Nocturnal enuresis and rapid maxillary expansion

– long-term effect, prognostic variables, respiration during sleep and quality of life

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Abstract

Background: The orthodontic technique rapid maxillary expansion (RME) has been reported to have a potentially curative effect on nocturnal enuresis (NE). The mechanism behind this is unknown but could possibly be due to placebo and/or effects on respiration during sleep.

Aim: This thesis aims to approach an answer to the following questions, with a randomized, placebo-controlled method: 1) Does rapid maxillary expansion have a curative effect on therapy-resistant NE? 2) Is the potential curative effect due to respiratory events that can be measured during sleep? 3) Do enuretic children have an impaired quality of life (QoL)?

Subjects & Methods: In study I we evaluated the QoL in enuretic children while assessing the test re-test reliability of a Swedish version of an established QoL questionnaire. Study II and IV assess respiration during sleep in children with NE; in study II comparisons are made with healthy control children and in study IV we evaluate the respiratory effects of RME. Study III is a randomized placebo-controlled study investigating whether RME is a useful therapy for NE and if the treatment effect is due to placebo.

Results: Study I: The Swedish version of the questionnaire proved to be a reliable tool (Chronbach’s alpha 0.87) with excellent test-retest stability (ICC = 0.762). Enuresis affects the children’s QoL and interactions with peers.

Study II: The hypopnea index (HI) and the oxygen desaturation index were both significantly higher in the enuretic children compared to the healthy controls, (p=0.04 and p=0.05) but all values fell within the normal range.

StudyIII: RME resulted in a significant reduction in wet nights i.e. the mean number of wet nights out of 14 was 11.4 before and 9.2 after RME. (p=0.003) This was not observed in the placebo group (p=0.40).

Study IV: There was a significant reduction of sleep efficiency during RME. (p=0.001) The mean HI was also affected. (p=0.005)

Conclusions:
• Children with nocturnal enuresis have an impaired self-esteem and their quality of life is affected in their relationship with friends.
• There were no major differences in respiration during sleep between enuretic children and controls.
• Rapid maxillary expansion reduces the number of wet nights in children with enuresis, but the effect is of limited clinical value.
• The antienuretic effect does not seem to be due to a placebo effect of the appliance.
• The majority of the children in our study sample did not have sleep disordered breathing as a co-morbidity to their nocturnal enuresis.

Keywords: Rapid maxillary expansion, nocturnal enuresis, sleep disordered breathing, respiration, polygraphic sleep recording, quality of life.

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Dedicated in ever loving memory of the three Karins
My mother, my friend and my idol
This thesis is based on the following papers, which are referred to in the text by their Roman numerals.


IV Jönson Ring I, Nevéus T, Bazargani F, Markström A. Respiratory changes during sleep in enuretic children treated with rapid maxillary expansion. Manuscript.

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Abbreviations

AASM  American Academy of Sleep Medicine
ADHD  Attention Deficit Hyperactivity Disorder
AHI   Apnea Hypopnea Index
EEG   Electro Encephalography
HI    Hypopnea Index
HI    Hypopnea Index
HRQoL Health Related Quality of Life
ICC   Intra-class Correlation Coefficient
ICCS  International Children’s Continence Society
MANOVA Multivariate Analysis of Variance
NE    Nocturnal Enuresis
NICE  National Institute for Health and Care Excellence
OR    Odds Ratio
OSA   Obstructive Sleep Apnea
OSA 18 Obstructive Sleep Apnea 18 questionnaire
PinQ Pediatric Incontinence Questionnaire
PinQ-SWE Pediatric Incontinence Questionnaire, Swedish
PSG   Polysomnography
QoL   Quality of Life
RIP   Respiratory Inductance Plethysmography
RME   Rapid Maxillary Expansion
SDB   Sleep Disordered Breathing
SE    Sleep Efficiency
T&A   Adenotonsillectomy
UAO   Upper Airway Obstruction
Definitions

Enuresis  Involuntary urine leakage during sleep in children aged five years or older. The condition is also classified as monosymptomatic or non-monosymptomatic depending on the presence or absence of daytime lower urinary tract symptoms.

Detrusor overactivity  The appearance of involuntary, uninhibited detrusor contractions.

Apnea  A discrete pause in breathing with cessation of airflow 10 sec or more.

Arousal  An interruption of continuous sleep, not necessary reaching a fully awake state.

Hypopnea  A 30% reduction of airflow with continued respiratory effort.

AHI  The mean number of apneas and hypopneas per hour of sleep.

AI  The mean number of apneas per hour of sleep.

HI  The mean number of hypopneas per hour.

OSA  An obstructive AHI of 5 or more.

Cross bite  A malocclusion where the buccal cusps of canine, premolars and molars of upper teeth occlude lingually to the buccal cusps of canine, premolars and molars of lower teeth.

Mid palatal suture  The suture that joins the right and left part of the palatine process of the maxilla.

Hyrax screw  The Hygienic Rapid Expander is a type of jack screw used for palatal expansion.
Introduction

Nocturnal Enuresis; epidemiology and pathogenesis

Bedwetting, or nocturnal enuresis (NE) is defined as involuntary urine leakage in discrete portions while asleep in children aged five years or older. Enuresis is considered primary if the child has never been reliably dry, and secondary when the bedwetting re-occurs after the child has been consistently dry for six months or more. The condition is also classified as monosymptomatic or non-monosymptomatic depending on the presence or absence of daytime lower urinary tract symptoms. The enuresis can occur at any stage of the sleep and also several times per night.

Thus, enuresis is diagnosed after the age of five or more and typically treated after the age of six or more. NE is common and not a trivial disorder. The prevalence at the age of seven is about 10%, and for many of these children it can persist into teen age or even adulthood (0.5-1%). Males are more commonly affected at all ages. Enuresis is often inherited. The risk of the child being affected is five to seven times higher if one, and 11.3 times higher if both parents have a history of NE.

Modern research has demonstrated three central causes in the pathogenesis of NE:

1) **Nocturnal polyuria** – Many enuretic children produce more urine at night than their bladder can physically hold. This nocturnal polyuria is often linked to a nocturnal lack of the antidiuretic hormone vasopressin. However, not all enuretic children have nocturnal polyuria and the polyuria itself does not explain why the children do not wake up when their bladder is full.

2) **Detrusor overactivity** – The detrusor is a major component of the bladder wall. It normally remains relaxed to allow the bladder to fill to capacity and should only contract as part of a coordinated micturition reflex and when allowed to by higher cortical centers. Detrusor overactivity denotes the appearance of involuntary, uninhibited detrusor contractions. Secondary detrusor overactivity can sometimes be linked to constipation. Some enuretic children have been shown to
exhibit detrusor overactivity, i.e. their bladder has a tendency to suddenly contract during sleep regardless of being full or not.\textsuperscript{12}

3) \textit{Sleep and arousal mechanisms} – Almost all enuretic children are considered difficult to arouse from sleep by their parents.\textsuperscript{13} This has also been corroborated by measurements of objective arousal thresholds.\textsuperscript{14} The reason for this is not quite clear but both detrusor contractions and bladder distension are recognized as strong arousal stimuli, yet these children fail to awaken.\textsuperscript{15} Still, it should be noted that although the sleep of enuretic children may be "deep", it is not necessarily good. In fact, their sleep may be disturbed by frequent, inefficient arousal reactions.\textsuperscript{16}

\textbf{Fig 1.} The three-system model of enuresis pathogenesis.

In summary, enuresis is not one condition but several and different children wet their beds for different reasons. This can be illustrated with the “three-system” model, in which enuresis is described as a result of a mismatch between urine production and bladder storage capacity, combined with high arousal thresholds. (Fig 1) Furthermore, it is not unusual that all three causes are present in the same child.\textsuperscript{17}

Upper airway obstruction (UAO) is usually not the primary cause of NE but has been shown to lead to enuresis in a subgroup of children.\textsuperscript{18,19} Enuresis has also been commonly found in children with obstructive sleep apnea syndrome.\textsuperscript{20} Hence, respiratory disturbances during sleep can also play an etiologic role in NE.
Consequences

Enuretic children often have a poor self-image and low self-esteem. This is not due to underlying psychopathology or insufficient parenting, as was previously thought. The general consensus today is that causation goes in the other direction; i.e. that enuresis often causes psychological problems via low self-esteem. Another link between enuresis and psychiatry is that the disorder, for unclear reasons, is overrepresented among children with neuropsychiatric conditions such as attention deficit hyperactivity disorder (ADHD). Other long-term consequences are increased risks of conduct problems and anxiety. All in all, the risk of comorbid psychological disorders or behavioral problems is two to four times higher than in non-enuretic children.

To suffer from enuresis has a negative influence on health related quality of life (HRQoL), in both children and their families. Enuretic children have lower perceived competence concerning physical appearance and global self-esteem and the condition has important negative effects on self-image and performance. The social and psychological distress afflict not only the child but also his or her family.

Sleep

As mentioned above, sleep and arousal mechanisms are crucial in the pathogenesis of NE. That these children are difficult to arouse from their sleep is universally reported by parents. Also, in wake-up tests, enuretic children have been confirmed to be more difficult to arouse at night compared with non-enuretic peers.

A number of polysomnography (PSG) studies of enuretic children, focused on sleep electroencephalography (EEG), have been carried out over the years without revealing any major differences in sleep architecture when compared to healthy controls. Evidence is, however accumulating that they may have a more disturbed sleep, as more bodily movements and sleep fragmentation have been found. Thus, enuretic children may be considered to be "deep" sleepers only in the sense that they have high arousal thresholds.

Sleep disordered breathing

Sleep disordered breathing (SDB) and NE are both common problems of sleep in childhood, and the two conditions have been reported to be associated with each other. SDB is characterized by an abnormal respiratory pattern during sleep, ranging from habitual snoring to obstructive sleep apnea, and is often found in children with upper airway obstruction. The prevalence of NE in
children with SDB was found to be 31%, in a systematic review. A recent study by Bascom et al. found that children referred for PSG, for sleep related symptoms, and who presented with NE, had greater respiratory abnormalities than children without NE. Adenotonsillar hypertrophy is a well-known risk factor for SDB in children, and adenotonsillectomy (T&A) has proven to have a positive effect on NE.

The connection between NE and SDB is complex and not fully understood. Increased respiratory efforts leads to increased negative intrathoracic pressure which in turn causes polyuria via increased secretion of atrial and brain natriuretic peptide. This could presumably result in enuresis due to nocturnal polyuria. Another possible explanation may be that repeated arousal stimuli from the airways leads to paradoxically increased arousal thresholds since otherwise the sleep would be constantly interrupted. As an illustration: if someone keeps knocking at your door you end up changing the locks.

**Sleep monitoring**

Polysomnography is the gold standard for diagnosing SDB and other sleep disorders. Standard PSG includes recording brain activity via EEG, as well as airflow, oxygen saturation, heart rate, respiratory effort, eye movements and muscle movements during the night. Overnight PSG is traditionally performed in a sleep laboratory. Information regarding sleep stages, arousal measurements, cardiovascular parameters, respiratory parameters and saturation can afterwards be extracted from the recording. As mentioned above, PSG studies have shown a fairly normal sleep stage distribution among enuretic children, i.e. their sleep architecture does not necessarily differ from that of healthy peers, although their sleep may be disturbed by recurrent, inefficient arousal reactions.

The PSG procedure is unfortunately costly and labor-intensive. Also, the number of sleep study facilities available is limited. During the examination the child and one caretaker have to sleep in a sleep laboratory at the hospital for overnight monitoring. This may cause the family some inconvenience and, more importantly, change the sleeping pattern of the child as compared to when sleeping at home. A variation in the sleep quality has been observed in PSG studies, which often results in a decreased total sleep time, as well as other changes to the polysomnogram. This phenomenon is referred to as “first night effect”. As a way to diminish this effect, home respiratory polygraphy has recently become a well-accepted alternative to PSG in adults.

Polygraphy is another sleep recording technique, albeit with limited parameters. Most devices rely on three primary signals in order to measure respiratory variables during sleep, namely airflow, respiratory effort and oximetry. The
technique has also emerged as a potentially useful and reliable method in children.\textsuperscript{48,49} Home registrations are performed with a portable device that usually measures airflow, respiratory effort, heart rate, and oxygen saturation. The appliance can be fitted by a trained person at the hospital, but more often by the patient itself or an assisting person at home. The benefits of this method is that it costs less, is less labor demanding and the patient can sleep at home in their own bed, likely with less “first night effect”.\textsuperscript{46} The disadvantage of a home study is obviously the more limited information but also an increased risk of signal failure as there is nobody monitoring the sleep and problems can arise when fitting the equipment at home. Some variables are also known to be underestimated when scoring polygraphic data, compared to PSG.\textsuperscript{50}

Quality of life (QoL)

QoL studies have attracted an increased interest over the last two to three decades. The World Health Organization defines QoL as “the individuals’ perception of their position in life in the context of culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns”.\textsuperscript{51}

QoL studies have shown that enuretic children often have a poor self-image and lower self-esteem than their healthy peers.\textsuperscript{21,26,52} This, in turn, may cause psychosocial dysfunction. Consequently, 20\%–30\% of children with enuresis show some degree of psychosocial distress which, in turn, may lead to a higher risk of behavioral problems.\textsuperscript{23}

There is no universal QoL instrument, but different tools have been developed for various patient groups. Attempts to develop a pediatric questionnaire with the specific aim to assess the impact of incontinence on a child’s everyday life were published at the turn of the millennium.\textsuperscript{53,54} Around the same time a QoL instrument for children with obstructive sleep apnea was made available.\textsuperscript{55}

The Pediatric Incontinence Questionnaire (PinQ)

Bower et al. in 2006, after rigorous efforts, managed to create a cross-cultural tool specific to children with lower urinary tract dysfunction, the PinQ.\textsuperscript{56} This instrument has proven to be a reliable and valid way to quantify the holistic effect of bladder dysfunction in children and it is the available tool recommended for assessing self-reported health related quality of life (HRQoL) in children with urinary incontinence.\textsuperscript{57} PinQ has also been used to measure changes in QoL during therapy.\textsuperscript{58,59} The questionnaire is easily administered and easy to complete and is now the most widely used tool in pediatric incontinence.
The Obstructive Sleep Apnea instrument (OSA 18)

OSA 18 is a valid and reliable questionnaire which is the most widely used QoL instrument in children with SDB. This is another disease specific tool developed by Franco et al. as a practical means of office-based QoL measure for children with obstructive sleep apnea syndrome. The questionnaire is suitable for use in a wide variety of situations, for example longitudinal change in disease specific QoL for children with SDB.

Enuresis management

Evaluation

A good case history is crucial in the primary evaluation of children with NE. Both the International Children’s Continence Society (ICCS) and National Institute for Health and Care Excellence (NICE) recommends that a thorough assessment is carried out when diagnosing NE. Underlying causes need to be identified or excluded. Comorbid conditions, such as constipation, behavioral issues or sleep-disordered breathing may be present and may affect the chances of a successful treatment. It is also desirable to understand the family situation and preferences when choosing treatment strategy.

Much of the history should be focused on voiding habits, and these data are preferably objectivized with the use of a bladder diary. Bladder diaries are used to assess 1) symptom severity, 2) daytime voiding habits, 3) nocturnal urine production, and 4) the family's capacity to adhere to instructions given. The standard bladder diary consists of two parts; a) a simple recording of wetting episodes during one or two weeks, and b) the recording, during 2-3 days and nights, of the volume and timing of each micturition as well as measurements of the amount of urine lost in bed via the weighing of diapers.

Provided there are no warning signs present in the case history, no blood tests or radiological/urodynamical investigations are needed.

First-line therapy

Understanding the pathogenesis behind each child’s enuresis is of great importance when selecting the appropriate treatment. There are two established and evidence-based first-line treatments of enuresis today: the enuresis alarm and the antidiuretic drug desmopressin.

The alarm device consists of a moisture detector, usually fitted in the child’s underwear, and an alarm. Each time urine activates the sensor the alarm will go off. The child then wakes up either by the alarm itself or, more often, by a
parent. The mechanism of the therapeutic effect is still not fully understood, but it can be assumed that the patient either is conditioned to awake before the bladder emptying or learns to inhibit the detrusor contraction without fully waking up. About half of the children in unselected enuretic populations can be expected to respond to alarm treatment. Successful alarm therapy requires motivated, compliant children with supportive families, since it takes some effort to use the device correctly. The first few weeks are usually the most demanding. Another issue with this treatment is that it requires more time than pharmacological interventions. Therefore, the alarm should perhaps not be recommended to families who already struggle to cope or who are not fully motivated.

Desmopressin is a synthetic analogue of vasopressin. It is taken at bedtime in order to decrease the urine production during the night. Desmopressin is usually not a curative treatment, but the medication can be given for long periods without risk and can also be used as a temporary relief, provided it works at all. Approximately one third of patients have a full response to desmopressin therapy, and the response (or nonresponse) will be apparent immediately. Since the antienuretic action of desmopressin is via reduction of nocturnal urine production, the chance for treatment success is greatest for children with nocturnal polyuria.

Second-line therapy

Anticholinergic drugs and tricyclic antidepressants can be used in difficult cases who don’t respond to first-line treatment. These treatments are, however, associated with a number of side effects and special caution should be taken.

About 25% of all children with NE do not respond to any first-line treatment, and second-line therapies are neither universally effective nor free from side effects. There is thus a need for new, safe therapies for enuretic children who do not respond to first-line therapy.

Adenotonsillectomy has been reported to lead to resolution in about half of the cases in the small group of children with both NE and SDB. Children with NE who snore heavily or suffer from sleep apnea should therefore be examined by an ear, nose and throat specialist.

One alternative treatment method that has been described reported to have a curative effect on NE is that of rapid maxillary expansion.
Enuresis and orthodontic therapy

In the early 1990’s Timms reported some cases of enuretic children with upper airway obstruction who became dry after orthodontically widening the palate, using the rapid maxillary expansion (RME) technique (explained below). 71 Since then a number of prospective studies have been carried out which, although neither randomized nor controlled, also suggest that the method can help against NE. 72-77 Kurol repeated Timms study but also carried out some radiographic examinations as well as anterior rhinomanometry. The reported short-term success rate was 70%. No association was found between improvement in NE and improvement in the nasal airway, age, amount of expansion nor nasopharyngeal dimensions as measured on cephalograms. In his discussion he speculates that the results can either be assigned to placebo effects or improved breathing and better oxygen saturation. 72 A similar rate of improvement was later reported in a study on eight children at an orphanage. However, none of these children became completely dry. 73 A follow-up on Kurol's study, with a slightly lower success rate, was then published. In this study younger children responded better to the treatment and the results were stable. 74 Then came a very promising study in which all patients had exhibited an improvement in their enuresis frequency. In this study an attempt to investigate a potential placebo effect was also carried out but no such effect could be found. It also confirmed that nasal airflow increased and nasal airway resistance decreased after RME. 75 A meta-analysis of the above articles, plus one more study published only in Persian, suggested a cure rate of 31% one year after treatment. 78 The most recent study, in which a population of decent size was recruited, reported that almost half of the children became dry or almost dry after RME treatment. 77 Worth mentioning is that most of the patients in this latter study were therapy resistant, in other words had tried both the alarm and desmopressin without success.

We still don’t know why RME sometimes seem to help enuretic children become dry, but the sleep of the children must somehow be involved. It may be speculated that the treatment affects the arousability via amelioration of sub-clinical airway obstruction.

Rapid Maxillary Expansion

RME is an orthodontic procedure used to widen the maxilla in cases with transverse deficiency, i.e. a narrow upper jaw. Force is applied to the maxilla and teeth by means of a brace, which leads to widening and gradual opening of the mid-palatal suture. (Fig 2) This orthopedic effect is clinically proved by the opening of a midline diastema between the upper central incisors. 79,80 The technique was first described by Angell in 1860, when he managed to separate
the maxillary bones on a 14-year old girl with an anterior cross-bite. The appliance/brace was designed with bearing ends against the first and second premolars on the one side and against only the second premolar on the other side. A jackscrew was placed in the middle across the roof of the mouth and was then activated by a parent on a daily basis until a satisfactory expansion had been achieved. The technique became popular about a century later when Haas re-introduced a similar device. Various designs have been developed over the years and RME is now a standard procedure in contemporary orthodontics.

Fig 2. Mid-palatal suture.

Most expanders consist of a jackscrew soldered to orthodontic bands and support wires made of stainless steel. (Fig 3) The expansion screw can also be incorporated in palatal acrylic pads and bonded acrylic splint expanders. More recently bone-borne and tooth-bone-borne appliances have been developed that are anchored to mini-implants in the roof of the mouth. A systematic review by Algharbi et al. found that all types of maxillary expansion appliances produced a significant expansion of the mid-palatal suture.
The screw is activated with a small tool-key and each turn usually generates an expansion of 0.2-0.25 mm. It is recommended that this procedure is carried out by an adult assisting person, not the patient him/herself. The suggested activation protocol is usually that the screw should be turned once or twice per day until the desired amount of expansion has been achieved. Expansion of the suture can also be achieved with a slower expansion-rate, with activation about twice per week or every other day.

RME increases the transversal width of the palate by opening the mid-palatal suture. The understanding of the sutural morphology and development became clear by Melsen's studies on human autopsy material. As the suture matures, it becomes more interdigitated and tortuous. Hence, separation of the suture becomes more difficult with increasing age and should ideally be carried out before the peak in skeletal growth velocity. Other skeletal effects observed after RME is a downward and forward displacement of the maxilla. The circummaxillary sutures also appear to be affected with an increased width. Dentoalveolar effects observed with the treatment is the opening of a diastema between the central incisors and buccal tipping of the maxillary posterior teeth. Anatomically, there is also an increase in volume of the nasal cavity and nasopharynx. The nasal airflow increases with less nasal airway resistance. No effect, however, has been found on the pharyngeal airway volume.
RME can be associated with some discomfort, such as pain and pressure sensations\textsuperscript{103,104} but is generally a well-tolerated treatment\textsuperscript{105}. Pain reported during RME could possibly be influenced by skeletal maturity\textsuperscript{106}. 
Aims of the thesis

The overall purpose of the thesis was to investigate the curative effect rapid maxillary expansion may have on nocturnal enuresis, and at the same time evaluate if the effect is due to respiratory events and if there are any prognostic variables that can be identified. We also wanted to look at health-related QoL in enuretic children.

I. The first study aims to evaluate QoL in Swedish children with NE and to test the reliability and test–retest stability of a Swedish translation of the PinQ instrument.

II. The second study aims to evaluate sleep disordered breathing in enuretic children and compare them with healthy control children without NE.

III. The third study is a randomized placebo-controlled trial investigating the curative effect RME may have on therapy-resistant NE.

IV. The fourth study aims to assess respiratory variables before and after RME in enuretic children.
Subjects and Methods

Subjects study I
The participants were recruited from two pediatric clinics: Uppsala University Children’s Hospital and Örebro University Hospital. Children from 6 to 18 years of age with NE who attended the specialist clinics between June 2013 and February 2016 were consecutively asked to participate in the study.

Subjects study II
Children 8-13 years old with nocturnal enuresis were invited to participate in the study. The children were recruited from the tertiary enuresis center, Uppsala University Children’s Hospital. A control group with healthy age- and gender-matched children were recruited among families known to the members of the research team. None of these children had micturition problems or a history of snoring.

Subjects study III and IV
Participants were recruited at the tertiary enuresis center at Uppsala University Children’s Hospital, Uppsala, Sweden. Children under the age of 14 years with primary NE were invited to participate in the study. A consecutive recruitment process was carried out between years 2013 and 2018.

Inclusion criteria for all the studies were (for the enuresis patients): primary nocturnal enuresis with at least seven wet nights out of 14. Exclusion criteria were: daytime incontinence, ongoing antienuretic treatment, or concomitant urological, endocrinological, nephrological, or psychiatric disorders. Well-functioning patients with treated ADHD were not excluded.

The majority of subjects were non-responders to first-line treatment and were therefore classified as “therapy resistant”.

Ethical considerations

Ethical approval for the studies was acquired from the Regional Ethics Review Board of Uppsala University, Sweden, registration number 2012/379. All procedures adhered to the Declaration of Helsinki.

Verbal informed consent was obtained from all patients and their guardians in study I. Written and verbal informed consent was obtained from all subjects and their guardians in study II, III and IV.

The study was registered at ClinicalTrials.gov, Identifier: NCT02178826 and Researchweb Sweden, document 108811.

Methods study I

In this study we tested the reliability and test–retest stability of a Swedish translation of the Pediatric Incontinence Questionnaire (PinQ), the internationally most relevant and widely used QoL instrument when it comes to bladder dysfunction in children. This was also a cross-sectional study evaluating HRQoL in children with NE in two tertiary care centers.

The PinQ instrument

This questionnaire was developed by an international group of clinicians within the field of childhood bladder dysfunction and has previously been available in English, Dutch, Chinese and German. It is specific to children with lower urinary tract dysfunction and has proved to be a reliable and valid tool in this group.

The PinQ consists of 20 items that measure the impact of bladder dysfunction on daily life for children with urinary incontinence. The items have five response options that follow a Likert scale: zero equals no/never, one is hardly ever, two is sometimes, three is often and four is all the time. A total score is calculated and a higher sum indicates a lower QoL. The tool has five subscales: social relations with peers, self-esteem, family and home, independence, and mental health. The maximum sum score is 80, and the ranges for the subscales are 0–24, 0–16, 0–16, 0–8 and 0–16, respectively.

The original version of the PinQ was translated into Swedish by an independent translation firm and the translated version was then discussed within the research group, which consisted of three members of the research team, all three bilingual English-speakers. Minor adjustments were made before the questionnaire was retranslated back into English. No major differences were
found between the original PinQ and the retranslated version. A final Swedish version, the PinQ-SWE, was then agreed upon.

Procedure
The first questionnaire was sent out by post and self-administered by the patient with the help of an adult, if required. The second questionnaire was completed in conjunction with the consultation in 33 cases (but still independently by the child and guardian). Occasional missing values were substituted if the missing values were no more than 25% of the items of each subscale. A mean sum score based on the other items in each subscale was used as substitute.

Methods study II
In this thesis we performed polygraphic home recordings focused on respiration, since our main interest was not EEG or sleep architecture, which has been studied in some detail before. To limit the effects of signal failure, a person from the research team (IJR) fitted all the appliances throughout the study.

Procedure
Each participant underwent one night of cardiorespiratory polygraphy. The recordings were performed with a portable sleep device (NOX T3, NOX Medical®, Iceland). Respiratory effort was measured using thoracic and abdominal strain gauges, nasal airflow was recorded via nasal cannula and pressure transducer and oxygen saturation (SpO₂) was collected via wireless finger pulse oximetry (Nonin® 3150 Wristox2 Bluetooth wrist pulse oximeter). To evaluate the sleep-wake pattern and arousals during sleep two central EEG electrodes were fitted (in the C3 and C4 positions) with contralateral mastoid reference electrodes (M1, M2). A ground electrode was placed on the forehead (Fpz). (Fig 4)

The records were autoscored using Noxturnal® Software, version 3.2.0 (NOX Medical®, Iceland) and then manually scored by an experienced physician accredited in sleep medicine (AM), according to American Academy of Sleep Medicine (AASM) standards. A respiratory event was scored as an apnea when the oronasal airflow dropped \( \geq 90\% \) of the pre-event baseline for the duration of more than two breaths. A hypopnea was scored when the oronasal airflow dropped \( \geq 30\% \) of pre-events baseline with \( \geq 3\% \) desaturation during more than two breaths. The apnea-hypopnea index (AHI) was calculated as the number of apneas and hypopneas per hour. An abrupt EEG frequency shift
greater than 16 Hz with a duration of three seconds or more was scored as an arousal reaction.

Variables typically extracted from the respiratory report are provided in Table 1.

**Table 1.** Polygraphic variables.

<table>
<thead>
<tr>
<th>Polygraphic variables</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total sleep time (TST)</td>
<td>Minutes</td>
</tr>
<tr>
<td>Sleep efficiency (SE)</td>
<td>TST/time in bed</td>
</tr>
<tr>
<td>Apnea/hypopnea index (AHI)</td>
<td># of apneas + hypopneas/hour TST</td>
</tr>
<tr>
<td>Apnea index (AI)</td>
<td># of apneas/hour TST</td>
</tr>
<tr>
<td>Hypopnea index (HI)</td>
<td># of hypopneas/hour TST</td>
</tr>
<tr>
<td>Snore index</td>
<td>Total duration of snore episodes as a percentage of time in bed</td>
</tr>
<tr>
<td>Flow limit index</td>
<td># of partial collapses of the airway with criteria not meeting that of a hypopnea/hour TST</td>
</tr>
<tr>
<td>Desaturation index (ODI)</td>
<td># of desaturation episodes/hour TST</td>
</tr>
<tr>
<td>SpO₂ nadir</td>
<td>Lowest oxygen saturation</td>
</tr>
<tr>
<td>SpO₂ mean</td>
<td>Average oxygen saturation</td>
</tr>
<tr>
<td>Heart rate</td>
<td>Number of contractions of the heart per minute</td>
</tr>
<tr>
<td>Oximeter quality</td>
<td>% acceptable signal from the oximeter</td>
</tr>
<tr>
<td>Flow quality</td>
<td>% acceptable signal from the nasal cannula</td>
</tr>
<tr>
<td>RIP quality</td>
<td>% acceptable signal from the thoracic and abdominal belts</td>
</tr>
</tbody>
</table>

The polygraphy appliance was fitted in the Sleep and Breathing Centre at Uppsala University Hospital and the recordings were then performed at the patient’s home, overnight, during sleep. To limit signal failure, the nasal cannula was fixated with plaster tape to the patients’ cheeks and electrodes were taped together to prevent limitation of movements.
The OSA 18 questionnaire

On the night of the registration the child, together with his/her parents, also completed the questionnaire OSA 18, a validated health-related quality of life (HRQoL) instrument used to evaluate issues related to sleep and breathing. This questionnaire consists of 18 items in 5 different domains: sleep disturbance, physical symptoms, emotional distress, daytime function and caregiver concerns. It also has one item with a 10-graded scale on the perceived general feeling of quality of life (QoL). In this study we looked at the total score (OSA 18 total score) and the domain sleep disturbance (OSA 18 sleep score). The range for OSA 18 total score and OSA 18 sleep score is 18-126 and 4-28, respectively, with a higher score indicating a more severe degree of subjective sleep disturbance. Scores less than 60 suggest a mild impact on HRQoL, whereas scores between 60 and 80 suggest a moderate and scores above 80 a large impact.
Methods study III

This was a randomized, placebo-controlled trial following the study protocol described in Fig 6. Patients were recruited at Uppsala University Children’s Hospital where they were examined by a pediatrician. A thorough medical history with focus on micturition habits, heredity, previous treatment and sleep disorders was taken and the families registered enuresis episodes in a voiding chart over two weeks and daytime voided volumes and nocturnal urine production (weighing diapers or sheet covers) during one weekend 2014, in accordance with the recommendations by the ICCS.1 The RME treatment was carried out at the Orthodontic department, Public Dental Service, Region Uppsala, Sweden, where the patients were randomly allocated to either the intervention group or the placebo group.

Evidence-based practice proposes that clinical problems that emerge from care practice or research be decomposed and organized using the PICO strategy.109 PICO represents an acronym for Patient, Intervention, Comparison and Outcome. These four components are essential elements of the research question. The PICO strategy for paper III is defined in Table 2.

Table 2. PICO strategy.

<table>
<thead>
<tr>
<th>P</th>
<th>Patient</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Children with Nocturnal Enuresis (NE)</td>
<td>Rapid Maxillary Expansion (RME)</td>
<td>Placebo appliance</td>
<td>Does RME have a curative effect on NE?</td>
</tr>
</tbody>
</table>

“In patients with nocturnal enuresis…”

…would rapid maxillary expansion …

…when compared with a placebo appliance…”

…lead to a curative effect on the enuresis?”

The RME appliance

The orthodontic appliance consisted of a Hyrax screw soldered to orthodontic bands on the permanent first upper molars and occlusal support wires extending to the first premolars. (Fig 5) Guardians were instructed to activate the Hyrax screw twice daily, which generated an expansion rate of approximately 0.5 mm per day. The end point was defined as when the occlusal surface of the palatal cusp of the upper first permanent molar came into contact with the occlusal surface of the buccal cusp of the lower first permanent molar.
Randomization
The randomization was based on a computer-generated sequence. To ensure homogeneity between the groups the random allocation was carried out in blocks of different size using a concealed principle in a 1:1 ratio. To keep the recruitment and randomization process separated, an independent member of staff at the orthodontic clinic administered the group allocation.

Sample size calculation
The sample size was based on previous studies by Nevèus et al. on similar populations.\(^{110}\) We can assume the number of wet nights out of 14 (±1 SD) to be 11.5±2.7 without treatment. The calculations indicated that 18 participants in each group were required in order to have a 90% chance of not missing a decrease of three wet nights or more in the intervention group compared to the placebo group. Smaller differences were not considered clinically relevant. The significance level was set at 5%.

The intervention
The patients in the intervention group were treated with RME for 10–14 days (T1), while the placebo group were treated with a sham appliance the same duration (T1). The sham appliance was identical to the RME appliance used for the intervention group, except that the expansion screw did not generate any expansion. The instructions were the same for both groups which was described earlier. The randomization was then revealed after the initial expansion. For the placebo group the sham appliance was removed and now replaced by an active RME appliance and the treatment again went on for 10–14 days. To prevent the bite from relapsing we kept the expanded appliance in situ for six months, after which it was removed and a final registration was carried out (T\(_{6\text{mon}}\)). Both groups continued documentation of wet and dry nights throughout the study period.

Figure 5. RME before (A) and after (B) expansion.
To make a prognostic analysis the children were at T6_{mon} classified as responders or non-responders, according to the ICCS definitions. Full response was defined as a reduction over 90%, intermediate response as reduction of 50% to 89% and no response as 0% to 49% reduction.

**Blinding**

The participants were blinded to the allocation sequence. It was however not possible to blind the clinician as the appliance had to be handled during the fitting.

**Dental study casts**

Dental study casts were taken at baseline (T0) and after 6 months (T6_{mon}). The baseline casts were used for classification of the occlusion, according to Angle. (Angle) The intermolar, interpmolar and intercanine distances were evaluated at T0 and T6_{mon}. The intermolar distances were measured at the shortest intermolar linear distance at the gingival margins and the mesiobuccal cusp tips of the teeth. The interpmolar and intercanine distances were measured at the buccal cusp tip. A digital caliper was used for all measurements (Pluradent Art.-Nr: 12842, Offenbach, Germany).

To evaluate the outcome reliability for the study cast measurements 20 randomly selected cases were measured twice. The random sequence was generated with a random integer set generator at www.random.org.

**Quality of life**

The PinQ-SWE was administered at baseline (T0) and after 6 months (T6_{mon}) to assess treatment effects on QoL.
Methods study IV
In this study we have evaluated respiration during sleep in the enuretic children who had been treated with RME. Polygraphic night registrations were carried out in the same way as in study II before, during and 6 months after RME.
Statistical analysis

The statistical analyses were performed with IBM SPSS statistics, version 22.0 for Windows, IBM SPSS statistics, version 22.0 for Mac OS, SPSS statistics, version 25.0 for Mac OS (IBM® SPSS Statistics®, Chicago, IL), IBM SPSS Statistics 22 (Armonk, NY, USA) and STATA release 14 (STATACorp, College Station, TX, USA).

A p-value of less than 5% (P < 0.05) was considered statistically significant.

Study I

Student’s t-test was used to test for differences according to gender and age, and multivariate analysis of variance (MANOVA) to test for these differences simultaneously. Cronbach’s alpha was calculated to check for internal consistency. Two-way random intra-class correlation coefficient (ICC) for single measures and absolute agreement were used to assess the test–retest reliability.

Study II

None of the variables were found to be normally distributed. Thus, the non-parametric Mann–Whitney U test was used to check for statistical differences between the two groups.

Study III

To evaluate the primary outcome, number of wet nights during 14 nights follow-up after the intervention/placebo treatment, a random intercept linear mixed model was used. Study groups (intervention/placebo), time (T0, T1) and the interaction variable groups*time were fixed factors, and the model’s estimated marginal mean differences of outcome within and between study groups was reported with 95% confidence intervals (CI). The mixed model is similar to the ANOVA for repeated measurement but has the advantage that patients with missing data were evaluated with the assumption of missing at random. The model residuals were tested with Shapiro-Wilk normality distribution test and no violation was present. A linear mixed model was also used to compare the number of wet nights during 14 nights follow-up at the end of the intervention (T1), when all study subjects had had the intervention, and after 6 months (T6mon) compared to T0. At T6mon, the study subjects were classified as responders/non-responders and analyzed with logistic regression to try to identify potential prognostic variables. The logistic regression was adjusted for the number of wet nights reported at T0. A responder was defined as having reported >50% reduction in the number of wet nights at T6mon.
compared to T0. Linear regression was used to identify potential prognostic variables for the continuous outcome, change of number of wet nights T0 to T6mon, adjusted for number of wet nights at T0.

In order to evaluate the reliability of measurements on study casts (intermolar width, interpremolar width, and intercanine width), 17 study patients were measured twice on examination at T0 and the intra class correlation (ICC) was estimated. The ICC was estimated for each outcome by linear mixed model with patients as random factor. As the ICC is the ratio of the outcome variance between patients divided by total variance (between and within patients), the standard deviation (SD) between and within patients from the mixed model was also presented.

Study IV

Summary statistics were calculated for the data at baseline (T0), during treatment (T1) and 6 months post treatment (T6mon). Since the variables were found to be non-normally distributed, Friedman’s Two-way Analysis of Variance by Ranks was used to analyze differences between the three measures.
Results

Study I

Forty-six patients (mean age 10.2 ± 2.6) with at least one complete PinQ-SWE questionnaire were included in this study. Of these patients, 33 individuals completed two questionnaires, as instructed, and were included in the test–retest evaluation. The results are presented in Table 3. Social relations with peers and self-esteem were the most affected domains. Items six, nine and 17, which were included in the most affected domains, and item five demonstrated the highest mean scores and ceiling effects. Item six, ‘I would feel better about myself if I didn’t have a bladder problem’, and item nine, ‘My bladder problem stops me from going on sleepovers or holidays’, were the two main areas of concern.

The highest reported peak scores, or individual scores, in the questionnaire were four for 71.7% of the study population, three for 17.4% and two for 10.9%. The domains social relations with peers and self-esteem had the highest number of fours, while independence seemed to be the least problematic area in this group. (Fig 7)

Fig 7. Peak scores for the PinQ.
Table 3. Scale, domain and item characteristics of PinQ-SWE with means and standard deviations, percentage distribution of lowest (floor effect) and highest (ceiling effect) possible scores and missing response rates.

<table>
<thead>
<tr>
<th>Score range</th>
<th>n</th>
<th>Mean</th>
<th>SD</th>
<th>Floor effect (%)</th>
<th>Ceiling effect (%)</th>
<th>Missing response (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sum score</td>
<td>46</td>
<td>20.3</td>
<td>13.3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Domains</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social relations with peers (Q: 3, 9, 12, 16, 17, 20)</td>
<td>(0–24)</td>
<td>46</td>
<td>9.4</td>
<td>4.04</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Self-esteem (Q: 1, 6, 7, 10)</td>
<td>(0–16)</td>
<td>46</td>
<td>6.9</td>
<td>3.78</td>
<td>4.3</td>
<td>0</td>
</tr>
<tr>
<td>Family and home (Q: 2, 5, 8, 11)</td>
<td>(0–16)</td>
<td>46</td>
<td>4.5</td>
<td>2.78</td>
<td>4.3</td>
<td>0</td>
</tr>
<tr>
<td>Independence (Q: 15, 18)</td>
<td>(0–8)</td>
<td>46</td>
<td>0.8</td>
<td>1.44</td>
<td>67.4</td>
<td>0</td>
</tr>
<tr>
<td>Mental health (Q: 4, 13, 14, 19)</td>
<td>(0–16)</td>
<td>46</td>
<td>4.6</td>
<td>4.08</td>
<td>19.6</td>
<td>2.2</td>
</tr>
<tr>
<td>Items</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1. I get shy because of my bladder problem</td>
<td>45</td>
<td>1.3</td>
<td>1.27</td>
<td>41.3</td>
<td>43</td>
<td>2.2</td>
</tr>
<tr>
<td>Q2. People in my family treat me in a different way because of my bladder problem</td>
<td>46</td>
<td>0.5</td>
<td>0.98</td>
<td>73.9</td>
<td>2.2</td>
<td>0</td>
</tr>
<tr>
<td>Q3. I am worried that people might think my clothes smell of woe</td>
<td>46</td>
<td>1.0</td>
<td>1.25</td>
<td>52.2</td>
<td>6.5</td>
<td>0</td>
</tr>
<tr>
<td>Q4. I think that my bladder won’t get better</td>
<td>46</td>
<td>1.2</td>
<td>1.36</td>
<td>50.0</td>
<td>6.5</td>
<td>0</td>
</tr>
<tr>
<td>Q5. Mum and dad worry about me because of my bladder problem</td>
<td>46</td>
<td>1.9</td>
<td>1.36</td>
<td>23.9</td>
<td>15.2</td>
<td>0</td>
</tr>
<tr>
<td>Q6. I would feel better about myself if I didn’t have a bladder problem</td>
<td>46</td>
<td>3.1</td>
<td>1.08</td>
<td>8.5</td>
<td>43.5</td>
<td>0</td>
</tr>
<tr>
<td>Q7. My bladder problem makes me feel nervous</td>
<td>46</td>
<td>1.2</td>
<td>1.19</td>
<td>43.5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Q8. Mum or dad sometimes seem a bit cranky because of my bladder problem</td>
<td>46</td>
<td>0.8</td>
<td>1.05</td>
<td>58.5</td>
<td>2.2</td>
<td>0</td>
</tr>
<tr>
<td>Q9. My bladder problem stops me from going on sleepovers or holidays</td>
<td>46</td>
<td>2.5</td>
<td>1.53</td>
<td>17.4</td>
<td>43.5</td>
<td>0</td>
</tr>
<tr>
<td>Q10. My bladder problem makes me feel bad about myself</td>
<td>46</td>
<td>1.3</td>
<td>1.33</td>
<td>41.1</td>
<td>8.7</td>
<td>0</td>
</tr>
<tr>
<td>Q11. I wake up during my sleep because of my bladder problem</td>
<td>45</td>
<td>1.2</td>
<td>1.19</td>
<td>34.8</td>
<td>4.3</td>
<td>2.2</td>
</tr>
<tr>
<td>Q12. I miss out on doing things because of my bladder problem</td>
<td>48</td>
<td>1.3</td>
<td>1.31</td>
<td>43.5</td>
<td>4.3</td>
<td>0</td>
</tr>
<tr>
<td>Q13. I feel unhappy because of my bladder problem</td>
<td>48</td>
<td>1.5</td>
<td>1.38</td>
<td>34.8</td>
<td>10.9</td>
<td>0</td>
</tr>
<tr>
<td>Q14. My bladder problem makes me feel sad</td>
<td>45</td>
<td>1.0</td>
<td>1.23</td>
<td>50.0</td>
<td>4.3</td>
<td>2.2</td>
</tr>
<tr>
<td>Q15. I think about my bladder problem when choosing which sport to play</td>
<td>44</td>
<td>0.3</td>
<td>0.66</td>
<td>80.4</td>
<td>0</td>
<td>4.3</td>
</tr>
<tr>
<td>Q16. I have to go to the toilet when I’m watching a movie</td>
<td>46</td>
<td>1.7</td>
<td>1.01</td>
<td>17.4</td>
<td>2.2</td>
<td>0</td>
</tr>
<tr>
<td>Q17. If my bladder problem was fixed I would invite more friends to my house</td>
<td>45</td>
<td>2.0</td>
<td>1.59</td>
<td>26.3</td>
<td>23.9</td>
<td>2.2</td>
</tr>
<tr>
<td>Q18. I choose hobbies that won’t be spoiled by stopping to go to the toilet</td>
<td>44</td>
<td>0.4</td>
<td>1.00</td>
<td>76.1</td>
<td>4.3</td>
<td>4.3</td>
</tr>
<tr>
<td>Q19. My bladder problem makes me feel different to other people</td>
<td>46</td>
<td>0.9</td>
<td>1.27</td>
<td>56.5</td>
<td>8.5</td>
<td>0</td>
</tr>
<tr>
<td>Q20. I miss out on being with friends because of my bladder problem</td>
<td>46</td>
<td>0.9</td>
<td>1.21</td>
<td>56.5</td>
<td>2.2</td>
<td>0</td>
</tr>
</tbody>
</table>

Q = question.
Cronbach’s alpha was 0.87 for the whole questionnaire, indicating good internal consistency.

The ICC for the total score was excellent, at 0.762. Most of the domains showed good agreement (0.6–0.74) and only independence showed fair agreement (0.4–0.59). (Table 4)

**Table 4.** Reliability in terms of internal consistency assessed by Cronbach’s alpha (α) for sum and domain scores of PinQ-SWE, reported in total and by gender

<table>
<thead>
<tr>
<th></th>
<th>All (α)</th>
<th>Boys (α)</th>
<th>Girls (α)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sum score</strong></td>
<td>0.87</td>
<td>0.84</td>
<td>0.93</td>
</tr>
<tr>
<td><strong>Domains</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social relations with peers</td>
<td>0.80</td>
<td>0.71</td>
<td>0.93</td>
</tr>
<tr>
<td>Self-esteem</td>
<td>0.77</td>
<td>0.72</td>
<td>0.88</td>
</tr>
<tr>
<td>Family and home</td>
<td>0.88</td>
<td>0.91</td>
<td>0.74</td>
</tr>
<tr>
<td>Independence</td>
<td>0.61</td>
<td>0.47</td>
<td>0.78</td>
</tr>
<tr>
<td>Mental health</td>
<td>0.84</td>
<td>0.85</td>
<td>0.83</td>
</tr>
</tbody>
</table>

In our first study we found that children with NE have impaired self-esteem and their reduced QoL affects their relationships with friends. PinQ-SWE proved to be a reliable and valid tool that we will use in our further studies.

**Study II**

Twenty study patients (19 boys and one girl) and 21 control children (18 boys and three girls) participated in the study. Overall, the proportion of interpretable recordings was high. The mean AHI values were 0.96 ± 0.8 for the patient group and 0.46 ± 0.4 for the control group. The hypopnea index was significantly higher for the enuretic children (p=0.04) but the values were very low in both groups (HI < 1), so the difference would not have any clinical relevance. The oxygen desaturation index was slightly higher for the children with NE (p=0.05), although this was largely explained by two outliers. No other differences were found in the respiratory variables. Both groups of children had a low frequency of arousals. (Table 5)
Table 5. Sleep and Respiratory Variables

<table>
<thead>
<tr>
<th>Patient details</th>
<th>Children with NE (n=20)</th>
<th>Controls (n=21)</th>
<th>p-value Mann Whitney U test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time in bed (min)</td>
<td>485 ± 88.2</td>
<td>471.67 ± 89.1</td>
<td>0.71</td>
</tr>
<tr>
<td>Sleep efficiency (%)</td>
<td>92.97 ± 2.8</td>
<td>91.85 ± 7.7</td>
<td>0.15</td>
</tr>
<tr>
<td>Apnea hypopnea index (AHI)</td>
<td>0.96 ± 0.8</td>
<td>0.46 ± 0.4</td>
<td>0.11</td>
</tr>
<tr>
<td>Apnea index (AI)</td>
<td>0.44 ± 0.5</td>
<td>0.33 ± 0.5</td>
<td>0.56</td>
</tr>
<tr>
<td>Hypopnea index (HI)</td>
<td>0.48 ± 0.4</td>
<td>0.22 ± 0.3</td>
<td>0.04*</td>
</tr>
<tr>
<td>Flow limit index</td>
<td>5.76 ± 4.6</td>
<td>6.62 ± 3.7</td>
<td>0.38</td>
</tr>
<tr>
<td>Paradox index</td>
<td>1.45 ± 2.4</td>
<td>1.51 ± 2.2</td>
<td>1.00</td>
</tr>
<tr>
<td>Snore (%)</td>
<td>1.30 ± 2.3</td>
<td>1.24 ± 2.5</td>
<td>0.73</td>
</tr>
<tr>
<td>Oxygen desaturation index</td>
<td>1.96 ± 1.9</td>
<td>0.91 ± 0.8</td>
<td>0.05*</td>
</tr>
<tr>
<td>Mean oxygen saturation (%)</td>
<td>96.61 ± 1.5</td>
<td>97.37 ± 0.8</td>
<td>0.07</td>
</tr>
<tr>
<td>Oxygen saturation Nadir (%)</td>
<td>91.65 ± 3.3</td>
<td>92.81 ± 3.0</td>
<td>0.33</td>
</tr>
<tr>
<td>Movement index</td>
<td>6.71 ± 2.0</td>
<td>7.62 ± 2.5</td>
<td>0.32</td>
</tr>
<tr>
<td>Arousal index</td>
<td>0.54 ± 0.43</td>
<td>0.45 ± 0.35</td>
<td>0.68</td>
</tr>
<tr>
<td>OSA 18 total score</td>
<td>35.7 ± 14.8</td>
<td>26.1 ± 6.5</td>
<td>0.03*</td>
</tr>
<tr>
<td>OSA 18 sleep disturbance</td>
<td>7.05 ± 3.1</td>
<td>4.71 ± 1.0</td>
<td>0.01*</td>
</tr>
</tbody>
</table>

The total score for the OSA 18 questionnaire and the score for the domain sleep disturbances are also reported in table 5. The enuretic children reported significantly more sleep disturbances and a lower QoL than their healthy peers.

No major differences in SDB were found between enuretic children and controls. Children with NE reported more subjective sleep disturbances than their healthy peers but only with a small impact on HRQoL.

**Study III**

Thirty-eight patients were enrolled in this study, 18 patients were allocated to the intervention group and 20 to the placebo group. Shortly after allocation two children from the placebo group dropped out. The whole patient flow through the study has already been demonstrated in Fig. 6.
The baseline data for the two groups were very similar which proved that the randomization process worked well. The majority of the patients had normal occlusions, although 35% presented with a class II malocclusion. Only five of the children had a narrow maxilla which resulted in a unilateral crossbite. Sixty percent of the study group had a positive family history of enuresis.

The reduction of wet nights during two weeks at T0 and T1, and the difference between the two groups, can be seen in Table 6. The intervention group had a significant reduction of wet nights from T0 to T1, mean -2.2 (95% CI -3.7 – -0.8), \(P = 0.003\), whereas the placebo group had no such reduction, mean -0.6 (95% CI -2.0 – 0.8), \(P = 0.40\). Even if the intervention group demonstrated a larger reduction in number of wet nights compared to the placebo group, the difference between the study groups was not statistically significant, mean -1.6 (95% CI -3.6 – -0.4), \(P = 0.11\). (Table 6)

Table 6. Number of wet nights during 2 weeks, pre and post intervention compared between the intervention and control group

<table>
<thead>
<tr>
<th></th>
<th>Intervention group</th>
<th>Placebo group</th>
<th>Intervention vs. Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=18)</td>
<td>(n=20)</td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>Mean (SD)</td>
<td>T0 vs. T1</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>(n=18)</td>
<td>Mean (SD)</td>
<td>Mean diff (95% CI)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Number of wet nights</td>
<td>11.4 (2.9)</td>
<td>-2.2 (-3.7 – -0.8)</td>
<td>12.4 (2.3)</td>
</tr>
<tr>
<td>(P = 0.003)</td>
<td>(P = 0.003)</td>
<td>(P = 0.003)</td>
<td>(P = 0.003)</td>
</tr>
</tbody>
</table>

The long-term effect was evaluated for the whole group six months after the intervention. The number of wet nights was reduced from mean 11.9 to mean 8.5, mean difference -3.2 (95% CI -4.5 – -1.8) from T0 to T6mon, and this reduction was highly statistically significant, \(P = 0.002\).

The trial resulted in one full responder, 10 intermediate responders, and 20 non-responders at T6mon. The outcome variable in the logistic regression was defined as full/intermediate responders vs. non-responders, since there was only one patient defined as a full responder. The logistic regression adjusted for number of wet nights at T0 showed no significant associations for any of the potential prognostic variables taken from the case history and voiding chart. The average daytime voided volume showed an OR of 1.093 (95% CI 0.998 – 1.198) indicating a possibly higher chance of responding to the therapy with increasing bladder storage capacity, \(P = 0.055\). Another possible trend was the mean intermolar width at T0 which showed an OR 1.43 (95% CI 0.94 – 2.16) suggesting a better prognosis with increasing distance, \(P = 0.09\). (Table 7)
Table 7. Logistic regression on 31 patients with intermediate-/non responders (n=11/20) at T6 as outcome.

<table>
<thead>
<tr>
<th>Outcome intermediate response</th>
<th>n (%)</th>
<th>OR¹ (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention group</td>
<td>4 (24%)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Placebo group</td>
<td>7 (50%)</td>
<td>4.4 (0.79 – 25)</td>
<td>0.09</td>
</tr>
<tr>
<td>Age (7–9 years)</td>
<td>5 (38%)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Age (10–13 years)</td>
<td>6 (33%)</td>
<td>0.71 (0.15 – 3.4)</td>
<td>0.67</td>
</tr>
</tbody>
</table>

**Occlusion**

<table>
<thead>
<tr>
<th></th>
<th>n (%)</th>
<th>OR¹ (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I occlusion</td>
<td>7 (35%)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Class II occlusion</td>
<td>4 (36%)</td>
<td>1.3 (0.25 – 6.4)</td>
<td>0.77</td>
</tr>
<tr>
<td>No cross bite</td>
<td>9 (35%)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Cross bite</td>
<td>2 (40%)</td>
<td>0.83 (0.10 – 7.0)</td>
<td>0.86</td>
</tr>
<tr>
<td>Intermolar width (T0) per unit (mm)</td>
<td>1.43 (0.94 – 2.16)</td>
<td>0.09</td>
<td></td>
</tr>
<tr>
<td>Inter canine width (T0) per unit (mm)</td>
<td>1.40 (0.91 – 2.17)</td>
<td>0.13</td>
<td></td>
</tr>
</tbody>
</table>

**Voiding chart data**

<table>
<thead>
<tr>
<th></th>
<th>OR¹ (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Micturition</td>
<td>0.76 (0.37 – 1.56)</td>
<td>0.45</td>
</tr>
<tr>
<td>Average Voiding Volume –</td>
<td>1.073 (0.982 – 1.173)</td>
<td>0.12</td>
</tr>
<tr>
<td>Average Voiding Volume +</td>
<td>1.093 (0.998 – 1.198)</td>
<td>0.055</td>
</tr>
<tr>
<td>Maximum Voiding Volume –</td>
<td>1.037 (0.995 – 1.080)</td>
<td>0.086</td>
</tr>
<tr>
<td>Maximum Voiding Volume +</td>
<td>1.043 (0.999 – 1.090)</td>
<td>0.057</td>
</tr>
<tr>
<td>Enuresis Volume</td>
<td>1.004 (0.978 – 1.030)</td>
<td>0.77</td>
</tr>
<tr>
<td>Urine production</td>
<td>1.008 (0.986 – 1.031)</td>
<td>0.48</td>
</tr>
</tbody>
</table>

¹ Odds Ratio, adjusted for number of wet nights at T0 as a continuous variable.
- first morning void excluded
+ first morning void included

The maxillary arch was somewhat expanded, still with good occlusion, and no other side effects on the dentition were apparent. The mean transverse maxillary expansion for the whole group was 4.8 ± 2.2 mm at the intermolar distance, 5.7 ± 1.7 mm at the inter premolar distance and 2.2 ± 1.3 mm at the inter canine distance.

The self-reported PinQ-SWE mean sum score, for the whole group, was 23.25 (SD 10.88) at T0 and 20.58 (SD 12.27) at T6mon. The slight reduction in PinQ score was not statistically significant.
Study IV

Thirty-eight children with NE (3 girls and 35 boys) were enrolled in this study. The majority of them had primary nonmonosymptomatic enuresis. Respiratory variables and scores from the OSA 18 questionnaire are presented in table 8. Some values were missing due to signal failure. Thus, recordings were included when the signal qualities; oxygen quality, flow quality and respiratory inductance plethysmography (RIP) quality was ≥ 75%. Poor signal from the pulse oximeter was present in 10% of the recordings. The flow from the nasal cannula had the highest failure rate, with values missing from 37% of the patients. In these cases, the flow was re-referenced to RIP quality which had a failure rate of 10%.

Sleep and respiratory variables

There was a significant difference in sleep efficiency (SE) between the three occasions ($P=0.001$). The median and ranges were 95% (84.3 – 100), 92.4% (73.1 – 97.4) and 94.4% (47.3 – 100) at T0, T1 and T6_{mon}, respectively. (Fig 3) The AHI was within expected norms, 0.55 (0 – 3.6) at T0. The values then increased at T1 and dropped back to more expected levels again at T6_{mon}. These trends, however, were not statistically significant. The changes in AHI were mainly due to change in the number of hypopneas; the median hypopnea index (HI) was 0.3 (0 – 3.6), 0.5 (0 – 8.9) and 0.2 (0 – 1.5) at T0, T1 and T6_{mon} respectively, (Table 8) and these changes were statistically significant ($P=0.005$). None of the other respiratory variables showed any statistically significant differences between the measures.

OSA 18

The median total score for the OSA 18 questionnaire were 31 (20 – 71) at T0, 31 (16 – 69) at T1, and 29 (18 – 58) at T6_{mon}. This statistically significant difference indicated a slight improvement in QoL over time ($P=0.015$). The median score for the OSA 18 sleep domain were: 6 (4 – 9) at T0, 4 (4 – 8) at T1, and 5 (4 – 6) at T6_{mon}, a difference that was also statistically significant ($P=0.01$).
Table 8. Sleep and respiratory variables.

<table>
<thead>
<tr>
<th>Variable</th>
<th>$T_0$</th>
<th>$T_1$</th>
<th>$T_6$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>min - max</td>
<td>median</td>
<td>min - max</td>
<td>median</td>
</tr>
<tr>
<td>TST (min)</td>
<td>272 - 630</td>
<td>514.50</td>
<td>180 - 620.5</td>
<td>429.80</td>
</tr>
<tr>
<td>SE (%)</td>
<td>84.3 - 100</td>
<td>95.00</td>
<td>73.1 - 97.40</td>
<td>92.40</td>
</tr>
<tr>
<td>AHI</td>
<td>0 - 3.60</td>
<td>0.55</td>
<td>0 - 9.40</td>
<td>1.15</td>
</tr>
<tr>
<td>AI</td>
<td>0 - 2.80</td>
<td>0.30</td>
<td>0 - 5.40</td>
<td>0.50</td>
</tr>
<tr>
<td>HI</td>
<td>0 - 3.60</td>
<td>0.30</td>
<td>0 - 8.90</td>
<td>0.50</td>
</tr>
<tr>
<td>Snore Index</td>
<td>0 - 10.5</td>
<td>0.40</td>
<td>0 - 28.6</td>
<td>0.75</td>
</tr>
<tr>
<td>ODI</td>
<td>0 - 4.20</td>
<td>1.10</td>
<td>0.20 - 12.10</td>
<td>1.40</td>
</tr>
<tr>
<td>SpO$_2$ mean (%)</td>
<td>91.50 - 98.50</td>
<td>97.65</td>
<td>94.40 - 98.90</td>
<td>97.60</td>
</tr>
<tr>
<td>SpO$_2$ nadir (%)</td>
<td>82.00 - 95.10</td>
<td>93.00</td>
<td>81.00 - 95.00</td>
<td>92.00</td>
</tr>
<tr>
<td>O quality (%)</td>
<td>0 - 99.9</td>
<td>99.15</td>
<td>0 - 99.9</td>
<td>99.55</td>
</tr>
<tr>
<td>Flow quality (%)</td>
<td>23.60 - 100</td>
<td>81.00</td>
<td>35.50 - 100</td>
<td>98.10</td>
</tr>
<tr>
<td>RIP quality (%)</td>
<td>0 - 100</td>
<td>100</td>
<td>0 - 100</td>
<td>100</td>
</tr>
<tr>
<td>Arousal Index</td>
<td>0 - 1.30</td>
<td>0.30</td>
<td>0.10 - 1.20</td>
<td>0.20</td>
</tr>
<tr>
<td>Move Index</td>
<td>0.10 - 13.60</td>
<td>6.95</td>
<td>4.70 - 30.60</td>
<td>7.80</td>
</tr>
<tr>
<td>OSA18 total</td>
<td>20 - 71</td>
<td>31</td>
<td>18 - 69</td>
<td>31</td>
</tr>
<tr>
<td>OSA18 sleep</td>
<td>4 - 9</td>
<td>6</td>
<td>4 - 8</td>
<td>4</td>
</tr>
</tbody>
</table>

TST = total sleep time, SE = sleep efficiency, AHI = apnea hypopnea index, AI = apnea index, HI = hypopnea index, ODI = oxygen desaturation index, SpO$_2$ mean = mean oxygen saturation, SpO$_2$ nadir = lowest oxygen saturation, O quality = oxygen saturation quality, Flow quality = nasal flow quality, RIP quality = respiratory inductance plethysmograph quality
Discussion

We have, in this thesis, evaluated the effect that rapid maxillary expansion may have on nocturnal enuresis and nocturnal respiration. At the same time, an effort was made to try to identify prognostic variables and investigate quality of life in this group of patients. The four studies have with different research methodology shed some light on the intriguing fact that some enuretic children stop wetting their bed after treatment with an orthodontic appliance.

Main findings

We have in study I found that children with therapy-resistant nocturnal enuresis have an impaired quality of life, affecting mainly self-esteem and relationships with friends. Low self-esteem is a known risk factor for psychiatric disorders and social adjustment problems. This confirms the work of other researchers and underscores the need for new, safe therapies for the group of enuretic children who do not respond to first-line therapy, i.e. desmopressin or the enuresis alarm.

In study III we found that RME has a statistically significant effect in reducing the number of wet nights for children with therapy-resistant enuresis, and that this effect does not seem to be due to placebo. Still, the effect found was less impressive than what some of the previous reports may have led us to expect, and the clinical usefulness of the method remains uncertain.

Two of our studies have evaluated respiration during sleep in enuretic children. In study II we found no major differences in respiration during sleep between enuretic children and healthy controls. The majority of the children in our study did not have sleep disordered breathing in addition to their NE. Study IV evaluated the effect of RME on respiration during sleep in the same group of enuretic children. We found minor although statistically significant effects that will be further discussed below.
Assets and limitations

All our patients came from a tertiary care center, and their symptom severity as well as therapy-resistance may thus not reflect enuretic children at large. This can be seen as a limitation, but, on the other hand, this is the most relevant patient group for whom new treatment modalities are most needed. The recruitment process has also been quite slow, about half of the patients who were invited to participate declined or chose other options.

Another limitation was the sample size calculation, which was mentioned earlier. Study III and IV are based on the same population but the studies were probably under-powered when it comes to the prognostic variables, quality of life data and possibly variables related to respiration as well.

Study I

In study I, our objective was to evaluate the QoL in children with NE. When planning the study, no relevant tool was available in the Swedish language. The PinQ was the most appropriate tool to use as it is an international, cross-cultural questionnaire specific to children with lower urinary tract dysfunction. It has previously proved to be a valid and reliable instrument which has been used in HRQoL assessments globally.57-59,107 With the kind permission of Dr Wendy F Bower we translated the questionnaire and tested the reliability of its Swedish version. The term reliability generally refers to the consistency of a measure and the test–retest approach is most commonly used. The translation and back-translation went well without any major differences. The internal consistency was good and the test–retest was excellent. We were pleased with this result and have kept using the PinQ-SWE in our following study. PinQ-SWE is ready to be used clinically and can be recommended in future studies about QoL and enuresis.

The major weakness of this study lies within our study population. Firstly, a larger study group would have increased the strength of our results. The study may have been underpowered as there was insufficient background data to make proper sample size calculations. Secondly, we have only tested PinQ-SWE in a group of children with therapy-resistant enuresis and can thus not draw much conclusions regarding children with less severe bedwetting. PinQ-SWE should preferably be used in enuretic children although we see no reasons to why it shouldn’t be of value in other groups of pediatric incontinence as well, considering the rigorous process when developing the tool and the robustness it has shown in the past.
Study II & IV

These were polygraphic studies focused on respiration during sleep. Study II was a prospective study of nocturnal respiration in children with enuresis compared with a control group, something which has not been done before. The control group consisted of healthy age- and gender-matched children. Respiratory variables were extracted from a polygraphic sleep registration and compared for statistical differences between the two groups. The strengths of this study were that we had a representative age- and gender-matched control group and that the patients could sleep at home in their natural sleep environment.

Study IV was a prospective study with a longitudinal approach comparing polygraphic respiratory data before, during and six months after RME. The OSA 18 questionnaire was used as a subjective measure to evaluate issues related to sleep and breathing. The recordings were of good interpretable quality and the NOX T3 is a valid portable monitor with good measurement agreement compared to PSG.\(^{113}\)

The limitations in these studies are due to the study procedure with the portable NOX T3 device. Polygraphic data are known to underscore compared to PSG and the risk of signal failure is higher.\(^{50,114}\) We also had poor readings form the EEG as it was limited to only two electrodes. Our main focus, however, was not EEG, which has already been extensively studied in enuretic children,\(^{3,31,44,115,116}\) but respiration. Polysomnography is regarded the gold standard when diagnosing SDB. Due to practical reasons PSG was not an option for our studies. We have instead chosen to use a home-based diagnostic approach with a restricted multichannel device. The NOX T3 device has previously demonstrated good measurement agreement compared to PSG\(^{113}\) but signal failure is unfortunately a common finding, especially regarding the nasal airflow.\(^{117}\) To limit problems with signal failure special measures were considered when fitting the appliance. This has been described earlier and our recordings had reasonably good quality compared to other studies.\(^{117-119}\) We did not have more signal failure than could have been expected.

Study III

This was a randomized placebo-controlled trial and the first of its kind for this indication, since previous studies in this field have been case series or uncontrolled trials. Thus, our study provides a higher level of evidence. Linear regression was used in an attempt to identify prognostic variables and QoL was assessed with PinQ-SWE.
The main weakness in this study was that the power analysis was calculated on the enuresis reduction and we investigated some other items as well. Hence, the study was probably under-powered when it came to the predictive analysis and quality of life part. Another weakness is that it is highly uncertain how much placebo that could be obtained with our sham appliance. At least some parents managed to figure out that they had received the placebo, but they did not tell the children.

**Interpretation**

**Rapid Maxillary Expansion to treat Nocturnal Enuresis**

We have in this thesis investigated if RME could be an alternative treatment method for children with therapy resistant nocturnal enuresis and found that it indeed seems to have a therapeutic effect in some children. The response rate in our study was 35%, which is better than the spontaneous resolution rate of 15% per year.120 The obvious question is: Why does it work?

It has been suggested that the antienuretic effect should be due to the restoration of normal sleep patterns through elimination of respiratory dysfunction caused by obstruction of the anterior nasal airway.71 There have been attempts to explain the antienuretic effect by anatomical changes due to RME in the past. Kurol et al. performed measurements on lateral cephalograms and computed tomography scans to assess changes in the pharyngeal airways and nasal cavity. The posterior airway showed the dimensions expected for the age group and no association was found between the treatment effect and the amount of expansion, mode of breathing, nasopharyngeal dimension, or age.72 Rhinomanometry has also been used in several studies to assess the effect on the nasal airway after RME,72,74,75,77 showing that the airflow increases and the nasal airway resistance decreases after the treatment as a result of an increased nasal volume. But, again, no correlation has been found between nasal airflow and antienuretic effect.77 Other proposed mechanisms include improved breathing capacity and better oxygen saturation72 or that the placement of an irritating orthodontic appliance could influence arousal mechanisms.74 Al Taai et al. even suggested an increase in vasopressin release after RME.75 Their study included measurements of plasma osmolality as a surrogate marker for vasopressin levels. They found that the plasma osmolality before treatment was higher than expected and that the levels decreased after the treatment. This indicates that the majority of their patients had polyuria.

Finally, it has also of course been speculated that the reduction of wet nights could be a mere placebo effect. Two studies have addressed this question by having an appliance fitted in the mouth but without expanding it.75,77 Wearing
a passive RME appliance for a month did not have any effect on the enuresis frequency in either study. Just like we have found in study III, the RME appliance per se does not seem to have a favorable effect on the enuresis frequency; the palate needs to be expanded.

Prognostic variables
Some prognostically valuable clues have been found recently. In study III we found that a larger average daytime voided volume and a wide maxilla may be associated with an increased chance of having the enuresis frequency reduced.

Small voided volumes represent an indirect sign of detrusor overactivity. Consequently, one could speculate that RME would work better in patients who have polyuria, rather than detrusor overactivity, as a crucial pathogenetic factor. The study that has reported the highest success rate so far, presumably mainly included enuretic children with nocturnal polyuria, as explained above. In our study, on the other hand, we did not have many children with nocturnal polyuria, since they usually respond to desmopressin.

Another prognostic factor which was found was the width of the maxilla. It is likely that children with a wider maxilla also have larger overall nasal airway dimensions. This fits well with previous work by Nevéus et al., who found that children responding to RME treatment had larger nasal airway volumes. In these cases, a minor dilatation may be enough to eliminate a subclinical airway obstruction and thereby allow arousal thresholds to decrease. Another study reported that the reduction in bedwetting frequency was not correlated to the presence of crossbite. Also, in a systematic review, it was concluded that the presence of a posterior cross bite significantly decreased the chance of improvement.

Non-responders have been found to suffer more frequent enuresis. Children with less frequent enuresis have been reported to have a better prognosis anyway.

Respiration during sleep
The patients in our studies were not found to have sleep disordered breathing. Their respiration during sleep did in fact not differ very much at all from that of the healthy controls. The hypopnea index and the oxygen desaturation index were both significantly higher for the enuretic children. Nevéus et al. also observed a tendency for their patients to experience hypopneas. Another finding was respiratory arousals, which were difficult to evaluate in our studies, due to the limited EEG set-up in our monitoring device. An increased
tendency to (inefficient) arousal reactions during sleep has been found previously in children with nocturnal polyuria and NE.\textsuperscript{45}

When evaluating the effect RME may have on respiration during sleep, we found that the sleep efficiency and HI was significantly affected by the RME. The sleep efficiency diminished during treatment, which may be interpreted as the procedure disturbing the sleep somehow. At the 6-month follow-up when the appliance had been removed, the sleep efficiency recovered. More surprisingly, we found that the HI increased during the treatment. As explained above, a hypopnea is a reduction in airflow $\geq 30\%$ lasting for a duration of 10 seconds or 2 breaths.\textsuperscript{108} One would have expected the opposite effect and that as the nasal cavity expands the airflow would improve, but this was not the case. The HI had also recovered at the 6-month follow up. A possible explanation for this paradoxical effect is that even if the size of the nasal cavity increases the intraoral appliance by itself may somehow affect the airflow and thus disturb the sleep.

NE is commonly seen in patients with SDB, and a frequent clinical finding then is adenotonsillar hypertrophy. T&A is the first-line treatment for this disorder and has been reported to have a curative effect on children with combined SDB and NE.\textsuperscript{40} Guilleminault et al. found that there could be an additional gain combining T&A with RME in the treatment of children with SDB.\textsuperscript{124} Our study groups have been recruited at a tertiary enuresis center, and none of them had SBD as a central complaint. The clientele seeking the help of an otorhinolaryngological clinic would of course be different.

To get some additional information on the impact sleep related respiratory issues may have on the patients we used the OSA 18 questionnaire. We have not considered OSA 18 to be a diagnostic tool but a valuable way to relate the clinical findings to the subjective experience of the patient and family. Although we didn’t find any major difference in the respiratory variables between the children with NE and the healthy controls there was a significant difference in the results from the OSA 18 questionnaire. The enuretic children scored higher on both the total score and the domain sleep disturbances. One explanation for this may be that the parents of these children are more aware of sleep related issues. Anyway, the total mean scores for both groups were lower than 60, which suggest a small impact on HRQoL. Similar results were found in study IV with a very slight reduction of the scores during the treatment and at the 6-month follow up. These differences were not statistically significant.
Quality of life

The QoL proved to be affected when measured with the PinQ questionnaire. The total score in study I was similar to most previous studies using the same instrument.59,107,125 A higher score was found in a study by Thibodeau et al., but they evaluated a study group with a high number of children with both day- and night-time wetting.126 One can assume that this would be a heavier burden for the child. A higher score indicates a lower QoL. The total score was slightly lower, about 3 points, for the children in study III. A slight reduction was found at the end of the study (T6mon), but the difference was not statistically significant. The explanation for the lower QoL score in study III remains unknown. An impression, however, is that all of the families participating in that study were very well functioning. There were many appointments, instructions and questionnaires to be completed. The families were generally very engaged and often the whole family came along for the visits. It is quite possible that it takes some good quality in life to be bothered at all to participate in a clinical study.

Clinical implications

Although rapid maxillary expansion may have a positive effect in a subgroup of patients with enuresis, our findings do not support for RME to be used as an alternative treatment method for NE in general. A wide maxilla and large voiding volumes could increase the chance of a successful treatment. Considering the results of our study and previous work in this field, RME could possibly be suggested in cases when other interventions have failed. The patient should ideally be of younger age, without crossbite but with polyuria as the main pathogenic factor.

The PinQ-SWE can now be used to measure QoL in children with pediatric incontinence. It should preferably be used in children with NE as this is the group of patients it’s been reliability tested for in the Swedish language.

Final remarks and future research

The impact that rapid maxillary expansion may have on children’s health has been reviewed in the past. Apart from expected dental and skeletal effects some other positive side effects have been described in the literature, such as: improved nose breathing and amelioration of obstructive sleep apnea syndrome, conductive hearing loss and nocturnal enuresis.127 The level of evidence behind these claims has, however, often been low. Our study is the first of its kind with a randomized placebo-controlled design. We have found that
RME has a modest effect on therapy-resistant NE. The method should probably only be considered in selected cases and as a part of multidisciplinary collaboration.

Future multidisciplinary studies that could be of interest are children with SDB and maxillary insufficiency, for example respiration in children with cleft lip and palate or Down syndrome. It may also be worthwhile to study the effect RME may have on enuretic children with SDB.
Conclusions

The main conclusions from this thesis are:

Children with nocturnal enuresis have impaired self-esteem and their impaired quality of life affects their relationships with friends.

No major differences were found in respiration during sleep between enuretic children and healthy controls.

Rapid maxillary expansion has a statistically significant effect on therapy-resistant nocturnal enuresis, but the clinical usefulness of this effect is minor.

The antienuretic effect does not seem to be due to a placebo effect of the appliance.

A wide maxillary width and large voided volumes at baseline seem to be positive predictors regarding response to the treatment.

The majority of the children did not have sleep disordered breathing in addition to their nocturnal enuresis.

The sleep efficiency and hypopnea index were significantly negatively affected by the orthodontic procedure.
Populärvetenskaplig sammanfattning på Svenska


Syftet med den här avhandlingen var att genom ett tvärvetenskapligt samarbete närma sig ett svar på om gomvidgning med hjälp av tandställning kan vara ett alternativt sätt att hjälpa barn med nattlig sängväta att bli torra, en misstanke som tidigare studier givit upphov till. En tänkbar förklaring till varför det här skulle kunna hjälpa barnen är att när gommen vidgas så vidgas även näshålan, vilket skulle kunna underlätta barnens andning på natten och därmed påverka sömnen så att de vaknar när blåsan är full eller drar ihop sig. Vi ville därför i avhandlingens delarbeten dels titta på hur barn med enures andas när de sover, jämfört med torra barn, dels hur både andningen och själva nattvästan påverkas av att gommen vidgas. Dessutom undersökte vi barnens livskvalitet.

I studie 1 har vi använt ett internationellt utprovat frågeformulär som mäter livskvalitet hos barn med kissproblem. Vi har översatt formuläret till svenska
och kontrollerat att det fungerar. Sedan använde vi formuläret på en grupp barn med enures för att se hur de mådde.

Studie II är en studie av andning under sömn. Vi registrerade andningen natetid hos en grupp barn med svårbehandlad enures och lika många utan kissproblem.

Under studie III har vi behandlat de sängvätande barnen med en tandställning som vidgar gommen under ett halvårsperiod. Vi häftade av barnen slumpades till att under de första två veckorna få en tandställning som bara sitter i gommen utan att vidga den. Vi tittade på tandställningens effekt på nattväten och om det var några skillnader mellan den gomvidgande tandställningen och den som bara var fusk.

Studie IV genomfördes parallellt med studie III, men nu undersökte vi tandställningens effekter på andningen.

Våra slutsatser var följande:

- Gomvidgningen minskade nattväten, men bara lite.
- Behandlingsresultatet verkar bero på att gommen vidgas, inte bara av att man har en tandställning.
- Vi hittade ingen större skillnad i andningen under sömn mellan barn med och utan nattlig sängväta.
- De flesta av barnen i studien hade en normal andning under sömn.
- Sömnen blev tillfälligt lite sämre under behandlingen.
- Barn med nattlig sängväta har en nedsatt självkänsla och försämrad livskvalitet som påverkar deras relationer med vänner.
Acknowledgements

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References


# Appendix

**OSA-18 Livskvalitetsinstrument**

Utvärdering av Sömnrelaterade andningsstörningar

För varje fråga nedan rita en ring kring siffran som bäst beskriver hur ofta varje symptom eller problem har inträffat någon gång under den senaste 4 veckorna. Var snäll och ringa in endast en siffra per fråga. Tack!

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**HUR VILL DU TOTALT SKATTA DITT BARNS LIVSKVALITET I RELATION TILL OVANSTÄENDE PROBLEM?**

(åtta en cirkel runt ett nummer)

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Översatt av Elisabeth Ericsson m.fl. Avd. för Oto-rhino-laryngologi, Hälsouniversitetet, Linköping och Hälsokollegskolan, Linköping, Sverige, 2009

Kontakt: Elisabeth.Ericsson@hhj.hj.se
Quality of life enkät - PinQ

1. Mitt problem med kissblåsan gör mig blyg
   □ NEJ □ NÄSTAN ALDRIG □ IBLAND □ OFTA □ HELA TIDEN

2. Min familj behandlar mig annorlunda på grund av mitt problem med blåsan
   □ NEJ □ NÄSTAN ALDRIG □ IBLAND □ OFTA □ HELA TIDEN

3. Jag oroar mig över att folk ska tycka att mina kläder luktar kiss
   □ NEJ □ NÄSTAN ALDRIG □ IBLAND □ OFTA □ HELA TIDEN

4. Jag tror att mitt problem med blåsan inte kommer att förbättras
   □ NEJ □ NÄSTAN ALDRIG □ IBLAND □ OFTA □ HELA TIDEN

5. Min mamma och pappa oroar sig för mig på grund av mitt problem med blåsan
   □ NEJ □ NÄSTAN ALDRIG □ IBLAND □ OFTA □ HELA TIDEN

6. Jag skulle trivas bättre med mig själv om jag inte hade problem med blåsan
   □ NEJ □ KANSKE □ ANTAGLIGEN □ JA □ ABSOLUT

7. Mitt problem med blåsan gör att jag känner mig nervös
   □ NEJ □ NÄSTAN ALDRIG □ IBLAND □ OFTA □ HELA TIDEN

8. Mamma eller pappa verkar lite sura ibland på grund av mitt problem med blåsan
   □ NEJ □ NÄSTAN ALDRIG □ IBLAND □ OFTA □ HELA TIDEN

9. Mitt problem med blåsan gör att jag inte vågar sova över hos kompisar eller följa med på resor
   □ NEJ □ NÄSTAN ALDRIG □ IBLAND □ OFTA □ HELA TIDEN

10. Mitt problem med blåsan får mig att skämmas över mig själv
    □ NEJ □ NÄSTAN ALDRIG □ IBLAND □ OFTA □ HELA TIDEN

11. Jag vaknar upp när jag sover på grund av mitt problem med blåsan
    □ NEJ □ NÄSTAN ALDRIG □ IBLAND □ OFTA □ HELA TIDEN

12. Jag går miste om att göra saker på grund av mitt problem med blåsan
    □ NEJ □ NÄSTAN ALDRIG □ IBLAND □ OFTA □ HELA TIDEN

13. Jag känner mig ledsen på grund av mitt problem med blåsan
    □ NEJ □ NÄSTAN ALDRIG □ IBLAND □ OFTA □ HELA TIDEN
14. Mitt problem med blåsan gör att jag känner mig sorgsen
☐ NEJ ☐ Nästan aldrig ☐ Ibländ ☐ Ofta ☐ Hele tid

15. Jag tankar på mitt problem med blåsan när jag väljer vilka sporter jag ska delta i
☐ NEJ ☐ Nästan aldrig ☐ Ibländ ☐ Ofta ☐ Hele tid

16. Jag måste gå på toaletten när jag tittar på en film
☐ NEJ ☐ Nästan aldrig ☐ Ibländ ☐ Ofta ☐ Hele tid

17. Om mitt problem med blåsan kunde botas skulle jag bjuda hem fler vänner
☐ NEJ ☐ kanske ☐ antagligen ☐ ja ☐ absolut

18. Jag väljer hobbyer som låter mig göra avbrott för att gå på toaletten
☐ NEJ ☐ Nästan aldrig ☐ Ibländ ☐ Ofta ☐ Hele tid

19. Mitt problem med blåsan gör att jag känner mig annorlunda gentemot andra människor
☐ NEJ ☐ Nästan aldrig ☐ Ibländ ☐ Ofta ☐ Hele tid

20. Jag går miste om att vara tillsammans med vänner på grund av mitt problem med blåsan
☐ NEJ ☐ Nästan aldrig ☐ Ibländ ☐ Ofta ☐ Hele tid

Ditt namn: ________________________
Datum __/__/___
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