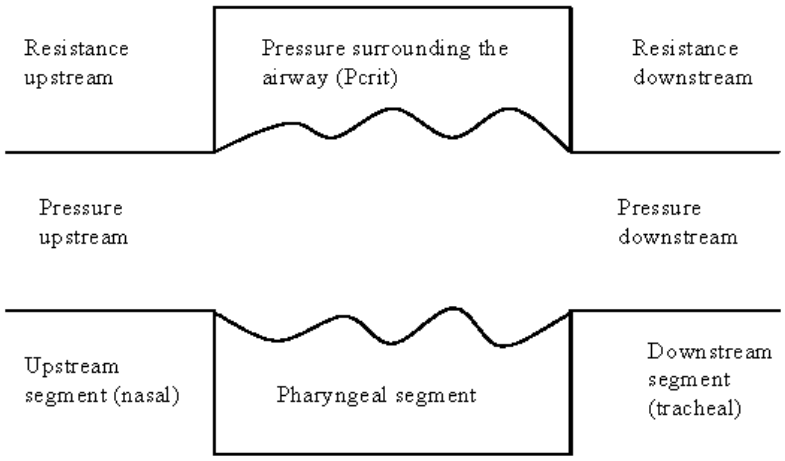

Figure 2*: Adapted from Marcus et al. (1994) The Starling resistor model of the upper airway. The airway is represented by a tube with a collapsible segment (pharynx) between two rigid segments with fixed diameters, resistances and pressures (nasal and tracheal segments). The airway collapses when the pressure surrounding the airway becomes greater than the pressure within the airway.*

In this model of the upper airway, inflow pressure at the airway opening (the nares) is atmospheric and downstream pressure is equal to tracheal pressure (diaphragm). Collapse would occur when the pressure surrounding the collapsible segment of the upper airway

(critical pressure or Pcrit) becomes greater than the pressure within the collapsible segment of the airway. Pcrit reflects upper airway neuromuscular control as well as anatomical factors, as discussed in Table 1.

Marcus et al. (1994) determined the Pcrit in OSA children by correlating the maximal inspiratory airflow with the level of positive or negative nasal pressure applied via a nasal mask. They found that the maximal inspiratory airflow varied in proportion to upstream (nasal) rather than downstream (tracheal) pressure changes. Pcrit was 1 +/- 3 cmH_2O in OSAS compared with -20 +/- 9 cmH_2O in primary snorers ($P< 0.002$). Three of these OSAS patients were further re-evaluated after tonsillectomy and adenoidectomy and Pcrit was found to have declined to -7.2 +/-4.0 cmH_2O. Children with OSA have a higher Pcrit than do the control subjects (Marcus et al., 2005) and children with habitual snoring (Marcus et al., 2005). However, the Pcrit in patients with OSA after adenotonsillectomy did not decrease to the level in control subjects (Marcus, CL et al.1994) or even primary snorers (Marcus et al., 2005), suggesting that subtle abnormalities of anatomy or neuromuscular control remain after treatment.

Gozal et al. (2004) measured the upper airway collapsibility (UAC) using acoustic pharyngometry before and after application of topical 1% cetacaine spray. The UAC was examined in twenty-seven control children and twenty-seven children with known SDB. The groups were matched for age, sex and ethnicity. Mean cross-sectional area (CSA) was 1.88 +/- 0.27 cm^2 in control children and 1.67 +/- 0.28 cm^2 in patients with SRDB ($p < 0.01$). Similarly, the minimal CSA was 1.03 +/-0.17 cm^2 in control children and 0.95 +/- 0.18 cm^2 in patients with SRDB, respectively, ($p < 0.04$). Mean UAC in control children was -5.3 +/-1.9%

compared with -40.7 +/- 1.6% in SDB ($p < 0.0001$). This study shows that the upper airway is smaller, and UAC is markedly and significantly greater, in children with SDB.

From both the above studies, it is clear that there is greater upper airway resistance in OSA patients than in the normal population, and that the upper airway is smaller and more collapsible than normal. Despite these changes, the upper airway muscles that are phasically activated during inspiration increase both the luminal size and the stiffness of the airway. It is only during the rapid eye movement stage of sleep that phasic muscle activity of the oropharyngeal dilator muscles may be significantly depressed. Diaphragmatic activation continues to generate negative oropharyngeal pressures, but the tone of the upper airway tissues is reduced, leading to increased upper airway resistance and partial or complete airway obstruction during inspiration. Anatomical obstruction and decreased muscle tone causes cessation of airflow, which leads to physiologic changes including acidosis, hypercapnia and hypoxemia. Once sufficient changes in the partial pressure of oxygen (PO_2), the partial pressure of carbon dioxide (PCO_2) and pH occur, central and peripheral chemoreceptors and baroreceptors are stimulated to cause arousal and awakening from sleep, which may occur many times in a night. Therefore, the quality of sleep, both physiologic and psychological restful sleep, is markedly disturbed, which may lead to behavioural changes such as hypersomnolence, hyperactivity and learning difficulties (Bradley et al., 1985).

Pharyngeal dilator muscles, including the genioglossus, hyoglossus and styloglossus, help in maintaining the patency of the upper airway lumen, but genioglossus muscle function has been studied extensively and measured by Elecromyography (EMG gg). The main function of

genioglossus is forward and outward movement of the tongue, thereby increasing the orophayrngeal dimension. Both tonic and phasic inspiratory activity of genioglossal activity have been noted in children (Kartz et al., 2003). When children are in a wakeful state, the EMGgg is greater in the OSA group than in the control group (Kartz et al., 2003). This could be due to an increase in upper airway resistance, in turn increasing the negative airway pressure, which would activate the reflex mechanoreceptors. Application of topical anaesthesia acts on these mechanoreceptors and decreases airway size in patients with OSA (Gozal et al., 2004).

With the onset of sleep, the EMGgg decreases in both normal and OSA patients (Kartz et al., 2003). This suggests that the central respiratory drive and/or neuromuscular compensatory mechanisms are diminished during the transition to sleep. The reduction in muscular activity results in increased airway resistance and collapsibility, as shown in the flowchart below.

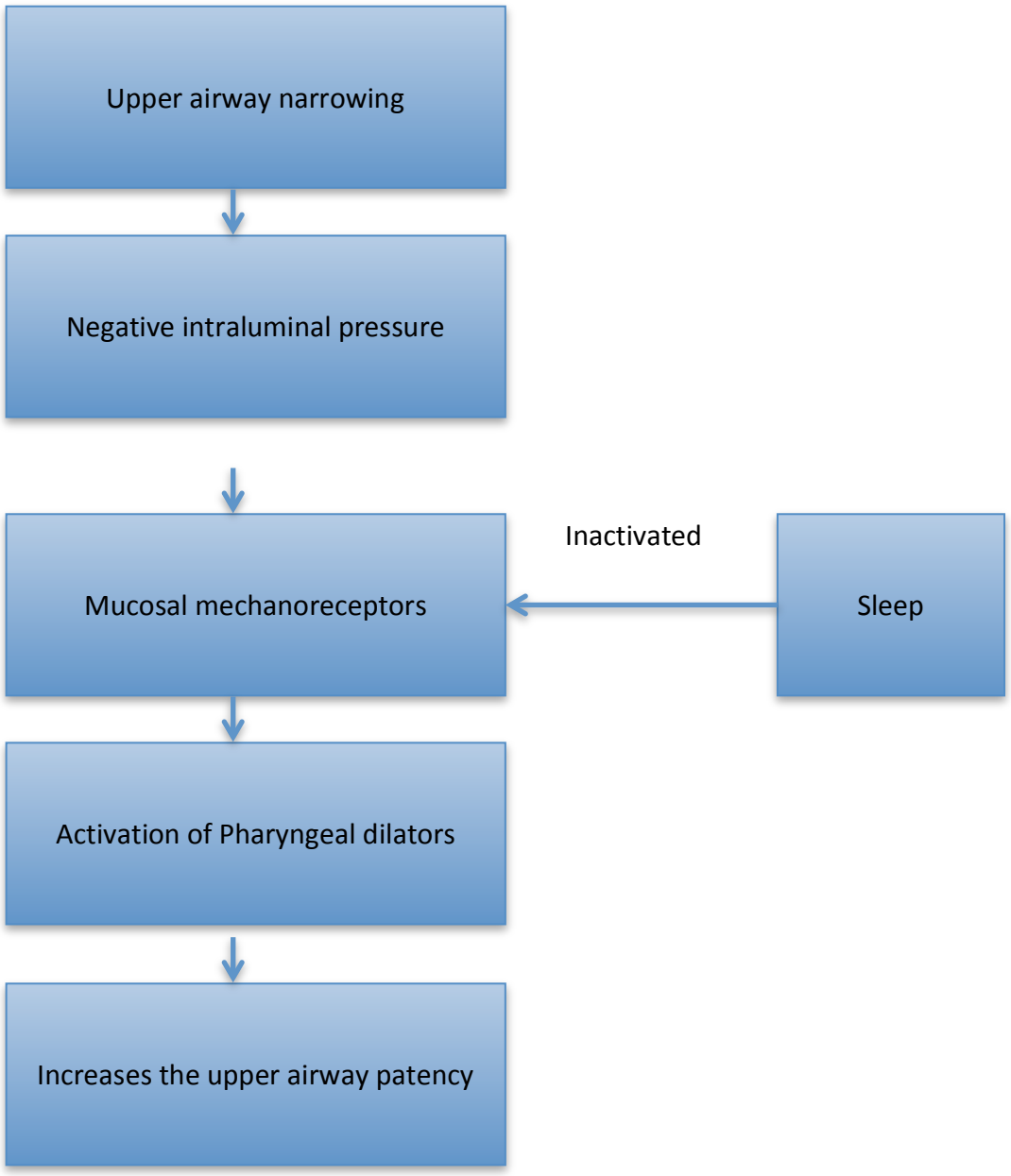

***Figure* 3** *The sequence of events in an OSA patient. Upper airway narrowing will increase the negative luminal pressure, which will activate the mucosal mechanoreceptors to increase the function of the upper airway dilators to maintain the upper airway patency. However, sleep will inactivate the function of the mucosal mechanoreceptors, leading to the collapse of the upper airway.*

In normal children, EMGgg remains below the wakeful baseline during stable Stage 2 and Stage 4 sleep, suggesting that additional neuromuscular activity is not necessary with a

mechanically stable airway (Katz et al., 2004). However, most children with severe OSA have a rebound increase in EMGgg activity during Stage 2 sleep, consistent with a reflex driven by mechano- and/or chemoreceptors (Katz et al., 2004). There is a significant correlation between OSA severity (i.e. AHI) and EMGgg activity in all sleep stages. Finally, applying continuous positive airway pressure to patients with OSA during sleep results in a reduction in the EMGgg coincident with reductions in respiratory effort and PCO2 (Katz et al., 2004).

As a consequence of the collapse of this upper airway, minute ventilation decreases, and to maintain adequate ventilation there is a compensatory increase in respiratory effort. In the initial stage of sleep, this can be compensated by the stimulation of mucosal mechanoreceptors causing an increase in upper airway patency, thus increasing the minute ventilation, and OSA patients can escape episodes of hypopnoea or apnoea. During the REM stage of sleep, in the absence of the activity of mucosal mechanoreceptors, this protective mechanism to maintain the patency of the upper airway is lost and minute ventilation decreases and induces a compensatory increase in the respiratory rate: this results in physiological responses like hypercapnia and hypoxemia. Once sufficient changes in partial pressure of oxygen (PO_2), partial pressure of carbon dioxide (PCO_2) and pH occur, central and peripheral chemoreceptors and baroreceptors are stimulated to cause arousal and awakening from sleep.

Arousal from sleep immediately opens the airway and normalizes gas exchange abnormalities. The principal stimulus for arousal appears to be respiratory effort and hypercapnia, whereas hypoxemia is a poor arousing stimulus. Increased respiratory effort alone may induce subtle frequency changes in the surface EEG (Lopes et al., 2006). Arousal

from sleep increases the gain of central chemoreceptors and augments neuromuscular activation of the upper airway, thereby decreasing airway resistance. But frequent arousal results in fragmentation of the sleep cycle and disturbed sleep.

To summarise, apart from anatomical narrowing, neuromuscular tone plays a important role in the pathogenesis of OSA. To overcome resistance in the upper airway, mucosal mechanoreceptors are stimulated during the wakeful state and in non-REM stages; however, this protective mechanism is not fully functional during the REM stage, resulting in obstructive events.

1.3 Signs and Symptoms of SRBD in Children

A thorough history of symptoms is the key to diagnosing SRBD in children. It is not physically possible to subject every suspected SRBD child to overnight objective investigation and most clinicians rely on history from parents before deciding on treatment options. Children will not be aware of symptoms, as these obstructive events occur during sleep and parents in the developed countries do not share the same bedroom with their children and hence may not give a detailed sequence of obstructive events. Often these children manifest with different signs and symptoms, corresponding to their developmental stage, underling aetiology and severity. The three most predictive symptoms are loud snoring, difficulty breathing during sleep and sleep-related pauses in breathing witnessed by the parents (Brouillette et al., 1984). Brouillette et al. (1984) assessed the frequency of signs and symptoms using a postal survey with a standard questionnaire to parents of twenty-three children who were diagnosed with OSA and forty-three age- and sex-matched controls, as detailed in the table below.

Signs and symptoms	Frequency OSAS Patients (%)	Frequency in Controls (%)
Difficulty breathing while asleep	96	2
Snoring	96	9
Stops breathing during sleep	78	5
Restless sleep	78	23
Chronic rhinorrhea	61	11
Mouth breathes when awake	87	18
Frequent upper respiratory infections	83	28
Frequent vomiting/ nausea	30	2
Difficulty swallowing	26	2
Sweating when asleep	50	16
Hearing problems	13	0
Excessive daytime somnolence	33	9
Poor appetite	30	9
Recurrent middle ear disease	43	17
Pathological shyness Social withdrawal	22	5

Table 3: *Adapted from Brouillette et al.'s (1984) study on the frequency of signs and symptoms in OSAS patients compared with controls*.

From the above study, it is clear that difficulty breathing while asleep, snoring, restless sleep and stopping breathing during sleep dominate the nocturnal symptoms in OSAS patients. As

an effect of sleep fragmentation and sleep disturbance, children with SRBD will also manifest with daytime symptoms, as outlined in the table below.

Nocturnal symptoms	Loud habitual snoring Difficulty breathing when asleep Apnoeic pauses Restless sleep Sweating Dry mouth Abnormal sleeping position Enuresis Night terrors/sleep walking Bruxism/teeth grinding
Daytime symptoms	Mouth breathing Morning headache Difficulty in waking up Mood changes Poor attention span/academic problems Increased nap/daytime sleepiness Chronic nasal congestion/rhinorrhea Frequent upper respiratory tract infections Difficulty in swallowing/poor appetite Hearing problems

Table 4*: Adapted from Au et al. (2009) Symptoms of childhood obstructive sleep apnoea.*

Almost all children with OSAS snore and have increased effort while breathing (Brouillette et al., 1984; Carroll et al., 1995). Parents often complain of difficulty breathing when asleep, apnoeic pauses, restless sleep and sweating (Brouillette et al., 1984).

Nocturnal enuresis was reported in 8-47% of children with OSAS (Hoban et al., 2009). Weider et al. (1991) reported a 77% reduction in the number of enuretic nights each week five months after adenotonsillectomy for OSA. Basha et al. (2005) described 61% resolution and 23% decrease in enuresis events following adenotonsillectomy in children with OSA. Normally spontaneous resolution of nocturnal enuresis occurs at a relatively regular and steady state throughout middle childhood, as the underlying cause is thought to be delayed maturation of the bladder mechanism, or of portions of central nervous system. The proposed mechanism for enuresis in children with OSA is secondary to increased negative intrathoracic pressure as a result of increased inspiratory effort during sleep. The continual swing in intrathoracic pressure causes cardiac distention, which can lead to the release of atrial natriuretic peptide, triggering enuresis. There is a positive correlation between plasma ANP levels and the degree of change in intra-thoracic pressure (Krieger et al., 1991; Gozal et al., 2001). Therefore, it can be assumed that by treating OSAS, there might eventually be a reduced atrial volume, which could reduce secretion of ANP, which in turn could decrease nocturnal urinary output.

Daytime symptoms like mouth breathing, morning headache, difficulty in waking up and increased naptime are common in children with SRBD. Excessive daytime sleepiness (EDS) is one of the most common findings in adult OSA patients. But studies have shown that EDS is not a major feature in children with OSA as assessed by parental questionnaire (Carroll et al., 1995), and objective tools like the multiple sleep latency test (Gozal et al., 2001). This does not mean that OSA children will have undisturbed sleep, but they will have fewer arousals, as demonstrated by fewer EEG arousals, compared to the adults, hence maintaining their sleep architecture (Marcus et al., 1994).

As a sequel to increased intra-thoracic pressure and disturbed sleep, children with OSA will develop reversible cardiopulmonary and neurocognitive behaviour changes. Severe untreated OSAS can lead to pulmonary hypertension and corpulmonale (Brouillette et al., 1982; Guilleminault et al., 1981). Recurrent hypoxia secondary to obstructive events in OSA will lead to pulmonary vasoconstriction, thereby increasing the pulmonary arterial pressure and pulmonary hypertension. Prolonged hypertension will result in cor pulmonale. Reversible cor pulmonale has been reported in severely affected OSA children (Luke, 1965; Sofer, 1988). Marcus et al. (1998) suggested that children with OSA had higher diastolic blood pressure during wakefulness and sleep compared with primary snorers. Kirk et al. (1998) reported the presence of diurnal systemic hypertension in 10% of 50 children with OSA. Kohyama et al. (2003) showed that children with OSA had higher diastolic blood pressure, which correlated with the AHI. However, Amin et al. (2004) found lower diastolic pressure among children with OSA during wakefulness and Kaunzman et al. (1991) were unable to show any abnormalities in diastolic or systolic arterial pressures in twenty-two children with OSA. These inconsistent findings of blood pressure in OSA children may be due to small sample size and lack of healthy controls.

Amin et al. (2004) investigated the heart size of twenty-eight patients, nine of whom had OSA and primary snoring, and found that the left ventricular mass index and wall thickness were greater in children with OSA. Those with an AHI of 10 or more had a right and left ventricular mass greater than the ninety-fifth percentile. From the above studies, it is clear that as a sequel of OSA, cardiopulmonary changes like pulmonary hypertension and cor pulmonale also occur in children. However, because of limited sample size and lack of

controls, further studies need to be done in children as well as in adults to evaluate the cardiopulmonary changes and their effect on quality of life.

Failure to thrive is one of the common features in OSA children. The pathogenesis associated with failure to thrive in children with OSA is likely to be a combination of various mechanisms that include increased resting energy expenditure due to increased effort of breathing during resting period, difficulty in swallowing secondary to enlarged tonsils, and abnormal release of growth-related hormones (Li et al., 2003). Caloric intake and sleeping energy expenditure, in addition to anthropomorphic measurements, were taken before and after adenotonsillectomy in fourteen children confirmed to have OSA. Average sleeping energy expenditure decreased and the mean weight z-score increased after surgery without any change in caloric intake (Li et al., 2003). Statistically significant increases in weight and insulin-like growth factor-I levels were found in a group of children with OSA after adenotonsillectomy (Bar et al., 1999). Fortunately, we are seeing less of this complication as parents are becoming more aware of this condition and seeking medical intervention early.

In 1899, a reference was made by Hill (1899) in the British Medical Journal: “The stupid lazy child who frequently suffers from headaches at school, breathes through his mouth instead of his nose, snores and is restless at night, and wakes up with a dry mouth in the morning, is well worthy of the solicitous attention of the school medical officer”. This describes the unfortunate sequelae resulting from lack of recognition and treatment of OSA in children. Since then, schooling problems have been repeatedly reported in children with SRBD (Ali et al., 1993; Chervin et al., 1997) and may underlie more extensive behavioural disturbances, such as restlessness, aggressive behaviour, hyperactivity and poor test performance. With

the use of parental reports, a few studies have documented behavioural disturbance in children with OSAS that resolve after adenotonsillectomy (Stradling et al., 1990; Ali et al., 1996). Ali et al. (1996) found, in twelve children with OSAS, that there was a significant reduction in inattention, aggression and hyperactivity after treatment with adenotonsillectomy, as assessed using a parent rating scale. Owens et al. (2000) found behavioural problems and mild deficits in executive functioning, attention and motor skills in a small group of children with mild to moderate OSAS that improved after adenotonsillectomy. O'Brien et al. (2004) evaluated a large cohort of 1st graders in the lowest 10th percentile of their class and found that there was increased incidence of snoring and nocturnal gas exchange abnormalities in 297 children, and there was a significant improvement in school grade following adenotonsillectomy. The findings from the above study suggest that there is a relationship between SRBD and neurocognitive deficit, but further research is needed to establish whether this is a causal relationship.

There is strong evidence to suggest an association between SRBD and attention deficit hyperactivity disorder (ADHD) in children. It is estimated that up to 30% of children with SRBD have inattention and hyperactivity (Chervin et al., 2003). Up to one third of children with frequent, loud snoring will display significant hyperactivity and inattention (Ali et al., 1996), while the reciprocal also appears to be true that the ADHD children exhibit more sleep disturbance when compared to normal children (Ball et al., 1997). The ADHD symptoms that these children exhibit may not be true ADHD, but rather a lack of behavioural inhibition secondary to repeated sleep arousals and intermittent hypoxic episodes that affect working memory, motor control and self-regulation of motivation (Chervin et al., 2003). Most of the studies on ADHD children have relied on parental

reporting rather than objective assessment like behaviour, depression or impaired school performance. To summarize, studies suggest that SRBD does have a role to play in neurocognitive deficit, and there is a relationship between ADHD and SRBD, but more studies involving objective assessment tools rather than parental questionnaires, as used in these studies, need to be done to further prove the relationship.

1.4: Diagnosis

Polysonmography (PSG) is the gold standard investigation to diagnose and quantify SRBD (Rembold et al., 2004; Schechter et al., 2002). Though PSG provides objective information about sleep architecture, cardiac, respiratory and gas exchange, it is inconvenient for both parent and child, as they have to spend a night in a sleep laboratory. Furthermore, PSG is a labour-intensive and onerous method for diagnosing SRBD, and limited availability of sleep laboratories and expertise, forced clinicians to limit the use of PSG in diagnosing SRBD. Thus the diagnosis is still made on a clinical basis without any objective evidence. The different methods used in diagnosing SRBD are discussed below.

1.4.1 Parent reported symptoms:

Clinicians depend on parental reported symptoms that are indicative of OSA (snoring, witnessed apnoea, laboured breathing and restless sleep). Certal et al. (2012) performed a systematic review to assess the evidence for diagnostic accuracy of individual or combined clinical symptoms and signs in predicting paediatric OSA and concluded that neither single nor combined symptoms and signs have satisfactory performance in predicting paediatric OSA. A review of the literature on parental reported symptom and their accuracy in detecting the OSA is detailed in the tables below.

Symptom: Snoring

Study	N	TP	TN	FP	FN	Sensitivity	Specificity
Carroll et al. (1995)	83	30	19	29	5	0.86	0.40
Chau et al. (2003)	62	20	30	10	2	0.91	0.75
Xu et al. (2006)	50	30	5	14	1	0.97	0.26
Leach et al. (1992)	93	32	12	32	8	0.76	0.27

Symptom: Excessive daytime sleepiness (EDS)

Study	N	TP	TN	FP	FN	Sensitivity	Specificity
Carroll et al. (1995)	83	3	40	8	32	0.09	0.83
Xu et al. (2006)	50	14	11	8	17	0.45	0.58
Leach et al. 1992)	93	6	38	6	28	0.18	0.86

Symptom: Difficulty in breathing

Study	N	TP	TN	FP	FN	Sensitivity	Specificity
Carroll et al. (1995)	83	31	20	28	4	0.89	0.42
Chau et al. (.2003)	62	15	31	8	7	0.68	0.79
Xu et al. (2006)	50	7	18	1	24	0.23	0.95
Leach et al. (1992)	93	4	39	5	30	0.12	0.89

Symptom: Observed apnoea

Study	N	TP	TN	FP	FN	Sensitivity	Specificity
Carroll et al. (1995)	83	26	26	22	9	0.74	0.54
Chau et al. (2003)	62	12	36	4	10	0.55	0.90
Xu et al. (2006)	50	11	18	1	18	0.35	0.95
Leach et al. (1992)	93	16	21	23	18	0.47	0.48

Table 5*: Diagnostic accuracy of clinical symptoms and signs of each study adapted from (Cetral et al., 2012) with slight modification. N=total number; TP=true positive; TN=true negative; FP=false positive; FN=false negative.*

In the above studies, common parental reported symptoms were compared with the PSG findings for OSA. In line with the recommendations of the American Association of Sleep Medicine (AASM), AHI >1 on PSG was considered as criteria for the diagnosis of OSA in these studies. Snoring reported by parents had high sensitivity in these studies. In contrast, EDS, difficulty in breathing and observed apnoea had relatively high specificity. For a disease entity, if the sensitivity of a test is high, then a negative result can be used to rule out the disease. Thus the absence of snoring may be useful to exclude the diagnosis of OSA. However, the lower specificity for snoring may lead to a false diagnosis of OSA. Similarly, if specificity is high, as in EDS, difficulty in breathing and observed apnoea for OSA, then a positive result can be used to confirm the diagnosis of OSA.

In a systematic review of clinical assessment of paediatric obstructive sleep apnoea, Certal et al. (2003) concluded that there is a need for a more reliable non-invasive diagnostic tool to diagnose this condition, as neither single nor combined symptoms and signs have satisfactory performance in predicting paediatric OSA.

1.4.2 Questionnaires

Sleep questionnaires like the Epworth Sleepiness Scale (ESS) and the Snoring Symptoms Inventory (SSI) are often used in screening the adult population for SRBD. These questionnaires are relatively cost effective, easy to use and suitable for longitudinal assessment of treatment effects. The optimal role of these questionnaire-based sleepiness assessments has been a subject of debate. For example, ESS> 10 demonstrated poor sensitivity and specificity as a predictor of reduced mean sleep latency (Chervin, 2000).

Neither the ESS nor the SSI is well suited or validated for use in children to screen for OSA. A review of the literature revealed many such questionnaires used to screen OSA in children. One of the first sleep questionnaires used to screen children was proposed by Brouillette and colleagues (Brouillette et al., 1984), who suggested that the OSA could be determined by a questionnaire score and only children who received an intermediate score would need further evaluation with overnight PSG. The sensitivity and specificity of these questionnaires were 35% and 39% respectively. This questionnaire was used by other investigators who found similar results, and hence is no longer being used.

Owens and colleagues (Owens et al., 2000) developed the children's sleep habit questionnaire (CSHQ) for use in school-aged children between four and ten years of age.

This CSHQ is a retrospective, 35-item parent reported questionnaire designed to access behaviour and a number of key scale domains. It includes the major presenting clinical sleep complaints in this age group, like bedtime resistance, sleep onset delay, sleep duration, anxiety around sleep, behaviour occurring during sleep, night walking, sleep disordered breathing, parasomnia and daytime sleepiness. Parents are asked to recall sleep behaviour occurring over a typical recent week. Item are rated on a three-point scale as *usually*- if the sleep behaviour occurred five to seven times in a week, *sometimes*- if the sleep behaviour occurred two to four times in a week, and *rarely*- for zero to one time in a week. Reliability and validity data have been collected on a sample of 495 elementary school children and a clinical sample from a paediatric sleep clinic. The CSHQ has a sensitivity of 80% and specificity of 72%.

A paediatric sleep questionnaire was developed by Chervin et al. (2000) to investigate the presence of childhood SRBD with snoring, excessive daytime sleepiness and inattentive/hyperactive behaviour in children aged two to eighteen years. Validity was established by comparison to objective criteria - PSG defined obstructive SRBD, and by demonstrating that the questionnaire scale had substantial ability to predict diagnostic classification. This is a parent-filled questionnaire to assess SRBD among this age group; the screening questions are focused on snoring, excessive daytime sleepiness and behaviour changes. There are sixty-nine items in total, with twenty-two items for SRBD score. This questionnaire showed that the snoring scores were associated with higher levels of inattention and hyperactivity in children at a child psychiatry clinic, which suggests that SRBD could be a cause of inattention and hyperactivity in some children. The sensitivity and specificity of this questionnaire are 85% and 87% respectively for the diagnosis of SRBD.

1.4.3 Sleep Diaries

A sleep diary is a self-report measure to quantify a child's sleep pattern. It requires parents or caregivers to document the time child went to sleep and woke up, any daytime naps along with any interventions to help the child fall back to sleep. A typical sleep dairy involves recording of the child's sleep pattern for two weeks (Moriwaki et al., 2009). This diary will provide important information about inadequate sleep hygiene, insomnia, frequent brief awakening spells or information on EDS. Sleep diaries are often used in conjunction with other techniques such as actigraphy.

1.4.4 Radiology

SRBD is a dynamic process occurring during sleep, so static films have a very limited role in diagnosing SRBD. Lateral soft tissue radiography of the neck when the child is awake may give an indication of the upper airway anatomy, but it may not predict the presence or severity of obstruction contributing to symptoms of SRBD. Furthermore, it may not be justified to expose the child to the effects of radiation in diagnosis or to use as a screening tool for SRBD.

On the other hand, non-ionizing radiation like MRI has been used extensively in adults. Moriwakia et al. (2009) evaluated dynamic changes in the pharyngeal airway of thirty-one adult patients with OSAS by using ultrafast dynamic MRI scanning and concluded that velopharynx is the commonest site for obstruction. Donnelly (2005) has reviewed the indication of cine MR sleep studies in paediatric OSA and concluded that cine MRI is helpful in depicting both anatomical causes of OSA and dynamic abnormalities that lead to functional collapse in the airway. The only disadvantage of using a dynamic cine MRI is

sedation of the child to induce sleep. Some argue that induced sleep using sedatives may not be the same as natural sleep: although this is true, the muscle tone would be decreased in both natural and induced sleep and the pathophysiology of OSA is a decrease in muscular tone, which is being measured in the cine MRI.

The process of cine MR imaging is similar to ordinary MR, but for the sedation of the child; once asleep, the child is placed in an appropriate size head and neck vascular coil. With this coil, the supraglottic airway from the nasopharynx can be imaged with the patient's cervical spine being in a neutral position. Cine MR sequences are performed in the midline sagittal, as well as the transverse plane at the level of the middle portion of the tongue. These images are then displayed in a cine format to create a real-time movie of airway motion.

1.4.5 Audiotaping

Overnight audiotaping has been used to assess the presence of snoring or apnoea episodes during sleep, but it has not been possible to reliably distinguish simple snoring from snoring associated with sleep apnoea. Lamm et al. (1999) studied thirty-six children with PSG confirmed OSAS, by audiotaping their sleep, and found that audiotaping was 71% sensitive and 80% specific in diagnosing OSAS. The authors concluded that if an abnormality in the sleeping pattern is detected on audiotaping, it may need to be further evaluated to assess the presence of sleep apnoea; however, if no abnormality is detected on audiotaping, then the child may not have SRBD.

1.4.6 Overnight Oximetry

The diagnostic value of pulse oximetry in OSA is controversial. Pulse oximetry is a non-

invasive method to measure oxygen desaturation. It would have a greater role in the diagnosis of OSA if all obstructive events were associated with oxygen desaturations. Because an obstructed event may not necessarily be associated with oxygen desaturation, a normal oximetry study may be mistaken for absence of OSA. The second controversy in the use of pulse oximetry as a screening tool is the number of desaturation events and the level of desaturation to diagnose OSA.

Nixon et al. (2005), in their three-phase study, developed and validated a severity scoring system for overnight oximetry. In phase 1, a severity score was developed by review of preoperative overnight oximetry in children who had urgent adenotonsillectomy in 1999–2000. In phase 2, the score was validated retrospectively in 155 children who had PSG before adenotonsillectomy in 1992–1998. In phase 3, a twelve-month prospective evaluation of a protocol based on the score was conducted. In phase 1, a 4-level severity score was developed on the basis of number and depth of desaturation events (normal to severely abnormal, categories 1–4). In phase 2, the McGill oximetry score correlated with severity of OSA by PSG criteria. In phase 3, a clinical management protocol was developed based on the score. From this three-phase study they devised the McGill Oximetry Scoring System, as shown in the table below.

Oximetry Score	Comment	No. of Drops in SaO2 90%	No. of Drops in SaO2 85%	No. of Drops in SaO2 80%	Other	Recommendation
1	Normal study in conclusive for OSA	<3	0	0	Baseline: stable (< 3 clusters of desaturation) and > 95%	Additional evaluation of breathing during sleep required to rule out OSA
2	OSA, mild	>3	<3	0	Three or more clusters of desaturation events	Recommend T&A on the waiting list
3	OSA, moderate	>3	>3	<3	Three or more clusters of desaturation events	Recommend surgery within 2 weeks
4	OSA, severe	>3	>3	>3	Three or more clusters of desaturation events	Recommend urgent surgery within days

Table 6 *–The McGill Oximetry Scoring System devised in phase I and validated in phases 2 and 3*

In the above table, the authors validated a severity scoring system for overnight oximetry from a three-phase study. This score reflects the severity of OSA and prioritises treatment on the basis of oximetry score. If the oximetry score is 1 then additional measures to rule out sleep apnoea, like PSG, should be employed. If the score is 2, then the patient needs to be added to the waiting list for adenotonsillectomy. If the score is 3, then surgery is recommended within two weeks, and if the score is 4, the surgery needs to be prioritized and done within days.

Brouillette et al. (2000) conducted a cross-sectional study on 349 children referred to a paediatric sleep lab for suspected OSA. Overnight pulse oximetry was compared with PSG and the authors concluded that a positive pulse oximetry result increased the probability of patients having OSA to 97%. However, 47% of children with negative or inconclusive oximetry readings were positive for OSA on PSG. From this study, it is evident that negative oximetry findings do not rule out OSA. Oeverland et al. (2002) conducted a prospective study on one hundred consecutive patients referred for PSG to rule out SRBD in the adult population and concluded that the sensitivity and specificity to diagnose moderate to severe sleep apnoea (AHI>15) were 0.86 and 0.88 respectively. The corresponding figures for milder sleep apnoea (AHI>5) were 0.91 and 0.67.

The Royal College of Paediatric and Child Health guidelines do suggest that there is a role for overnight pulse oximetry (ONPO) in diagnosing SRBD, as a sequel of SRBD ventilation is affected, and the simplest method of assessing ventilation is measurement of oxygenation by ONPO. Abnormal desaturations in pulse oximetry recordings are

1) > 4 dips per hour of > 4% below baseline saturations
2) Abnormal clusters of 4% desaturations(5 or more such events in 30 min)
3) Prolonged desaturation below 90%.

Oximetry is affected by movement artefacts and by poor tissue perfusion. Visualisation of the pulse waveform improves differentiation of genuine desaturations from artefacts (Lafontaine et al., 1996).

From the above studies and review of literature, it can be concluded that pulse oximetry has a role in the diagnosis of OSA, but that negative oximetry results in the presence of symptoms of OSA should be evaluated further using other methods.

1.4.7 Polysomnography

Polysomnography (PSG), the gold standard diagnostic tool for diagnosing paediatric SRBD, is a recording of the physiological changes during sleep. These parameters are similar to the adult ones, with a few exceptions. The characteristic montage as described in American Academy of Sleep Medicine includes.

- Electroencephalogram (EEG)
- Electromyogram (EMG)
- Electrooculogram (EOG)
- ECG
- Nasal Pressure
- Oro nasal airflow
- End tidal PCO2
- Arterial oxygen saturation (spO_2) with pulse waveform
- Chest and abdominal wall motion

- Body position monitor
- Snoring microphone
- Video

Electroencephalogram (EEG) measures the brain neuronal activity. EEG measurement involves placing two electrodes in the occipital region, three in the cranial region and three in the frontal region to record the brain waves. Brain waves have a characteristic frequency, amplitude and morphology and each stage of sleep has a characteristic brain wave

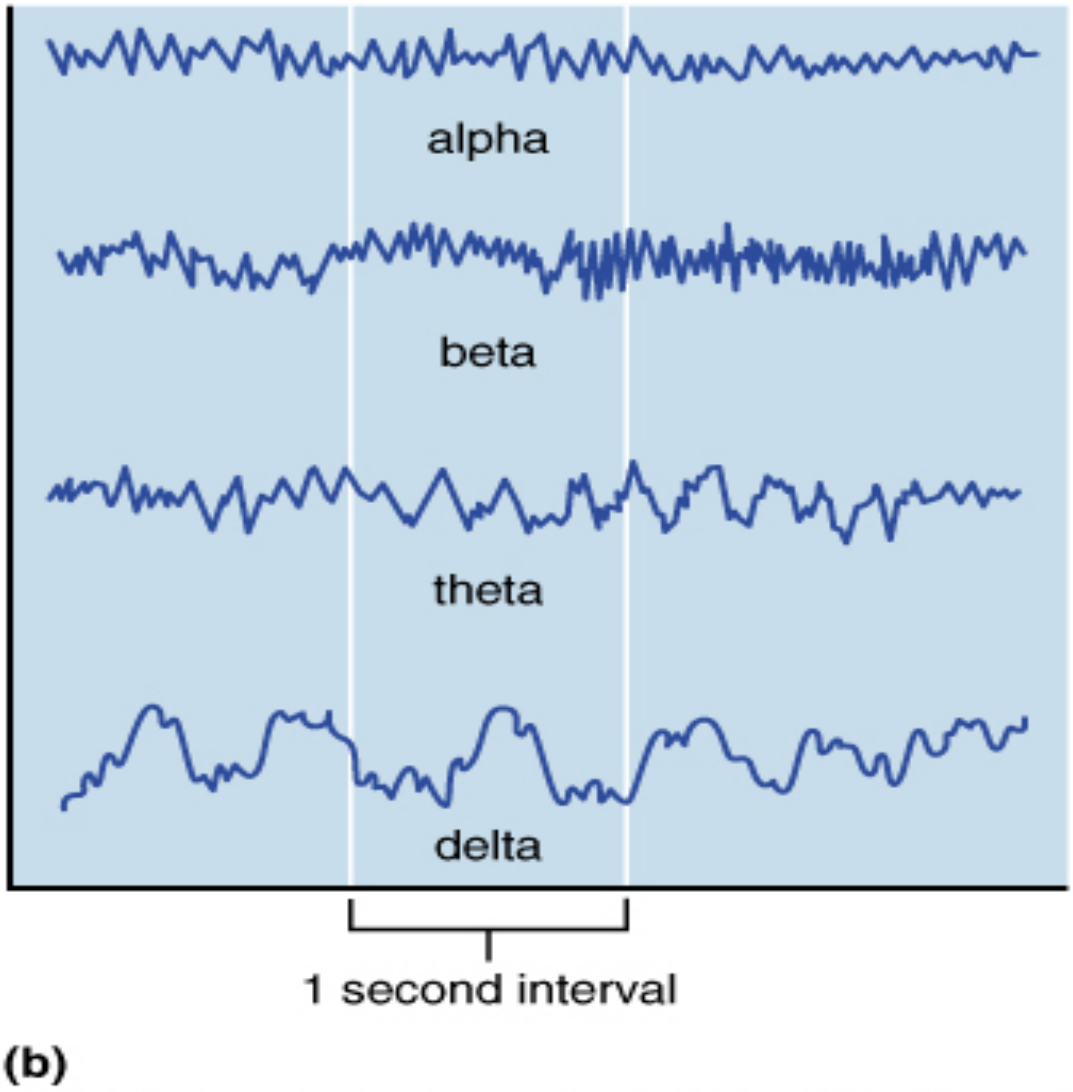

***Figure 4**: Brain waves with different frequency, morphology and amplitude.*

Alpha waves are the first brain waves: they are predominant in the relaxed wakefulness state and have a frequency of 8-13 Hz. Beta waves (spindle and K complexes) are characteristic of stage 2 NREM sleep; they occur in the setting of variable low frequency waves. Theta waves are predominant in stage 1 NREM and have a frequency of 12-14 Hz. Delta waves are predominant in stage 3-4 NREM sleep and have a frequency between 0.5 and 2 Hz. The EEG of REM sleep is very similar to the stage 1 NREM, but is characterized by rapid oscillating eye movement and skeletal muscle atony.
Electromyogram (EMG) involves placing one electrode on the chin and one on each leg to measure muscular activity during sleep.

Electrooculogram (EOG) involves placing one electrode about half an inch on either side of the lateral canthi to measure eye movements during sleep. Electrocardiogram (ECG) records cardiac events during sleep.

Nasal pressure and oro nasal airflow- A thermistor is used to measure nasal pressure and oro nasal airflow, particularly in children, as many of them have enlarged adenoids and therefore breathe through their mouths.

End tidal CO_2- End tidal CO_2 is a measure of hypoventilation, and is usually measured as a side stream from a nasal cannula, or in an intubated patient, from the endotracheal tube.

Pulse Oximetry with waveform is often useful to correlate desaturation events with the waveform to distinguish motion artefacts from true desaturation.

Respiratory effort- Sensors to measure the chest wall and abdominal wall movement are used to monitor respiratory effort. Body positioning is frequently monitored, although this is not as important as in adults. Snoring microphone and videotaping of the sleep pattern are valuable adjuncts in polysomnography.

Mitchell et al. (2007), in their prospective cohort study, assessed the persistence of OSA symptoms before and after adenotonsillectomy on seventy-nine children between three and fourteen years using polysomnography. This study showed that mean preoperative AHI for the study population was 27.5%, which was statistically different from the mean post-operative AHI of 3.5%. Similarly, many studies (Bixler et al., 2009; Goodwin et al., 2010) have used PSG to diagnose SRBD. There is no doubt that PSG is a gold standard in diagnosing SRBD, but the limitation of using PSG as a diagnostic tool is the non-availability of sleep centres equipped with PSG and the need for the child to spend the night in an unfamiliar environment, apart from the cost factor. Moreover, the diagnostic tests described so far assess the sequelae of upper airway obstruction, but not the severity of upper airway obstruction, which would then lead onto SRBD.

A proposal is put forward in this thesis is that as the crux for SRBD is upper airway obstruction, management can be streamlined if a simple diagnostic test can measure severity of upper airway obstruction. A review of the literature did not reveal any study to measure the severity of upper airway obstruction, but there are a few studies that have used spirometry to access the lower airway function (pulmonary function test) in children with adenotonsillar hypertrophy. Yadav et al. (2003) used spirometry to measure pulmonary function in forty children before and after adenotonsillectomy and found that there was

statistically significant improvement in the pulmonary function, such as FIF50%, FEF50%, FEV1/PEFR and FEV1/FEV0.5 ratios after the surgery. Niedzielska et al. (2008) measured pulmonary function and nasal flow in thirty children with adenoid hypertrophy by spirometry and nasometric test and found a statistically significant improvement in the nasometric flows and VC, FVC, PEF, FEV1/PEF and FEV1/FVC after adenoidectomy. In both these studies, spirometry has been used to demonstrate improvement in pulmonary function test after the surgery, which is again a sequel of SRBD.

Chapter 2

Methodology

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2.1 Objective of the study

The objective of this pilot study was to assess the severity of airway obstruction in patients undergoing tonsillectomy with or without adenoidectomy by measuring peak nasal and oral inspiratory airflow.

2.2 Ethical Approval

The study was approved by the South East Wales Local Research Ethics Committee and conducted in accordance with the International Conference of Harmonization's Guidelines for Good Clinical Practice and the World Medical Association's Declaration of Helsinki. All subjects had to sign a consent form before being enrolled onto the study and in the case of the paediatric population, informed consent was obtained from the parent/guardian.

2.3 Assessment of safety and ethical issues

The measurement of peak nasal and oral inspiratory flow is a non-invasive measurement that is harmless, and no safety issues are expected. Any adverse events were documented and any serious adverse events were aimed to be reported within 48 hours to the sponsor and the ethics committee. Adverse events and serious adverse events related to the surgery were not reported to the sponsor or the ethics committee, as they are not a consequence of this study.

One ethical issue considered by the investigators was that the patients and parents or guardians should not feel in any way that they were obliged to participate in this study in order to receive or accelerate their surgical treatment. In order to ensure that patients did not feel under any pressure to join in the study, the first contact with the patients was by

letter, explaining the study and asking them to respond if they wished to participate. Only after patients had responded in the affirmative were they contacted by phone by the investigator, to discuss the study and explain any aspects that were not clear to the patient. Again, it was made clear at this stage that participation was entirely voluntary and would not in any way affect their treatment.

Another ethical issue was confidentiality of patient records and any information obtained from the records. All information from records was maintained confidentially and the records were only assessed by the clinical investigator.

2.4 Trial design and recruitment of patients

This was a prospective study carried out at University Hospital Wales and the Common Cold Centre at Cardiff University. Recruitment was done from a cohort of patients on the waiting list for tonsillectomy with or without adenoidectomy at University Hospital Wales, Cardiff. These patients were sent a letter of invitation along with a patient information leaflet to explain the research project and a response letter to convey their decision on participation. Once patients had confirmed their willingness to take part, the investigator contacted them over the telephone to discuss the project and answer any questions.

On the day of surgery, the investigator obtained informed consent and a thorough otorhinolaryngology examination was carried out and the tonsils were graded using the Brodsky scale. The investigator measured peak oral and nasal inspiratory flow on the patient using a portable inspiratory flow meter. An invitation was sent after surgery for a follow-up visit to the Common Cold Centre one month later, to repeat peak inspiratory oral and nasal

flow measurements. The study recruited fifty patients who underwent pre-operative measurement of airflow and twenty-five of these patients returned for the second visit at the Common Cold Centre.

2.5 Selection and Withdrawal of Subjects

Recruitment was done from a cohort of patients on the waiting list for Tonsillectomy with or without Adenoidectomy at the University Hospital Wales, Cardiff.

Inclusion criteria- Patients referred for tonsillectomy with or without adenoidectomy

Exclusion Criteria- Children less than five years of age and tonsillectomy done to rule out malignancy.

2.6 Methods and Measurements

Peak Nasal Inspiratory Flow

The measurement of Peak Nasal Inspiratory Flow (PNIF) (litres/minute) was performed using the In-Check portable flow meter manufactured by Clement Clarke International Limited, England.

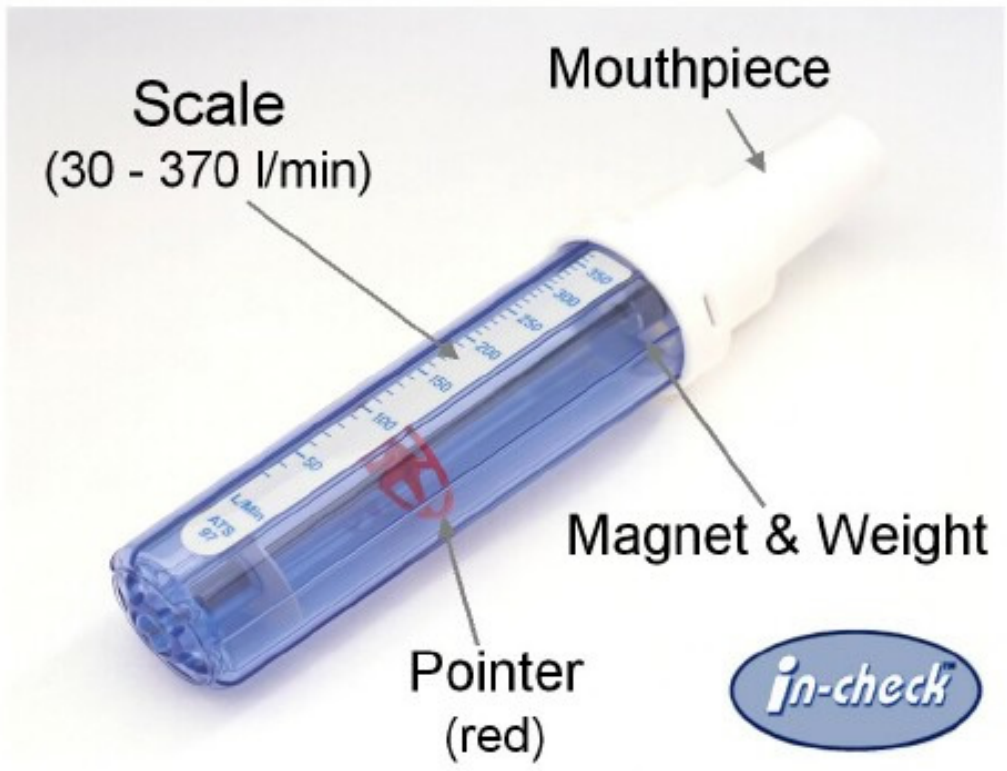

***Figure 5**: In-check Peak flow meter*

The measurement of PNIF has been previously used to measure nasal obstruction (Starling-Schwanz et al., 2005). The technique involves the subject placing a mask over the nose and making a maximum effort to breathe in through the nose, as shown in the figure below. The subject was asked if they wished to gently blow their nose prior to any measurement.

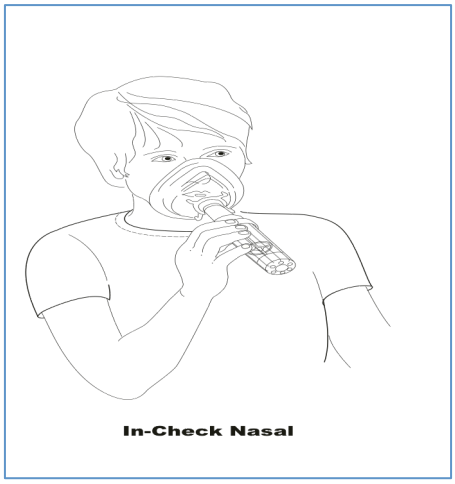

Figure 6: *Nasal mask attached to the in-check portable inspiratory flow meter for measurement of PNIF*

The following data were recorded at the pre-operative visit 1: -

i. First PNIF value = PNIF (1)

ii. Second PNIF value = PNIF (2)

iii. Third PNIF value = PNIF (3)

The following data was recorded at the post-operative visit 2: -

i. Fourth PNIF value = PNIF (4)

ii. Fifth PNIF value = PNIF (5)

iii. Sixth PNIF value = PNIF (6)

<u>Peak Oral Inspiratory Flow</u>

The measurement of Peak Oral Inspiratory Flow (POIF) (litres/minute) was performed with the In-Check portable flow meter manufactured by Clement Clarke International Limited,

England. The measurement of Peak oral expiratory flow is often used to measure lower airway obstruction. However, measurement of POIF can be used as a measure of oral obstruction, as the oral resistance due to anatomical narrowing secondary to enlarged tonsillar tissue occurs during inspiration. The technique involves the subject placing the peak inspiratory flow meter in the mouth and making a maximum effort to breathe in through the mouth, as shown in the figure below.

***Figure** 7: Oral cannula attached to the peak inspiratory flow meter to measure the POIF.*

The following data were recorded at the pre-operative visit 1: -

i. First POIF value = POIF (1)

ii. Second POIF value = POIF (2)

iii. Third POIF value = POIF (3)

The following data were recorded at the post-operative visit 2: -

i. Fourth POIF value = POIF (4)

ii. Fifth POIF value = POIF (5)

iii. Sixth POIF value = POIF (6)

2.7 Patient expenses

A single payment of £25 pounds was made to the participants attending the second phase of the study at the Common Cold Centre.

2.8 Statistical analysis

This was a pilot study to assess the upper airway obstruction in patients undergoing tonsillectomy with or without adenoidectomy. The null hypothesis that there is no difference between preoperative and postoperative peak inspiratory flow measurements was tested. The Statistical Package for the Social Sciences version 20 for the Macintosh platform was utilised for statistical analysis. Normal distributions were determined using the quantile-quantile (Q-Q) plot and the Kolmogorov-Smirnov test of normality. Pearson's correlation coefficient method was used to determine associations between normally distributed data. Scatter diagrams were used to understand the association between variables. A p-value of less than or equal to 0.05 was taken as being statistically significant.

Chapter 3

Results

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3.1 Pre-operative data analysis

3.1 (A) Demographics

The first fifty patients on the waiting list for tonsillectomy with or without adenoidectomy at University Hospital of Wales who confirmed their acceptance to take part were recruited in the first phase of the study. There were twenty-eight females (56%) and twenty-two males (44%). The mean age was 18.08 years with a range from five to forty-six years and a standard deviation of 10.92. The total numbers of patients in different age groups are listed in the table below.

Age range	No of subjects	OSA
5-10	17	12
11-18	10	2
>19	23	3

***Table 7**: Demographic data*

All patients had suffered from attacks of recurrent tonsillitis at the time of surgery. Among the fifty patients, thirty-nine (78%) had a history of snoring, seventeen (34%) had symptoms suggestive of Obstructive Sleep Apnoea (twelve of them in the age group 5 -10, two in the age group 11-18 and three in the age group >19), of whom three had overnight pulse oximetry to confirm the diagnosis.

The size of the tonsils was graded as per the Brodsky grade (Grade 1-Tonsil occupying less than 25% of oropharynx, Grade 2- Tonsil occupying between 25-50% of oropharynx, Grade 3- Tonsil occupying between 50- 75% of oropharynx and Grade 4- Tonsil occupying more than 75% of oropharynx).

Brodsky Grade	Frequency	Percent (%)
1	2	4.0
2	12	24.0
3	33	66.0
4	3	6.0
Total	50	100.0

***Table 8**: Frequency of tonsil size graded as per Brodsky's grading in the study group.*

The past medical history of four patients included asthma, and they were on regular inhalers. They had been stable on these medications for many years. None of the patients were allergic to any medications.

3.1(B) Pre-operative data of the study group

N	POIF 1	POIF 2	POIF 3	POIF-M	PNIF 1	PNIF 2	PNIF 3	PNIF -M
1	110	150	150	150	30	30	30	30
2	150	140	140	150	50	40	30	50
3	150	160	200	200	30	30	30	30
4	320	320	330	330	70	50	70	70
5	220	270	220	270	50	70	70	70
6	150	200	250	250	50	70	70	70
7	150	160	160	160	50	50	40	50
8	170	210	240	240	50	70	70	70
9	150	170	170	170	50	40	40	50
10	80	100	100	100	40	50	50	50
11	150	160	170	170	80	60	60	80
12	150	160	160	160	30	40	50	50
13	100	140	150	150	70	70	70	70
14	150	170	170	170	50	70	90	90
15	70	120	120	120	40	40	50	50
16	80	70	80	80	30	40	30	40
17	70	80	80	80	40	40	50	50
18	70	80	70	80	40	40	40	40
19	180	170	190	190	80	70	70	80
20	200	250	270	270	50	50	50	50
21	150	150	170	170	30	40	40	40
22	80	90	80	90	30	30	40	40
23	100	120	120	120	40	50	50	50
24	250	270	270	270	80	120	120	120
25	300	350	300	350	70	60	50	70
26	80	70	80	80	30	30	40	40
27	120	150	170	170	70	70	50	70
28	300	350	300	350	50	80	80	80
29	200	300	300	300	90	100	140	140
30	140	150	140	150	50	60	70	70
31	160	200	160	200	60	60	40	60
32	120	140	150	150	50	50	50	50
33	250	300	300	300	50	40	50	50
34	300	300	300	300	90	70	70	90

35	100	120	120	120	50	60	50	60
36	80	90	90	90	30	40	50	50
37	70	70	50	70	30	40	40	40
38	50	60	70	70	40	40	40	40
39	200	180	180	200	100	90	70	100
40	150	170	180	180	50	50	50	50
41	200	250	250	250	50	60	60	60
42	50	60	70	70	40	40	40	40
43	100	90	80	100	40	40	50	50
44	100	90	90	100	50	40	40	50
45	90	120	130	130	50	60	50	60
46	120	130	100	130	50	40	40	50
47	200	200	240	240	50	30	50	50
48	200	220	230	230	70	70	80	80
49	70	80	60	80	30	40	40	40
50	150	170	170	170	50	70	70	70

***Table 9**: Pre-operative data.*

3.1 (C) Data analysis of pre-operative peak oral inspiratory flow (POIF)

	N	Minimum	Maximum	Mean	Std. Deviation
POIF 1	50	50	320	147.00	69.142

***Table 10**: Pre-operative peak oral inspiratory flow 1*

POIF-1 was the first peak oral inspiratory flow measured in the participant group. The minimum measurement was 50 l/min, the maximum measurement was 320 l/min, and the mean was 147 l/min with a standard deviation of 69.142.

	N	Minimum	Maximum	Mean	Std. Deviation
POIF 2	50	60	350	166.40	78.552

***Table 11**: Pre-operative peak oral inspiratory flow 2*

POIF-2 was the second peak oral inspiratory flow measured in the participant group. The minimum measurement was 60 l/min, the maximum measurement was 350 l/min, and the mean was 166.40 l/min with a standard deviation of 78.55.

	N	Minimum	Maximum	Mean	Std. Deviation
POIF 3	50	50	330	167.40	77.191

***Table 12**: Pre-operative peak oral inspiratory flow 3*

POIF-3 was the third peak oral inspiratory flow measured in the participant group. The minimum measurement was 50 l/min, the maximum measurement was 330 l/min, and the mean was 167.40 l/min with a standard deviation of 69.142.

	N	Minimum	Maximum	Mean	Std. Deviation
POIF-M	50	70	350	174.40	79.595

***Table 13**: Pre-operative maximum peak oral inspiratory flow*

POIF-M was the maximum peak oral inspiratory flow measured in the participant group. The minimum measurement was 70 l/min, the maximum measurement was 350 l/min, and the mean was 174.40 l/min with a standard deviation of 79.595.

In order to normalize the measurements, so as to obtain a normal distribution, which will also help to predict the repeatability of the measurements, the first measurement of peak oral inspiratory flow (POIF-1) was taken as 1. The ratio of the second measurement of peak oral inspiratory flow (POIF-2) with that of POIF-1 was calculated to derive POIF 2-1. Similarly, the ratio of the third measurement of peak oral inspiratory flow (POIF-3) with that of POIF-1 was calculated to derive POIF 3-1.

	N	Minimum	Maximum	Mean	Std. Deviation
POIF 2-1	50	0.8700	1.7100	1.137	0.161

Table 14*: POIF 2-1*

POIF 2-1 is the normalized value of the second measurement of POIF. POIF 2-1 was calculated for all fifty participants: the maximum POIF 2-1 was 1.71 and the minimum was 0.87 with a mean of 1.137 and standard deviation of 0.161.

	N	Minimum	Maximum	Mean	Std. Deviation
POIF 3-1	50	0.7100	1.7100	1.149	0.215

Table 15*: POIF 3-1*

POIF 3-1 is the normalized value of the third measurement of POIF. The maximum POIF 3-1 was 1.71 and the minimum was 0.71 with a mean of 1.149 and standard deviation of 0.215.

3.1(D) Relationship between POIF-1, POIF 2-1,POIF 3-1

A one-sample t-test was used to test the relationship between POIF 1 and POIF 2-1. The mean difference in the ratio was 0.137 [0.091, 0.183] and $t(49) = 6.07$, $p < 0.0001$.

A one-sample t-test was used to test the relationship between POIF 1 and POIF 3-1. The mean difference in the ratio was 0.150 [0.088, 0.210] and the t (49) = 4.907, p < 0.0001.

3.1 (E) Effects of age on POIF-M

Using a linear regression model, with age as an independent factor and POIF-M as a dependent factor, there appears to be a linear relationship between age and POIF-M.

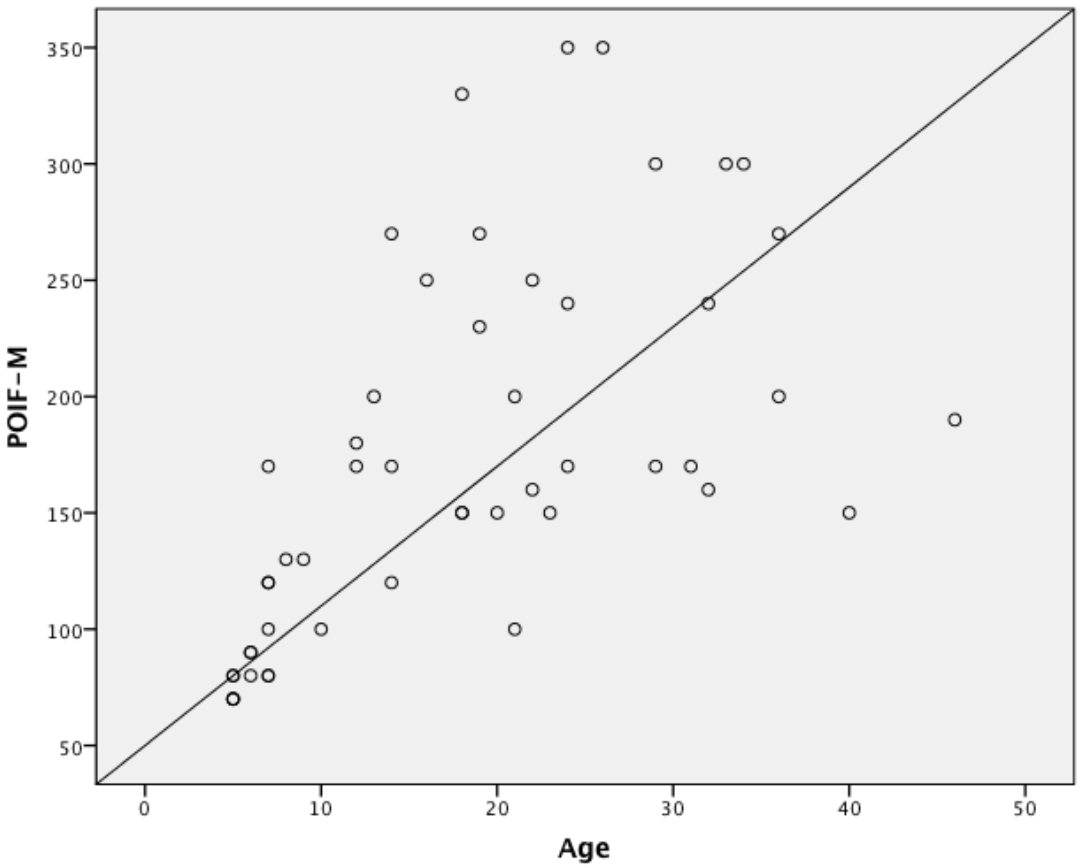

Figure 8: *Relation between age on X axis and POIF-M on Y axis.*

From the above scatter plot graph, age appears to have an influence on the POIF. The correlation determined by Pearson's product moment correlation coefficient (r) of 0.603, p<0.001. For every year's increase in age, the POIF increases by 4.394 l/min.

3.1 (F) Descriptive analysis of PNIF (pre operative)

Three measurement of PNIF, namely PNIF-1, PNIF-2 and PNIF-3, were obtained from all the participants and the maximum PNIF (PNIF-M) measurement was taken for final data analysis.

	N	Minimum	Maximum	Mean	Std. Deviation
PNIF 1	50	30	100	51.00	17.642

***Table 16**: Pre-operative peak nasal inspiratory flow 1*

PNIF-1 was the first peak nasal inspiratory flow measured in the participant group. The minimum measurement was 30 l/min, the maximum measurement was 100 l/min, and the mean was 51 l/min with a standard deviation of 17.642.

	N	Minimum	Maximum	Mean	Std. Deviation
PNIF 2	50	30	120	53.80	18.940

***Table 17**: Pre-operative peak nasal inspiratory flow 2*

PNIF-2 was the second peak nasal inspiratory flow measured in the participant group. The minimum measurement was 30 l/min, the maximum measurement was 120 l/min, and the mean was 53.80 l/min with a standard deviation of 18.940.

	N	Minimum	Maximum	Mean	Std. Deviation
PNIF 3	50	30	140	55.40	21.209

***Table 18**: Pre-operative peak nasal inspiratory flow 3*

PNIF-3 was the third peak nasal inspiratory flow measured in the participant group. The minimum measurement was 30 l/min, the maximum measurement was 140 l/min and the mean was 55.40 l/min with a standard deviation of 21.209.

	N	Minimum	Maximum	Mean	Std. Deviation
PNIF-M	50	30	140	60.00	21.665

***Table 19**: Pre-operative maximum peak nasal inspiratory flow*

PNIF-M was the maximum peak nasal inspiratory flow measured in the participant group. The minimum measurement was 30 l/min, the maximum measurement was 140 l/min, and the mean was 60.00 l/min with a standard deviation of 21.665.

In order to normalize the measurements, so as to obtain a normal distribution, which will also help to predict the repeatability of the measurements, the first measurement of peak nasal inspiratory flow (PNIF-1) was taken as 1. The ratio of the second measurement of peak nasal inspiratory flow (PNIF-2) with that of PNIF-1 was calculated to derive PNIF 2-1.

Similarly, the ratio of the third measurement of peak nasal inspiratory flow (PNIF-3) with that of PNIF-1 was calculated to derive PNIF 3-1.

	N	Minimum	Maximum	Mean	Std. Deviation
PNIF 2-1	50	1	2	1.04	0.198

***Table 20**: PNIF 2-1*

PNIF 2-1 is the normalized value of the second measurement of PNIF. PNIF 2-1 was calculated for all fifty participants: the maximum PNIF 2-1 was 2 and the minimum 1, with a mean of 1.04 and standard deviation of 0.198.

	N	Minimum	Maximum	Mean	Std. Deviation
PNIF 3-1	50	1	2	1.12	0.328

***Table 21**: PNIF 3-1*

PNIF 3-1 is the normalized value of the third measurement of PNIF. PNIF 3-1 was calculated for all fifty participants: the maximum PNIF 3-1 was 2, and the minimum 1, with a mean of 1.12 and standard deviation of 0.328.

3.1 (G) Relationship between PNIF 1, PNIF 2-1,PNIF 3-1

A one-sample t-test was used to test the relationship between PNIF 1 and PNIF 2-1. The mean difference in the ratio was 0.40 [0.02, 0.10] and t (49) = 1.49, $p < 0.0001$.

A one-sample t-test was used to test the relationship between PNIF 1 and PNIF 3-1. The mean difference in the ratio was 0.120 [0.03, 0.21] and t (49) = 2.585, $p < 0.0001$.

3.1 (H) Effects of age on PNIF-M

Using a linear regression model, with age as an independent factor and PNIF-M as a dependent factor, there appears to be a linear relationship between age and PNIF-M.

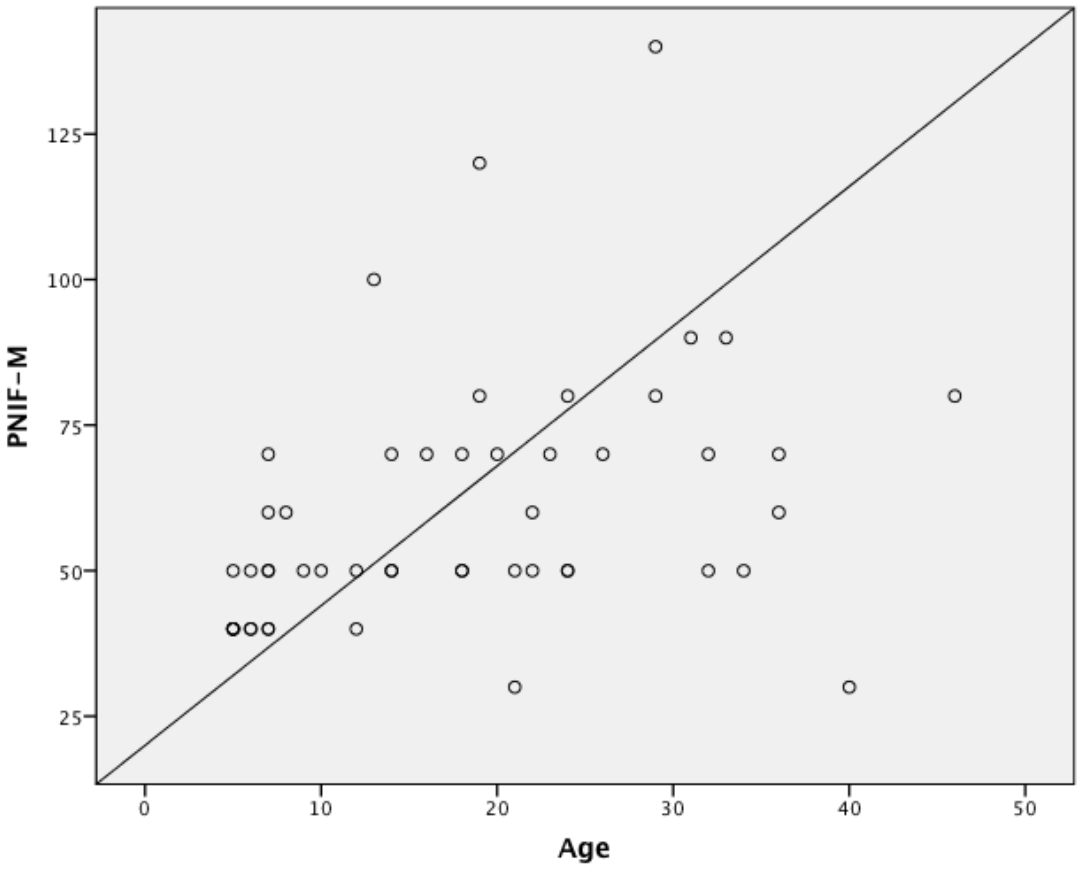

Figure 9*: Relationship between age on the x- axis and PNIF-M on the y-axis.*

Form the above scatter plot graph, age appears to have an influence on the PNIF. The correlation determined by Pearson's product moment correlation coefficient (r) was 0.381, p<0.006. For every year's increase in age, the PNIF increases by 0.756 l/min.

3. 1(I) Relationship between pre-operative POIF and PNIF

The relationship between POIF and PNIF in each participant was tested using the Pearson correlation. The correlation coefficient (r) was 0.585, p<.0001. This shows that there is a good correlation between POIF and PNIF, as demonstrated in the scatter plot below.

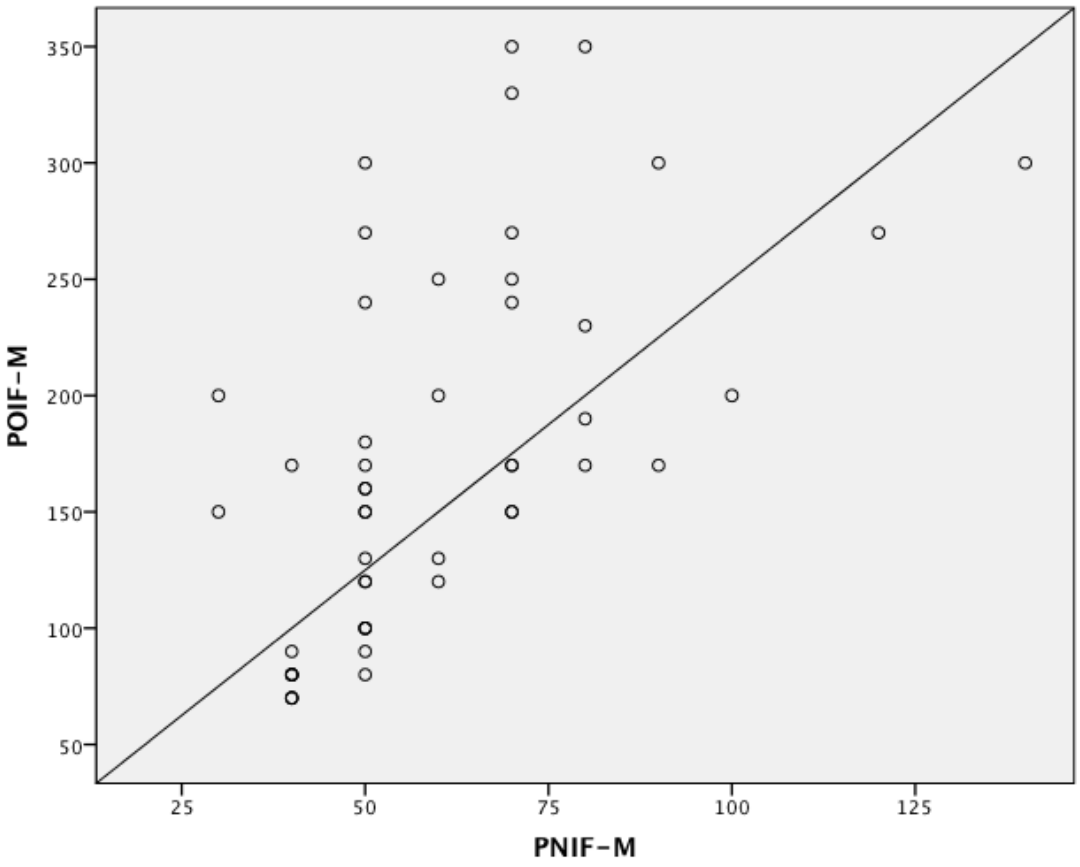

***Figure 10**: Relationship between PNIF-M on the x-axis and POIF-M on the y-axis.*

3.2 Post-operative data analysis

3.2 (A) Demographics

Twenty-five (50%) of the first phase participants agreed to take part in the second phase of the study. There were thirteen females (52%) and twelve males (48%). The mean age was 20.76 years with a range from five to forty-six years and a standard deviation of 11.68. All patients had suffered from attacks of recurrent tonsillitis at the time of surgery. Among the twenty-five patients, nineteen (76%) had history of snoring and five (20%) had symptoms suggestive of Obstructive Sleep Apnoea.

3.2(B) Post-operative data

N	POIF 4	POIF 5	POIF 6	POIF-M1	PNIF 4	PNIF 5	PNIF 6	PNIF-M1
1	200	250	200	250	50	50	40	50
2	300	320	300	320	80	90	100	100
3	150	170	190	190	50	70	70	70
4	110	120	100	120	50	60	50	60
5	160	170	160	170	60	60	70	70
6	220	230	250	250	90	90	90	90
7	200	260	240	260	90	90	90	90
8	280	300	280	300	150	130	150	150
9	150	150	140	150	50	50	40	50
10	120	100	120	120	50	60	70	70
11	340	350	350	350	100	120	120	120
12	250	270	250	270	90	90	90	90
13	180	240	250	250	80	80	100	100
14	330	320	350	350	160	160	120	160
15	350	350	350	350	80	80	80	80
16	220	200	200	220	70	70	90	90
17	320	350	350	350	130	150	180	180
18	350	350	350	350	120	140	140	140
19	120	140	150	150	50	50	50	50
20	350	350	300	350	90	70	70	90
21	100	100	100	100	50	50	50	50
22	170	180	150	180	70	70	50	70
23	140	160	170	170	50	70	50	70
24	120	150	160	160	50	70	90	90
25	60	70	80	80	40	50	40	50

Table 22: *Post-Operative data*

3.2 (C) Descriptive analysis of post-operative POIF.

	N	Minimum	Maximum	Mean	Std. Deviation
POIF 4	25	60	350	211.60	92.000

***Table 23**: Post-operative POIF-4*

POIF-4 was the first peak oral inspiratory flow measured in the participant group after surgery. The minimum measurement was 60 l/min, the maximum measurement was 350 l/min, and the mean was 211.60 l/min with a standard deviation of 92.0.

	N	Minimum	Maximum	Mean	Std. Deviation
POIF-5	25	70	350	226.00	92.105

***Table 24**: Post-operative POIF-5*

POIF-5 was the second peak oral inspiratory flow measured in the participant group after surgery. The minimum measurement was 70 l/min, the maximum measurement was 350 l/min, and the mean was 226 l/min with a standard deviation of 92.10.

	N	Minimum	Maximum	Mean	Std. Deviation
POIF- 6	25	80	350	221.60	88.961

***Table 25**: Post-operative POIF-6*

POIF-6 was the third peak oral inspiratory flow measured in the participant group after surgery. The minimum measurement was 80 l/min, the maximum measurement was 350 l/min, and the mean was 221.60 l/min with a standard deviation of 88.961.

	N	Minimum	Maximum	Mean	Std. Deviation
POIF-M1	25	80	350	232.40	90.290

***Table 26**: Post-operative POIF-M1*

POIF-M1 was the maximum peak oral inspiratory flow measured in the participant group after surgery. The minimum measurement was 80 l/min, the maximum measurement was 350 l/min, and the mean was 232.40 l/min with a standard deviation of 90.290.

3.2 (D) Descriptive analysis of post-operative PNIF.

	N	Minimum	Maximum	Mean	Std. Deviation
PNIF-4	25	40	160	78.00	33.166

***Table 27**: Post-operative PNIF-4*

PNIF-4 was the first peak nasal inspiratory flow measured in the participant group after surgery. The minimum measurement was 40 l/min, the maximum measurement was 160 l/min, and the mean was 78 l/min with a standard deviation of 33.166.

	N	Minimum	Maximum	Mean	Std. Deviation
PNIF-5	25	50	160	82.80	32.599

***Table 28**: Post-operative PNIF-5*

PNIF-5 was the second peak nasal inspiratory flow measured in the participant group after surgery. The minimum measurement was 50 l/min, the maximum measurement was 160 l/min, and the mean was 82.80 l/min with a standard deviation of 32.599.

	N	Minimum	Maximum	Mean	Std. Deviation
PNIF-6	25	40	180	83.60	36.729

***Table 29**: Post-operative PNIF-6*

PNIF-6 was the third peak nasal inspiratory flow measured in the participant group after surgery. The minimum measurement was 40 l/min, the maximum measurement was 180 l/min, and the mean was 83.60 l/min with a standard deviation of 36.729.

	N	Minimum	Maximum	Mean	Std. Deviation
PNIF-M1	25	50	180	89.20	36.046

Table 30: Post-operative PNIF-MI

PNIF-M1 was the maximum peak nasal inspiratory flow measured in the participant group after surgery. The minimum measurement was 50 l/min, the maximum measurement was 180 l/min, and the mean was 89.20 l/min with a standard deviation of 36.046.

3.3 Relationship between POIF M (Pre-operative maximum) and POIF M1 (Post-operative maximum)

The maximum pre-operative peak oral inspiratory flow (POIF M) of the twenty-five patients attending the second phase of the study was compared with their maximum postoperative peak oral inspiratory flow (POIF M1).

1) POIF M1 > POIF M - 17/25 (68%)
2) POIF M1= POIF M - 6/25 (24%)
3) POIF M1< POIF M - 2/25 (8%)

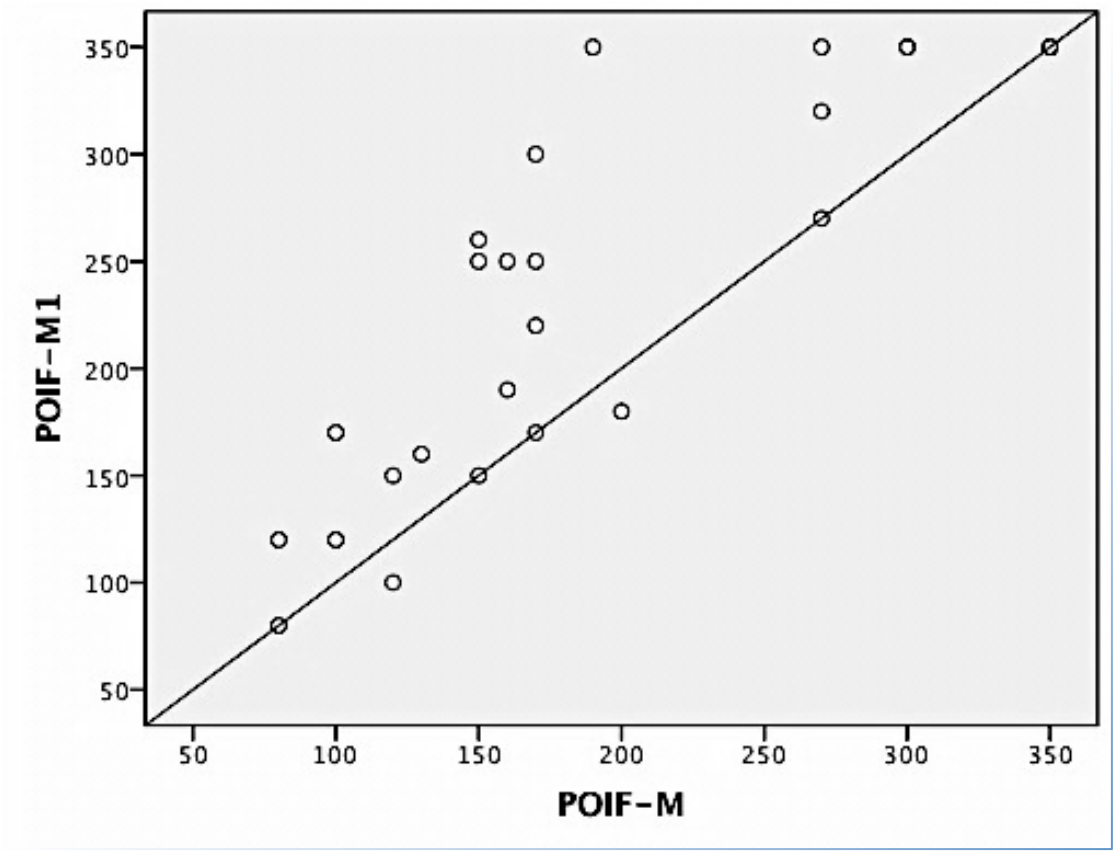

***Figure 11**: Relationship between POIF M on the x- axis and POIF M1 on the y-axis.*

The correlation of POIF M with POIF M1 in each participant was tested using Pearson's correlation. The correlation coefficient (r) was 0.850, $p<0.0001$. This shows that there is a good correlation between POIF M1 and POIF M, as demonstrated in the scatter plot above.

A paired sample t-test was used to find the relationship between POIF M1 and POIF M. The mean of POIF M in the second phase of the study was 187.20 and the mean of POIF M1 was 232.40. The paired difference mean between POIF M1 and POIF M was 45.20 [25.471, 64.929]:$t(24) = 4.729$, $p<0.0001$.

3.4 Relationship between PNIF M (pre-operative maximum) and PNIF M1 (Post-operative maximum)

The maximum pre-operative peak nasal inspiratory flow (PNIF M) of the twenty-five patients attending the second phase of the study was compared with the maximum post-operative peak nasal inspiratory flow (PNIF M1).

1) PNIF M1 > PNIF M - 18/25 (72%)
2) PNIF M1= PNIF M - 4/25 (16%)
3) POIF M1< POIF M - 3/25 (12%)

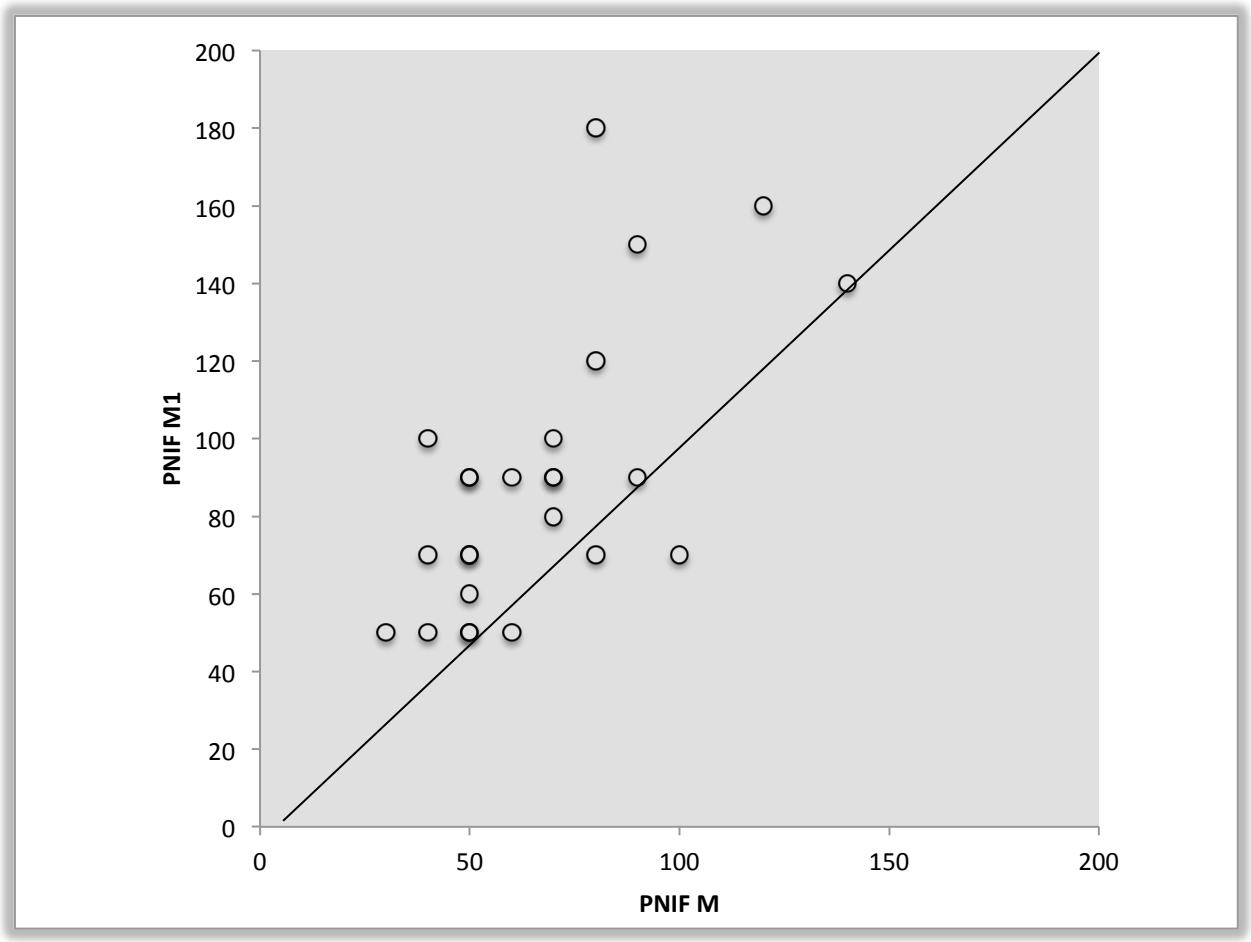

Figure 12*: Relationship between PNIF M1 (Post-operative) on the y-axis and PNIF M (Pre-operative) on the x- axis.*

Correlation of PNIF M with PNIF M1 in each participant was tested using Pearson's correlation. The correlation coefficient (r) was 0.663, $p<0.0001$. This shows that there is a good correlation between PNIF M1 and PNIF M, as demonstrated in the scatter plot above.

A paired sample t test was used to find the relationship between PNIF M1 and PNIF M. The mean of PNIF M in the second phase of the study was 67.20 and the mean of PNIF M1 was 89.20. The paired difference mean between PNIF M1 and PNIF M was 22.00 [10.8222, 33.178]: $t(24) = 4.062$, $p<0.0001$.

Chapter 4

Discussion

The aim of this thesis was to assess the severity of airway obstruction in patients undergoing tonsillectomy+/- adenoidectomy. Clinicians often rely on patient reported symptoms of SRBD and clinical examination to decide on the removal of the tonsils with or without adenoids to relieve upper airway obstruction. The limitations and feasibility of obtaining overnight polysomnography, which is the gold standard investigation for SRBD, is the main reason to look for alternative means to assess upper airway obstruction. Evidence for a simple non-invasive, easily available and cost-effective objective investigation method to assess the severity of upper airway obstruction would guide clinicians in their decision-making process for surgical intervention.

In the introduction part of this thesis, the aetiology, pathogenesis and various diagnostic methods to diagnose SRBD were discussed. Although the emphasis was more on SRBD in children, patients across different age groups undergoing tonsillectomy were included in this study, so as to have a comparable group. But as this is a pilot study and the numbers in the each group were very small, it was decided to analyse the results of whole study group rather than according to different age groups. As discussed in the section on the pathogenesis of SRBD, upper airway obstruction in these patients occurs during the inspiratory phase of breathing. Measurement of the severity of upper airway obstruction during inspiration could guide the decision-making process with regard to relieving upper airway obstruction by removing the tonsils with or without adenoids. In this study, peak oral and nasal inspiratory flow meters have been used to measure obstruction caused in the upper airway due to pathology of tonsil and adenoid tissue. The size of these lymphoid tissues in the upper airway could be the main determinant factor in causing obstruction. The

participant's tonsil size, as discussed in the demographics section in Chapter 3, were graded using the Brodsky scale and it was found that 66% had grade 3 enlarged tonsils and 6% had grade 4 enlarged tonsils. In total, 72% of this group had their oropharyngeal space narrowed by more than three quarters due to enlarged tonsils. This shows that there may be a correlation between size of tonsils and tonsilar pathology (infection or obstruction).

PNIF has previously been used to assess nasal patency in children aged from five to eighteen years in the normal population (Papachristou et al., 2008; Van Spronsen et al., 2012) and in patients with lower airway disease, but not with upper airway disease. POIF has not previously been used to assess upper airway disease. The age group of our population varied from five to forty-six years. At the start of this study, there were concerns about training a five year-old child to perform PNIF and POIF. Papchristou et al. (2008) measured PNIF in healthy children aged five to eighteen years, suggesting that it is possible to instruct children as young as five years. In this study, there were five participants aged five years and upon proper instruction and demonstration, they performed both the PNIF and POIF.

Each participant was instructed to perform three attempts of both POIF and PNIF measurements, and the maximum value of these three measurements was taken for statistical assessments. As the age range in the study population varied from five to forty-six years, a big difference in these measurements was expected, as lung volume will obviously increase with any increase in the body size due to normal growth towards puberty. Someone as young as five years old would have a lower lung volume, as reflected by lower POIF and PNIF measurements, when compared to an adult participant. The minimum pre-operative POIF was 70 l/min and the maximum POIF was 350 l/min with a mean of 174.40

l/min and standard deviation of 79.59. The minimum pre-operative PNIF was 30 l/min and the maximum PNIF was 140 l/min with a mean of 60 l/min and standard deviation of 21.66. Linear regression models were used to show the relationship between age and both POIF and PNIF. As demonstrated in Figure 8 (p. 81), there appears to be a linear relationship between age and pre-operative maximum value of POIF, with $r=0.603$, $p<0.0001$. This study also suggested that POIF increases by 4.394 l/min for every year increase in the age. Similarly, the relationship between age and PNIF was demonstrated in Figure 9 (p.85), with a correlation coefficient of $r=0.381$, $p<0.0001$. This study suggested that PNIF increases by 0.756 l/min for every year increase in age.

As discussed above, the age of the study population varied between five and forty-six years. In order to normalize the measurements, so as to obtain a normal distribution, which will also help to predict the repeatability of the measurements, the first measurement of peak oral inspiratory flow (POIF-1) was taken as 1. The ratio of the second measurement of peak oral inspiratory flow (POIF-2) with that of POIF-1 was calculated to derive POIF 2-1. Similarly, the ratio of the third measurement of peak oral inspiratory flow (POIF-3) with that of POIF-1 was calculated to derive POIF 3-1. Similarly, the first measurement of peak nasal inspiratory flow (PNIF-1) was taken as 1. The ratio of the second measurement of peak nasal inspiratory flow (PNIF-2) with that of PNIF-1 was calculated to derive PNIF 2-1. Similarly, the ratio of the third measurement of peak nasal inspiratory flow (PNIF-3) with that of PNIF-1 was calculated to derive PNIF 3-1.

A null hypothesis of no relationship between repeated measurements of both POIF and PNIF was tested.

A one-sample t-test was used to test the relationship between the first measurement of POIF, which was presumed to be 1 and POIF 2-1. The mean difference in the ratio was 0.137 [0.091, 0.183] and t (49) = 6.07, $p < 0.0001$. Similarly one-sample t-test was used to test the relationship between the first measurement of POIF, which was presumed to be 1 and POIF 3-1.The mean difference in the ratio was 0.150 [0.088, 0.210], t (49) = 4.907, $p < 0.0001$. This test shows that if POIF is repeated in 100 participants, 95 percent of the participants will show a mean difference in the ratio of 0.137 between the first and the second measurement and 0.150 between the first and the third measurement.

A one-sample t-test was used to test the relationship between the first measurement of PNIF, which was presumed to be 1 and PNIF 2-1. The mean difference in the ratio was 0.40 [0.02, 0.10] and t (49) = 1.49, $p < 0.0001$. Similarly one-sample t-test was used to test the relation between the first measurement of PNIF, which was presumed to be 1 and PNIF 3-1. The mean difference in the ratio was 0.120 [0.03, 0.21] and the t (49) = 2.585, $p < 0.0001$. This test shows that if PNIF is repeated in 100 participants, 95 percent will show a mean difference in the ratio of 0.40 between the first and the second measurement and 0.120 between the first and the third measurement.

The null hypothesis was rejected and the alternative hypothesis of a relationship between repeated measurements of both PNIF and POIF was accepted. The test shows that repeated practice will increase the measurements of both PNIF and POIF. Wihl et al. (1988) demonstrated a difference of 5l/min between repeated PNIF measurements, but contrary

to that, this study population did not show any such fixed increment on repeated measurements in each individual participant.

Figure 10 (p.86) demonstrates the relationship between pre-operative maximum values of POIF and PNIF. In this study, there appears to be a correlation between POIF and PNIF pre-operatively as demonstrated with a Pearson correlation coefficient (r) of 0.585, which is statistically significant at $p<0.0001$. The values of POIF and PNIF are related as they are both determined by the size of the lungs.

During the inspiratory phase of breathing, the obstruction caused by the enlarged lymphoid tissue in the nasopharynx and oropharynx will have an impact on the PNIF measurements, while the enlarged lymphoid tissue in the oropharynx will impact the POIF measurements. Post-operative change in PNIF will be secondary to the removal of the adenoids and tonsils; similarly, post- operative change in POIF will be due to the removal of the tonsils. In this study, all the participants underwent tonsillectomy and none of them had adenoidectomy; despite this, post-operative PNIF showed an increase compared to preoperative PNIF measurements. The increase in the postoperative PNIF could be due to the increase in the nasopharyngeal space dimension due to the removal of the tonsils. As 76% of this study population had tonsils that occupied more than three-quarters of the oropharyngeal space as per Bodsky's scale, the reduction in the nasopharyngeal space could be due to the impingement of the soft palate towards the nasopharynx. After tonsillectomy, this space would have opened up, leading to an increase in the measurement of PNIF.

This study was designed to see if there was any difference between the maximum values of pre-operative and post-operative POIF and PNIF. The scatter graph in Figure 11 (p. 93) demonstrates the relationship between the maximum values of pre-operative and post-operative POIF measurements. Of the twenty-five participants who completed the second part of the study, seventeen participants (68%) demonstrated an increase in the postoperative POIF, while in six participants (24%), postoperative POIF was similar to pre-operative POIF and in two participants (8%), postoperative POIF was less than the pre-operative POIF. The minimum pre-operative maximum value of POIF in the second phase of the study was 80 l/min and the maximum value was 350 l/min, with a mean of 187.20 l/min and standard deviation of 79.595. The minimum postoperative maximum value of POIF was 80 l/min and the maximum value was 350 l/min, with a mean of 232.40 l/min and a standard deviation of 90.290. A paired sample t-test was used to find the relationship between maximum values of preoperative and postoperative POIF. The paired difference mean between these both maximum value was 45.20 [25.471, 64.929], t (24) = 4.729, $p<0.0001$. This test suggests that if 100 patients were to have tonsillectomy, the post-operative POIF would increase in 95% of the patients by 45 l/min.

The scatter graph in Figure 12 (P.96) demonstrates the relationship between the maximum values of pre-operative and post-operative PNIF. Of the twenty-five participants who completed the second part of the study, eighteen participants (72%) demonstrated an increase in the post-operative PNIF, while in four participants (16%), post-operative PNIF was similar to pre-operative PNIF and in three participants (12%) post-operative PNIF was less than pre-operative PNIF. The minimum pre-operative maximum value of PNIF was 30 l/min and the maximum value was 140 l/min, with a mean of 67.20 l/min and a standard

deviation of 21.665. The minimum postoperative maximum value of PNIF was 50 l/min and the maximum value was 180 l/min, with a mean of 89.20 l/min and standard deviation of 36.046. A paired sample t-test was used to find the relationship between maximum values of preoperative and postoperative PNIF. The paired difference mean between these both maximum value was 22.00 [10.8222, 33.178]: $t(24) = 4.062$, $p<0.0001$. This test suggests that if 100 patients having tonsillectomy, the postoperative PNIF would increase in 95% of the patients by 22 l/min.

A paired sample t-test was used in this study to investigate the relationship of POIF and PNIF before and after surgical treatment. The null hypothesis was rejected and alternative hypothesis of a statistically significant difference in both POIF and PNIF following tonsillectomy was accepted. The change in measurements of both POIF and PNIF could also be due to the learning effect of repeated measurements, as demonstrated earlier. However, a review of the literature (Groth et al., 1986) on the effect of learning on repeated measurements of lung function revealed that lung function is influenced by a variety of confounding factors such as age sex, height, weight and other physical parameters, but not due to intra-individual difference between the first and second measurements.

Chapter 5

Conclusion

This study has demonstrated that a simple non-invasive inspiratory flow meter could be used to measure both POIF and PNIF. Both these measurements can be performed by children as young as five years. Post-operative POIF and PNIF demonstrated a statistically significant increase compared to pre-operative POIF and PNIF.

This pilot study was designed to assess the severity of airway obstruction in patients undergoing tonsillectomy with or without adenoidectomy by measuring peak nasal and oral inspiratory airflow. The primary objective of the study was to obtain new knowledge about the severity of airway obstruction in patients undergoing tonsillectomy with or without adenoidectomy.

The results of this study show that the three measurements of POIF and PNIF are reproducible. There appears to be correlation between pre-operative POIF and PNIF, and both these measurements have a linear relationship with age. This study also demonstrated that there is a good correlation between the maximum value of pre-operative POIF and the maximum value of post-operative POIF, and POIF increased on an average by 45 l/min after surgery. A similar correlation has been demonstrated between maximum values of pre-operative PNIF and maximum values of post-operative POIF, and postoperative PNIF increased on average by 22 l/min after surgery.

The findings of this study suggest that peak flow measurements can be used as an objective method to assess the severity of upper airway obstruction and aid clinicians in the decision-making process for surgical intervention to relieve upper airway obstruction. Both nasal and

oral peak flow measurements are non-invasive, cost effective and time effective methods of assessing upper airway obstructive when compared with other objective upper airway obstructive assessment methods.

Although the current study is based on a small sample of participants, the findings suggest that peak flow methods can be used as measures to assess upper airway obstruction, and that surgery of the upper airway does increase peak inspiratory flow rates.

Several limitations of this pilot study need to be acknowledged. The sample size is small, with fifty participants in the first phase and an attrition rate of fifty percent in the second phase to twenty-five participants. The attrition rate was greater in children compared to adults, as it was difficult to convince parents to take time off work to accompany their children to the second phase of this study in a non-hospital environment. This attrition rate could have been decreased by conducting the second phase of this study in a hospital environment.

The second limitation of this study is that the increase in the postoperative peak inspiratory flow could be due to other confounding factors, such as the variability of lung volumes, pre-operatively starved participants, anxiety before the surgery and body mass index.

The third limitation of this study is clinical assessment of adenoid hypertrophy. None of the participants had a direct visualization of the adenoid tissue prior to surgery. It is challenging to assess the adenoid tissue, particularly in children, by flexible nasendoscopic examination, as this could be distressing to the participants prior to surgery.

The other significant limitation to this study is that participants were listed for tonsillectomy for recurrent tonsillitis, although thirty-four percent of the participants clearly demonstrated symptoms of sleep-related breathing disorders. This could potentially be overcome by using objective assessment methods rather than just clinical judgement.

Larger multi-centred randomized control trails using the same methodology could provide more definitive evidence regarding the use of peak inspiratory flow measures in assessing the severity of upper airway obstruction in patients with sleep-related breathing disorders.

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Appendices

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Appendix 1

PROTOCOL TITLE: A pilot study on the assessment of upper airway obstruction in patients undergoing tonsillectomy +/- adenoidectomy

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Summary

Adenotonsillectomy is currently indicated as a treatment for sleep-related breathing disorders in children because removal of the tonsils opens up the airway and lowers airway resistance to breathing. Overnight pulse oximetry and polysomnography are the two common investigations for the diagnosis of sleep-related breathing disorders, but these are overnight and time-consuming procedures. We propose that simple non-invasive measurements of peak inspiratory flow rates may help in decision-making for patient selection for surgical treatment of sleep-related breathing disorders. Since the upper airway cause of any sleep-related breathing disorder is believed to be obstruction of the oral and nasal airways due to enlarged tonsils or adenoids, it seems reasonable that patient selection for surgery could be better managed using simple measurements of the severity of airway obstruction rather than the consequences of this obstruction as determined by overnight studies.

1.0 Background

A recent well-designed cross sectional study of about seven hundred children in the USA found that the prevalence of primary snoring was 15.5% and sleep apnoea 1.2% (Bixler et al., 2009). The increasing interest in sleep-related breathing disorders has led to more diagnoses, and a position paper published by ENT-UK (the British Association of Otorhinolaryngology—Head and Neck Surgery) has estimated that about a quarter of the 27,400 paediatric tonsillectomies in 2008-9 in the UK were carried out for obstructive conditions (Nixon et al., 2005). Overnight pulse oximetry and polysomnography are the two common investigations for sleep related breathing disorders. Polysomnography (sleep

study) and pulse oximetry are overnight and time-consuming (Goldstein et al., 2011; Kohler et al., 2008). A proposal put forward in thesis that a simple non-invasive measurements of peak inspiratory flow rates could help in decision-making for adeno/tonsillectomy for the treatment of sleep-related breathing disorders. Peak inspiratory flow is a simple non-invasive measure of lower airway obstruction that may also be used to measure obstruction of the upper airway due to tonsil enlargement. Peak oral inspiratory flow would give a measure of oral obstruction due to enlarged tonsils and peak nasal inspiratory flow would give a measure of nasal obstruction due to enlarged adenoids. Peak nasal inspiratory flow has previously been used to measure nasal airway resistance in children (Goodwin, et al., 2010; Hultcrantz et al., 1995), but peak oral inspiratory flow has not been previously measured in children, although it has been used to measure upper airway obstruction in adults (Anuntaseree et al., 2001).

2.0 Objective and purpose:

This pilot study will assess the severity of airway obstruction in patients undergoing tonsillectomy +/- adenoidectomy by measuring peak nasal and oral inspiratory airflow. The primary objective of the study is to obtain new knowledge about the severity of airway obstruction in those patients selected for surgery for the treatment of sleep-related breathing disorders.

3.0 Trial design and recruitment of patients

Prospective study at University Hospital Wales and the Common Cold Centre, Cardiff University. Recruitment will be done from the cohort of patients on the waiting list for tonsillectomy +/- adenoidectomy at University Hospital Wales, Cardiff. These patients will

be sent a letter of invitation along with a patient information leaflet to explain the research project and a response letter to convey their decision on participation. If the patients are willing to take part in the study, then the investigator will contact them by telephone to discuss the project and answer any questions they have regarding the project. On the day of surgery, the investigator will obtain informed consent and a thorough otorhinolaryngology examination will be carried out and the tonsils will be graded using the Brodsky scale. The investigator will measure peak oral and nasal inspiratory flow on the patient using a portable inspiratory flow meter. An invitation will be sent after surgery to attend a Follow-up visit to the Common Cold Centre one month later to repeat the peak inspiratory oral and nasal flow measurements. The study aims to recruit fifty patients to undergo the pre-operative measurement of airflow and it is anticipated that around thirty patients will return for the second visit at the Common Cold Centre.

4.0 Selection and Withdrawal of Subjects:

Recruitment will be done from the Cohort of patients on the waiting list for Tonsillectomy +/- Adenoidectomy at the University Hospital Wales, Cardiff.

4.1 Inclusion criteria- Patients referred for tonsillectomy +/- adenoidectomy

4.2 Exclusion Criteria- Children less than five years of age and tonsillectomy done to rule out malignancy.

5.0 Treatment of Subjects

This study will not affect the surgical treatment of the patients in any way. There are no interventions apart from the examination of the patient to assess tonsil size and the measurements of peak nasal and oral inspiratory flow.

6.0 Methods and Measurements

Peak Nasal Inspiratory Flow

The measurement of Peak Nasal Inspiratory Flow (PNIF) (litres/minute) will be performed using the In-Check portable nasal flow meter manufactured by Clement Clarke International Limited, England, according to the study site documented procedure for Measurement of Peak Nasal Inspiratory Flow.

The measurement of PNIF has been previously used to measure nasal obstruction. The technique involves the subject placing a mask over the nose and making a maximum effort to breathe in through the nose. The subject will be asked if they wish to gently blow their nose prior to any measurement.

The following data will be recorded at the pre-operative visit 1: -

iv. First PNIF value = PNIF (1)

v. Second PNIF value = PNIF (2)

vi. Third PNIF value = PNIF (3)

Peak Oral Inspiratory Flow

The measurement of Peak Oral Inspiratory Flow (POIF) (litres/minute) will be performed using the In-Check portable nasal flow meter manufactured by Clement Clarke International Limited, England. The measurement of POIF is often used to measure lower airway obstruction but can also be used as a measure of oral obstruction if the oral resistance is high, as in cases of tonsillar obstruction of the oral airway.

The following data will be recorded at the pre-operative visit 1: -

iv. First POIF value = PNIF (1)

v. Second POIF value = PNIF (2)

vi. Third POIF value = PNIF (3)

7.0 Assessment of safety and ethical issues

The measurement of peak nasal and oral inspiratory flow is a non-invasive measurement that is harmless and no safety issues are expected. Any adverse events will be documented and any serious adverse events will be reported within 48 hours to the sponsor and the ethics committee. Adverse events and serious adverse events related to the surgery will not be reported to the sponsor or the ethics committee, as they are not a consequence of this study.

One ethical issue considered by the investigators is that the patients and their parents or guardians should not feel in any way that they are obliged to participate in this study in order to receive or accelerate their surgical treatment. In order to ensure that the patients do not feel under any pressure to join in the study, the first contact with the patients will be

by letter explaining the study and asking them to respond if they wish to participate. Only after the patients have responded in a positive way will they be contacted by phone by the investigator, to discuss the study and explain any aspects that may not be clear to the patient. Again, it will be made clear at this stage that participation is entirely voluntary and will not in any way affect their treatment.

Another ethical issue is confidentiality of patient records and any information obtained from these records. All information from records will be kept confidential and the records will only be accessed by the clinical investigator.

8.0 Statistics

This is a pilot study to obtain new knowledge and no formal statistical plan is proposed apart from exploration of the data in tables and graphs. The data obtained from the study may be used for a power calculation for a larger study at a later stage. Examples of the type of exploratory analysis that will be performed are:

1. Scatter graphs of the data to look for outliers, and to examine distribution of data to determine if there is a normal distribution or other.
2. Comparisons of pre-operative and post-operative peak flow measurements with normal population data in the published literature.
3. Assessments of changes in peak flow due to surgery.

9.0 Funding and use of University and Hospital facilities and resources

The study will be funded from the research funds of the Common Cold Centre, Cardiff University. The study will form part of the research undertaken by the Clinical Investigator,

who is a qualified ENT surgeon, during his appointment as an ENT Research Fellow at the Common Cold Centre, Cardiff University. The study will not involve the use of any extra resources in terms of staff or space at the University Hospital, as participating patients will be seen by the Clinical Investigator during their normal pre-operative assessment. The Clinical Investigator will also see the patients at the Common Cold Centre as part of his normal research work.

10.0 Regulatory and Governance Approval and Indemnity

The study is not a clinical trial and does not need regulatory approval. The study will be submitted for approval to Cardiff University Research and Commercial Division, Cardiff and Vale Research and Development Office and the South East Wales Ethics Committee.

The study will be indemnified by the sponsor, Cardiff University, for any harm patients may suffer during participation in the study.

Appendix 2

Participant Information & Informed Consent

Study title

Study Title: **A pilot study on the assessment of upper airway obstruction in patients undergoing Tonsillectomy +/- Adenoidectomy for sleep related breathing disorders.**

Part 1 tells you the purpose of the study and what will happen to you if you take part.

Part 2 gives you more detailed information about the conduct of the study.

The study will investigate the effect of tonsillectomy and adenoidectomy on obstruction of the nose and throat.

This research is sponsored by:

Cardiff University, Cardiff.

PART 1 of the Information Sheet

What is the purpose of this study?

Obstruction of the nose and throat by enlarged tonsils may disturb breathing during sleep. The aim of this study is to investigate if surgery to remove tonsils and adenoids will relieve obstruction of the nose and throat.

Why have I been chosen?

You have been invited to participate because you are on the waiting list to have surgery to remove Adenoids+/- Tonsils.

Do I have to take part?

No, taking part is your decision. If you decide you don't want to take part, your care will not change in any way. But if you decide to take part then we will ask you to sign a consent form to show you have agreed to participate. You are free to withdraw at any time, without giving a reason.

What will happen if I decide to take part and how long will it take?

You will be contacted by one of the research team, who will discuss the project with you over the telephone and answer any queries. On the day of surgery at University Hospital, the researcher will examine you, and after obtaining written consent, will take measurements of obstruction of the nose and throat by asking you to breathe in rapidly through a Peak Flow meter. This will usually take about 3 -5 minutes in total. If you get upset at any time during the study, we will stop. An invitation will be sent after the surgery for a follow-up visit to the Common Cold Centre one month later, to repeat the same peak flow measurement.

What is a peak flow meter?

It is a small, hand-held device used to measure a person's ability to breathe air in or out through the nose or mouth. This type of meter is commonly used to measure breathing difficulty in persons suffering from asthma and the measurement is harmless.

What will I have to do during this peak flow measurement?

In order to measure nasal obstruction, you will be asked to breathe in as rapidly as possible through the nose whilst using a facemask connected to the meter. In order to measure throat obstruction, you will be asked to breathe in as rapidly as possible through the mouth via a plastic tube connected to the meter. Each measurement will be repeated three times, with six measurements in total.

What are the possible side effects of the test?

The measurement of nasal and throat airflow is harmless and this type of measurement is commonly made on patients with asthma, so no side effects are expected.

What are the possible disadvantages/ inconvenience of taking part in the study?

On the day of surgery, the researcher will examine you, and after obtaining written consent, will take measurements using the Peak flow meter. An invitation will be sent after the surgery for a follow-up visit to the Common Cold Centre one month later, to repeat the same peak flow measurement. You will be paid £25 travel expenses for the visit to the Common Cold Centre. The Centre is situated on Museum Avenue in Cardiff City Centre.

What are the probable benefits of taking part in the study?

Your treatment will not be affected in any way but we may find out more information about how your tonsils and adenoids may be obstructing your nose and throat and affecting your breathing. The study will help us to identify whether doing surgery on Adenoids and Tonsils will improve breathing through the nose and throat. This research may help the selection of patients for the treatment of sleep-related breathing disorders.

During the course of the study you can contact the Principal Investigator.

Mr Srinivasalu Bathala

Research Fellow,

Common Cold Centre

Biomedical Building

Museum Avenue

Cardiff University

Cardiff.

PART 2 of the Information Sheet

What if new relevant information becomes available?

Sometimes during the course of a research project, new information becomes available about the study. If this happens, your research doctor will tell you in a timely manner about it and discuss with you whether you want to continue in the study. If you decide to withdraw, your research doctor will make arrangements for your care to continue. If you decide to continue in the study, you will be asked to sign an updated consent form. Also, on receiving new information, your research doctor might consider it to be in your best interests to withdraw you from the study. He will explain the reasons and arrange for your care to continue.

What will happen if I don't want to carry on with the study?

If you decide to withdraw from the study, this will not affect your treatment. All data provided by you before withdrawal will still be recorded for use in the study

What happens if there is a problem?

Complaints: If you have concerns about any aspect of the study, you should speak to the researcher, who will do his best to answer any questions. Any complaints that you have about the study or the way it is conducted should be sent to: Professor Ron Eccles, Director, Common Cold Centre and Healthcare Clinical Trials, Cardiff University, Cardiff CF10 3AX, Tel: 02920 874102, email: eccles@cardiff.ac.uk. OR to Corporate Compliance Unit (COCOM), Cardiff University, email: cocom@cardiff.ac.uk, Tel: 02920 879639.

A copy of this information and signed Consent Form will be handed out to you.

Will my taking part in this study be kept confidential?

Yes, all the information will be anonymous. All those persons involved in looking at data from the study will have a duty of confidentiality to you as a research participant and we will do our best to meet this duty.

Involvement of the General Practitioner/Family doctor (GP)

Your GP will not be contacted. However, we may ask you to contact your GP if there are any findings from the tests that require further medical investigation.

What will happen to the results of the research study?

We may publish the results in scientific journals, but you will not be identified in any report or publication. However, no personal data will be sent outside the Centre. The protocol summary may be posted on a publicly available protocol register and a summary of the study results may be posted on a publicly available results register.

Who is organising and funding the research?

Cardiff University.

Who has reviewed the study?

This research has been reviewed and approved by:

South East Wales Local Research Ethics Committees

Business Services Centre,

Churchill House

17 Churchill Way

Cardiff,

CF10 2TW

During the course of the study you can contact the Principal Investigator.

Mr Srinivasalu Bathala

Research Fellow

Common Cold Centre

Biomedical Building

Museum Avenue

Cardiff University

Cardiff

CF10 3AX

Mobile no- 07912503865.

Patient Reply Slip.

I am willing /not willing to take part in the above mentioned study.

I can/ cannot be contacted over the telephone.

My telephone number is……

Signature……

Name ……..

Study Number:					
Screening Number:					
Patient Initials:					

Informed Consent Form

Study Title: **A pilot study on the assessment of upper airway obstruction in patients undergoing Tonsillectomy +/- Adenoidectomy for sleep-related breathing disorder**

Name of Researcher: Mr Srinivasalu Bathala

Information	Please Initial box
1. I confirm that I have read and understood the patient information leaflet for the above study. I have had the opportunity to consider the information, ask questions and have these answered satisfactorily.	
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without medical care or legal rights being affected.	
3. I understand that the relevant section of my medical notes and data collected during the study may be looked at by individuals from this NHS Health Board,	

where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records and understand that such information will be treated as confidential.	
4. I have the right to ask to see the data about me that has been collected and if anything is incorrect I can ask to have it corrected	
5. I agree to the information being processed and stored in coded form, so that my identity is kept confidential.	
6. I agree to take part in the above study	

Investigator delegate (Person taking Consent) I have explained and discussed with the patient the nature and purpose and requirements of the study. I will ensure a copy of this patient information leaflet is provided to the patient.

PARTICIPANT (PARENT OR GUARDIAN IF UNDER 18 YEAYEARS OF AGE)

Signed…….

Name (BLOCK LETTERS) ……

Date (dd/mmm/yy)……..

INVESTIGATOR/ DESIGNEE

Signed…….

Name (BLOCK LETTERS) ……

Date (dd/mmm/yy)…….

I have explained the study to the above participant and he/she has indicated his/her willingness to take part.

Appendix 3

Information sheet for Children aged 5- 10 years

This information is to be shown/ read by their parent or guardian

What is happening to me?

You are in the hospital to have your tonsils removed. While you are here, we are asking if you would take part in a test called a study.

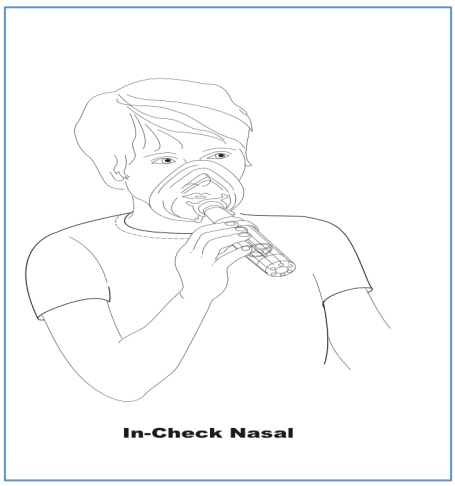
We would like to tell you about this.

Your mom and dad talked to the doctors and said it was ok for you to take part in the study.

What will the doctor do?

The doctor will examine you and ask you to breathe in through a tube, as shown below.

In order to measure how blocked your nose is, you will be asked to breathe in as rapidly as possible through the nose via a plastic tube connected to the meter as shown in the diagram below. Each measurement will be repeated three times and it takes about three minutes for this measurement to be taken.

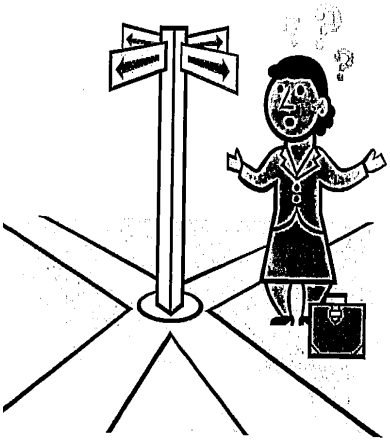


In order to measure how blocked your throat is, you will be asked to breathe in as rapidly as possible through the mouth via a plastic tube connected to the meter as shown in the diagram below. Each measurement will be repeated three times and it takes about three minutes for this measurement to be taken.

In-Check Oral

Do I have to do the study?

No, not at all.



It is up to you. Just say if you don't want to carry on. Nobody will mind and you will still be looked after. If you do, you will need to write your name (if you can) on the form.

Will I have to come back to the hospital again?

No, although you will come to see the same doctor in one month's time at Cardiff University and the doctor will ask you to breathe in through a tube as before.

Assent form for Children

Study Title: **A pilot study on the assessment of upper airway obstruction in patients undergoing Tonsillectomy +/- Adenoidectomy for sleep-related breathing disorders.**

(To be completed by the child and their parent/guardian)

Child (or if unable, parent on their behalf)/young person to circle all they agree with:

Has somebody explained this project to you? Yes/No

Do you understand what this project is about? Yes/No

Have you asked all the questions you want? Yes/ No

Have you had your questions answered

in a way you want? Yes/ No

Do you understand it's OK to stop taking

part at any time? Yes/No

Are you happy to take part? Yes/No

If any answers are No or you don't want to take part, don't sign your name.

If you do want to take part, you can write your name below.

Your name

Date

The doctor who explained this procedure to you needs to sign too:

Print Name

Sign Date

Consent for participation in study by parent/guardian.

Study Title: **A pilot study on the assessment of upper airway obstruction in patients undergoing Tonsillectomy +/- Adenoidectomy for sleep-related breathing disorders.**

I have read and understood the nature of the above study as explained in the information sent to me by Mr Bathala. I confirm that I have had the opportunity to ask questions.
I understand that as part of the study: (Please put your initials in the boxes if you agree to sign at the bottom of the letter where indicated)

Information	Please Initial Box
1. I confirm that I have read and understood the patient information leaflet for the above study. I have had the opportunity to consider the information, ask questions and have these answered satisfactorily.	
2. I understand that my child's participation is voluntary and that we are free to withdraw at any time without giving any reason, without medical care or legal rights being affected.	
3. I understand that the relevant section of my child's medical notes and data collected during the study may be	

looked at by individuals from this NHS Health Board, where it is relevant to my child's taking part in this research. I give permission for these individuals to have access to my child's records and understand that such information will be treated as confidential.	
4. I have the right to ask to see the data about my child that has been collected and if anything is incorrect I can ask to have it corrected	
5. I agree to the information being processed and stored in coded form, so that my child's identity is kept confidential.	
6. I agree for my child to take part in the above study	

Investigator delegate (Person taking consent) I have explained and discussed with the patient the nature and purpose and requirements of the study. I will ensure that a copy of this patient information leaflet is provided to the patient.

(PARENT OR GUARDIAN)

Signed…….

Name (BLOCK LETTERS) ……

Relationship to Patient

Date (dd/mmm/yy)……..

INVESTIGATOR/ DESIGNEE

Signed……

Name (BLOCK LETTERS) ……

Date (dd/mmm/yy)……..

I have explained the study to the above parent and he/she has indicated their child's willingness to take part.

Appendix 4

Information sheet for children (11-16 years)

This information is to be shown/ read by their parent or guardian

Aim: To assess your breathing after surgery on Tonsils +/- Adenoids.

Why have I been chosen?

With your help, we can find out whether removing the tonsils and adenoids has any effect on obstruction in the nose and throat. This will help doctors to select patients.

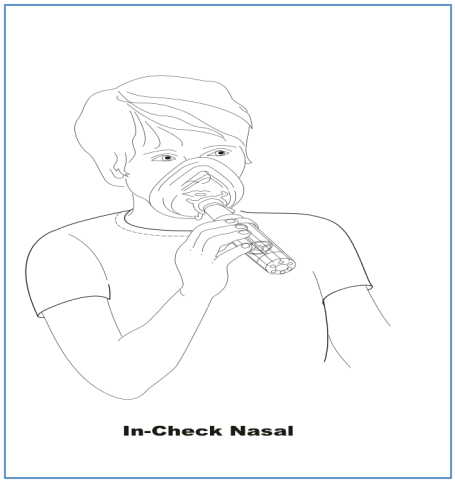
What will happen next?

On the day of surgery, the doctor will examine you and ask you to breathe in through a Peak Flow meter. The pictures on the next page show how this might be done.

Will I have to come back again to the hospital?

No, although you will have to come back one month later to Cardiff University to see the same doctor, who will ask you to again breathe in through a Peak Flow meter.

In order to measure how blocked your nose is, you will be asked to breathe in as rapidly as possible through the nose via a plastic tube connected to the meter as shown in the diagram below. Each measurement will be repeated three times and it takes about 3 minutes for this measurement to be taken.



In order to measure how blocked your throat is, you will be asked to breathe in as rapidly as possible through the mouth via a plastic tube connected to the meter as shown in the diagram above. Each measurement will be repeated three times and it takes about 3 minutes for this measurement to be taken.

Assent form for Children

Study Title: **A pilot study on the assessment of upper airway obstruction in patients undergoing Tonsillectomy +/- Adenoidectomy for sleep-related breathing disorders.**

(To be completed by the child and their parent/guardian)

Child (or if unable, parent on their behalf)/young person to circle all they agree with:

Has somebody explained this project to you? Yes/No

Do you understand what this project is about? Yes/No

Have you asked all the questions you want? Yes/ No

Have you had your questions answered

in a way you want? Yes/ No

Do you understand it's OK to stop taking

part at any time? Yes/No

Are you happy to take part? Yes/No

If any answers are No or you don't want to take part, don't sign your name.

If you do want to take part, you can write your name below.

Your name

Date

The doctor who explained this procedure to you needs to sign too:

Print Name

Sign Date

Consent for participation in study by parent/guardian.

Study Title: **A pilot study on the assessment of upper airway obstruction in patients undergoing Tonsillectomy +/- Adenoidectomy for sleep-related breathing disorders.**

I have read and understood the nature of the above study as explained in the information sent to me by Mr Bathala. I confirm that I have had the opportunity to ask questions.
I understand that as part of the study: (Please put your initials in the boxes if you agree to sign at the bottom of the letter where indicated)

Information	Please Initial Box
1. I confirm that I have read and understood the patient information leaflet for the above study. I have had the opportunity to consider the information, ask questions and have these answered satisfactorily.	
2. I understand that my child's participation is voluntary and that we are free to withdraw at any time without giving any reason, without medical care or legal rights being affected.	
3. I understand that the relevant section of my child's medical notes and data collected during the study may be	

looked at by individuals from this NHS Health Board, where it is relevant to my child's taking part in this research. I give permission for these individuals to have access to my child's records and understand that such information will be treated as confidential.	
4. I have the right to ask to see the data about my child that has been collected and if anything is incorrect I can ask to have it corrected	
5. I agree to the information being processed and stored in coded form, so that my child's identity is kept confidential.	
6. I agree for my child to take part in the above study	

Investigator delegate (Person taking consent) I have explained and discussed with the patient the nature and purpose and requirements of the study. I will ensure that a copy of this patient information leaflet is provided to the patient.

(PARENT OR GUARDIAN)

Signed…….

Name (BLOCK LETTERS) ……

Relationship to Patient

Date (dd/mmm/yy)……..

INVESTIGATOR/ DESIGNEE

Signed……

Name (BLOCK LETTERS) ……

Date (dd/mmm/yy)……..

I have explained the study to the above parent and he/she has indicated their child's willingness to take part.

Appendix 5

Demographics data

N	Sex	Age	RT	S	GASPING	OSA	INV	MED H/O	BRODSKY Grade
1	F	40	YES	YES	NO	NO	NO	ASTHMA	3
2	F	18	YES	YES	YES	NO	NO	ASTHMA	3
3	F	21	YES	YES	NO	NO	NO	NO	3
4	M	18	YES	NO	NO	NO	NO	NO	1
5	F	36	YES	YES	NO	NO	NO	NO	3
6	F	16	YES	YES	NO	NO	NO	ASTHMA	2
7	F	22	YES	NO	NO	NO	NO	NO	2
8	M	32	YES	YES	YES	YES	YES-ONPO	NO	3
9	M	24	YES	NO	NO	NO	NO	NO	3
10	F	21	YES	YES	NO	NO	NO	NO	2
11	M	29	YES	YES	NO	NO	NO	NO	3
12	F	32	YES	YES	NO	NO	NO	NO	4
13	M	23	YES	YES	NO	NO	NO	NO	2
14	F	31	YES	YES	NO	NO	NO	NO	3
15	F	7	YES	YES	YES	YES	NO	NO	3
16	M	7	YES	YES	YES	YES	NO	NO	4
17	F	5	YES	YES	YES	YES	NO	NO	4
18	M	7	YES	YES	YES	YES	NO	NO	3
19	M	46	YES	YES	NO	NO	NO	NO	3
20	F	14	YES	YES	NO	NO	NO	NO	2
21	M	12	YES	YES	YES	YES	NO	ASTHMA	3
22	F	6	YES	YES	YES	YES	NO	NO	3
23	F	14	YES	YES	NO	NO	NO	VW D	2
24	M	19	YES	YES	YES	YES	NO	NO	3
25	M	26	YES	NO	NO	NO	NO	NO	2
26	M	6	YES	YES	YES	YES	YES-ONPO	ASTHMA	3
27	F	7	YES	NO	NO	NO	NO	NO	3
28	M	24	YES	YES	NO	NO	NO	NO	2
29	M	29	YES	NO	NO	NO	NO	NO	3
30	F	20	YES	YES	NO	NO	NO	NO	3
31	M	36	YES	YES	YES	YES	YES-ONPO	NO	3
32	F	18	YES	NO	NO	NO	NO	NO	2
33	M	34	YES	NO	NO	NO	NO	NO	3
34	M	33	YES	YES	NO	NO	NO	NO	1

35	F	7	YES	NO	NO	NO	NO	NO	3
36	F	6	YES	NO	NO	NO	NO	NO	3
37	F	5	YES	YES	YES	YES	NO	ASTHMA	3
38	M	5	YES	YES	YES	YES	NO	NO	3
39	F	13	YES	YES	YES	NO	NO	NO	2
40	F	12	YES	YES	YES	NO	NO	NO	2
41	F	22	YES	YES	NO	NO	NO	NO	3
42	F	5	YES	YES	YES	YES	NO	NO	3
43	M	10	YES	YES	NO	NO	NO	NO	3
44	M	7	YES	YES	YES	YES	NO	NO	3
45	M	8	YES	YES	YES	YES	NO	NO	3
46	F	9	YES	YES	YES	YES	NO	NO	3
47	F	24	YES	YES	NO	NO	NO	NO	2
48	F	19	YES	NO	NO	NO	NO	NO	3
49	F	5	YES	YES	NO	NO	NO	NO	3
50	M	14	YES	YES	YES	YES	NO	NO	3