University of Alberta

The Association Between Positive Airway Pressure (PAP) Therapy and Midfacial Growth: A cross-sectional cephalometric comparison

by

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A thesis submitted to the Faculty of Graduate Studies and Research

in partial fulfillment of the requirements for the degree of

Master of Science

in

Medical Sciences - Orthodontics

Spring 2012

Edmonton, Alberta

ABSTRACT

Pediatric Obstructive Sleep Apnea Syndrome (OSAS) is a form of sleep-disordered breathing in children that is characterized by recurrent episodes of partial or complete airway obstruction during sleep. Treatment options include adenotonsillectomy and Positive Airway Pressure (PAP) therapy delivered via nasal/oral mask. A cross-sectional cephalometric comparison was conducted to compare two groups of children with OSAS, a Study group consisting of patients using PAP therapy and a control group not using PAP therapy. Lateral cephalograms were obtained from 3-dimensional volumetric scans and digitized to obtain a series of 14 cephalometric variables that were measured for each subject. Statistical analysis comparing the two groups showed no significant difference in craniofacial morphology between them but significant differences between the study groups and normative data. The major differences were shorter cranial base and a more vertical facial growth pattern in children with OSAS as compared to normative data.

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LIST OF SYMBOLS AND ABBREVIATIONS

OSAS	Obstructive Sleep Apnea Syndrome
PAP	Positive Airway Pressure
CPAP	Continuous Positive Airway Pressure
BiPAP	Bi-level Positive Airway Pressure
PSG	Polysomnography
UARS	Upper Airway Resistance Syndrome

CHAPTER 1 - Introduction

1.1 Obstructive Sleep Apnea Syndrome (OSAS)

Obstructive sleep apnea syndrome (OSAS) is a form of sleep-disordered breathing (SDB) characterized by recurrent episodes of partial or complete airway obstruction during sleep. Both adults and children can be affected, however the prevalence, etiology, and pathophysiology of the disease is different between the two groups.

Subjective symptoms and clinical sequelae of OSAS in both adults and children vary according to the severity of disease and patient-specific factors. The most common symptoms are chronic snoring, daytime fatigue and sleepiness, nocturnal enuresis, irritability and other behavioral and neurocognitive changes[1-3]. In children, these changes often present as poor academic performance and social adjustment problems[4]. Successful treatment of OSA has been associated with reversible improvement in these areas, with reported recurrence of these problems associated with recurrence of OSA[5]. In severe cases of untreated or poorly-controlled OSA, more serious complications such as failure to thrive, pulmonary hypertension, cor pulmonale, congestive heart failure, and sudden death can occur[2].

1.1.1 OSAS in adults

In the adult population, the prevalence of OSA is about 2% in women and 4% in men. Middle-aged and older obese males are the largest demographic of adult OSA patients [6]. Obesity and reduced muscle tone of various muscle groups along the upper airway are the primary etiologic factors in adults, though other factors such as age, lifestyle, alcohol intake, medications, and psychological factors can also play a role [7].

The primary symptom of OSA in adults is excessive daytime sleepiness [8], though much more serious sequelae can occur depending on disease severity and host susceptibility. The cardiovascular complications include hypertension, congestive heart failure, cardiac ischemia and arrhythmia. Other clinical consequences include neurocognitive dysfunction, cor pulmonale, and metabolic dysfunction [9]. Treatment options for OSA include dietary and lifestyle modification for weight loss and improved sleep patterns, positive airway pressure (PAP) therapy, oral appliances, pharmacologic management, and surgical advancement of the maxilla or mandible [10 11].

1.1.2 OSAS in children

The prevalence of OSA in children is reported in the range of 1-3%[12-15]. In contrast to adults, the most common cause of pediatric OSA is adenotonsillar hypertrophy[14, 16]. Several anatomic risk factors are associated with childhood OSAS. These include macroglossia, mandibular and/or midface hypoplasia, and other craniofacial anomalies. Other risk factors include obesity, various syndromes affecting craniofacial growth and development (eg Down Syndrome, Pierre Robin sequence, Apert's syndrome, and Treacher Collins syndrome), and some neuromuscular disorders[15].

The pathophysiology of OSA in any given patient will depend on the specific primary etiologic factor(s), but the overarching causative mechanism in non-centrally-mediated OSA is partial physical occlusion of the upper airway due to an anatomic obstruction. This obstruction can occur anywhere from the nares to the epiglottis, but most commonly appears to be a result of adenotonsillar hypertrophy, chronic inflammatory conditions (eg. allergic rhinitis or asthma) or pathologic changes (eg. nasal polyps, fibrosis) in the nasal mucosa, or unfavorable craniofacial skeletal morphology and growth patterns [17 18 19]. In centrally-mediated OSA, there is primary suppression of the respiratory drive usually at the brainstem

level and a physical obstruction of the upper airway is not necessarily present during episodes of apnea or hypopnea[15, 20].

1.1.3 OSAS diagnosis

The diagnosis of OSA remains a challenge and begins with detailed history-taking and physical examination. In children, the clinical examination should include careful evaluation of craniofacial characteristics primarily of the middle and lower face. In particular, midface hypoplasia and mandibular retrognathism should be evaluated. These findings, along with a high-arched narrow palate, maxillary posterior crossbites, anterior open bite, and a vertical growth pattern are all indicators of a potential upper airway problem[21, 22]. A thorough nasal examination, including examination of the nasal septum, turbinates, and perinasal sinuses should be performed. An intra-oral examination should include evaluation of dental occlusal relationships, resting tongue size and posture, and chronic oral habits. Visual examination of the tonsils and adenoids is essential, with tonsillar hypertrophy being a clear trigger for clinicians to investigate the potential for the presence of some form of sleep-disordered breathing[23]. An intra-oral examination should include evaluation of dental occlusal relationships, resting tongue size and posture, and chronic oral habits.

The current gold standard in the diagnosis of sleep-disordered breathing problems is overnight polysomnography (PSG). The lack of consensus in the interpretation of PSG data and inconsistent correlation of polysomnographic evidence of abnormality to clinical signs and symptoms of OSA limit the sensitivity and specificity of this technique as the primary diagnostic test for OSA[24, 25]. Further, PSGs reflect only a “snapshot” of patients’ typical sleep patterns and take place in unfamiliar surroundings to the patient, which may affect sleep quality and duration independently of SDB status. Practice parameters aimed at selecting the most appropriate patients for PSG testing were introduced in 1997[26]

and updated in 2005[27]. The latest guidelines on the indications for and interpretation of PSG tests in children were published in 2011[28]. These guidelines suggest the use of PSG in conjunction with clinical assessment where the diagnosis of OSAS is suspected, as well as for the evaluation of treatment outcome following various interventions such as tonsillectomy/adenoidectomy, initiation and titration of positive airway pressure (PAP) therapy, rapid maxillary expansion, and oral appliances for the treatment of OSA.

Despite its limitations, PSG still offers the most objective assessment of sleep architecture and physiology and remains the primary test in both the diagnosis of SDB problems and the evaluation of treatment response. Ambulatory sleep monitoring (eg. Overnight home oximetry) is also in widespread use as a helpful adjunct to PSG and clinical examination in the detection of SDB problems such as OSA. In patients with a high probability of OSA, home oximetry can be helpful in confirming the diagnosis [29]. No other ambulatory testing devices that offer more data than simple oximetry have been validated in pediatrics or have sufficient sensitivity or specificity to be used widely. As previously mentioned, detailed history recording with validated questionnaires is also helpful in identifying high-risk patients. The Epworth Sleepines Scale (ESS) and the Sleep Apnea Clinical Score (SACS) can be used in adult patients, with scores of >10 and >15 respectively being associated with higher probability of OSA [30].

Advances in 2-dimensional and 3-dimensional digital radiography have provided additional diagnostic tools that have shed new light on the morphologic aspects of the diagnosis of SDB in both adults and children[31-33]. Specialized software is currently available with which airway shape analysis and volumetric assessment can be conducted[34]. The reliability of the identification of key upper airway landmarks, however, depends on image quality and operator experience[35]. Further, the static assessment of dynamic airway structures such as the soft palate, tongue, adenoid tissue, and pharyngeal wall musculature provides only a limited understanding of any potential etiologic contribution of these structures and their changing relationships to one another. Recent reports by Lee at al have explored

interesting new concepts in the use of 3-dimensional photogrammetry and craniofacial topographic analysis to accurately predict the presence of OSA in Caucasian subjects[36, 37].

1.1.4 OSAS and craniofacial growth and development

It is hypothesized that an OSAS-associated change in respiratory mode to predominantly oral breathing can alter the balance of pressures from the orofacial musculature on the underlying facial bones resulting in unfavourable craniofacial growth patterns in children with OSAS. The term "adenoid facies" was coined to refer to a characteristic set of facial features often observed in individuals with upper airway obstruction and chronic mouth-breathing[21, 38, 39]. Changes in mode of breathing or habitual mandibular posture can affect the equilibrium of forces exerted on the jaws and teeth by the perioral musculature. However the level to which this equilibrium must be altered to affect significant skeletal or dental change remains unclear, as is the ability of a change in mode of breathing to reach that threshold.

As mentioned earlier, midface hypoplasia is one of the anatomic risk factors for OSAS. The relative contribution of midface hypoplasia to the etiology of upper airway resistance is variable, and is most prominent in the presence of syndromes with craniosynostosis such as Apert's syndrome, Crouzon's disease, Pfieffer's syndrome, and achondroplasia**.** In cases where midface hypoplasia is thought to be a major contributor to the etiology of upper airway resistance, orthodontic maxillary expansion and/or protraction using surgical or non-surgical means may be curative[11, 40]**.** The orthodontic diagnosis in these cases is based on clinical and radiographic observation of maxillary antero-posterior and transverse constriction, a straight or concave facial profile, and a history of snoring and mouth breathing, in conjunction with a thorough review of the medical history including consultation with a sleep medicine specialist.

1.1.5 OSAS treatment

Pediatric patients diagnosed with Obstructive Sleep Apnea Syndrome have several treatment options available. Depending on the primary etiologic factor, the treatment may involve surgical intervention, medical management, or a combination of both. The first-line surgical treatment for pediatric OSA is adenotonsillectomy, with a reasonably good rate and significant improvement in quality of life post-operatively[10]. Other surgical options include uvulopalatopharyngoplasty, and in severe, refractory cases, tracheostomy[41, 42]. Pharmacologic management options include the use of topical or systemic corticosteroids and leukotriene receptor antagonists for chronic nasal mucosal inflammation[43, 44].

However, for patients who do not present with clinical evidence of adenotonsillar hypertrophy, are unresponsive to adenotonsillectomy, or where the procedure is contraindicated, medical management includes continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP) via a nasal mask as the second line of treatment[45]. Both CPAP and BiPAP supply external pressure to the upper airway to prevent its collapse during sleep. CPAP provides a continuous level of pressure, whereas BiPAP allows different pressure settings for inhalation and exhalation, making it more suitable for patients with neuromuscular disorders, those requiring very high CPAP pressures or those that are intolerant of CPAP[10].

In order for nasal mask-delivered CPAP or BiPAP devices to be effective, an airtight seal between the nasal mask and the peri-nasal area must be achieved. A tight seal is obtained by ensuring adequate pressure and fit by the mask flanges against the facial skin using the supplied headgear strap(s). The pressure exerted by the mask on the soft tissues and underlying growing and remodeling bones of the midface may be a potential cause of mid-face retrusion in growing children who are on long term CPAP or BiPAP therapy during their peak growth years[46]. If such an association exists, it would be safe to assume that its magnitude and impact would be directly related to the length of the CPAP therapy,

patient compliance, the magnitude and direction of pressure exerted on various areas of the face, potential impact of underlying neuromuscular weakness or skeletal disorders, and the timing of the initiation of treatment in relation to the degree of skeletal and developmental maturation of the nasal-maxillary complex.

1.2 Cause-effect relationships between upper airway problems and craniofacial morphology

The interrelationships between form and function in the upper airway are central to current understanding of the etiology and treatment of upper airway resistance conditions in children. Cause-effect relationships between specific craniofacial growth patterns and the presence of sleep-disordered breathing conditions such as Obstructive Sleep Apnea Syndrome (OSAS) in children have been the focus of much of the research in this area. Over the last 15 years, a growing body of published research has described specific patterns of craniofacial growth and development associated with sleep disordered breathing and other upper airway resistance syndromes[21, 39, 47-51].

If a cause-effect relationship between upper airway resistance and altered craniofacial growth is assumed, it can be generally viewed from two opposing perspectives. First, the hypothesis that increased upper airway resistance or obstruction due to adenoid and/or tonsillar hypertrophy leads to the predominance of mouth-breathing as the primary mode of breathing due to nasopharyngeal airway obstruction [39]. This results in a series of chronic alterations in the musculo-skeletal equilibrium of the lower face that ultimately lead to a more vertical mandibular growth pattern characterized by a long lower face, a more obtuse gonial angle, tendency towards anterior open bite and lip incompetence, narrow maxillary dental arch with posterior crossbite, and postero-inferior rotation of the mandible. This is the more commonly-held view, and forms the basis of most current mainstream treatment protocols for children with upper airway resistance syndromes [39 52 50 53].

The opposite perspective on the cause-effect relationship between UAR and craniofacial growth is one where an unfavorable underlying (genetically-predetermined) craniofacial growth pattern is viewed as an etiological contributor to the increased upper airway resistance rather than being caused by it. Under this hypothesis, the characteristic facial growth patterns observed in children with UARS are thought to be inherent phenotypic expressions of genetic profiles rather than the result of a change in mode of breathing to oral breathing at an early age [54] [51].

It is quite possible that a combination of both theories may be present in many children with sleep-disordered breathing who are within the age range of peak lymphoid tissue growth (age 6-9), whereby lymphoid tissue hypertrophy combined with unfavorable underlying craniofacial morphology leads to symptomatic compromise of the upper airway during sleep. This may also explain the lack of absolute cure in SDB with surgical treatment (adenotonsillectomy).

1.3 Current practice

Although physical form and physiologic function are intimately related in the human body, they are often viewed separately by specialist practitioners involved in the management of pediatric sleep disordered breathing. Medical specialists such as pediatric sleep medicine specialists, respirologists, and otorhinolaryngologists, tend to focus on the functional aspects of pediatric respirology, using procedures and tests aimed at measuring various physiologic parameters such as the overnight oxygen saturation patterns, peak end-tidal CO2 levels, neuromuscular activity, and brain activity during sleep. Interventions are primarily aimed at providing surgical (usually tonsilloadenectomy) and/or ventilatory support (CPAP or BiPAP therapy).

On the other hand, dentists and orthodontists are more concerned with the anatomical form of the craniofacial skeleton and the morphology of the hard and soft tissues of the face and mouth, with

interventions aimed at orthopedic or orthodontic correction of skeletal or dental disharmonies that may contribute to upper airway resistance. It is clear that optimal care for pediatric patients with sleep disordered breathing requires a multidisciplinary approach that encompasses both the anatomic and physiologic aspects of this multi-faceted and dynamic problem.

The respiratory disturbance index (RDI) or apnea hypopnea index (AHI) is the polysomnographic parameter most commonly used to arrive at a diagnosis of OSAS by sleep medicine specialists. The limitation here also is that children can be symptomatic with SDB and yet the PSG does not reflect the degree of impact or conversely, the PSG is abnormal but this patient reports no symptoms from SDB. The 2-dimensional lateral cephalometric analysis remains the most commonly used tool for the assessment of craniofacial morphology by orthodontists. Unfortunately, there is still little cross-training between specialists in these two disciplines in the area of diagnosis, where significant overlap exists in the anatomic regions of interest and treatment objectives between the two specialties.

1.4 Study purpose and design

If long term use of CPAP devices is shown to contribute to a midface hypoplastic growth pattern, an argument can be made that it is having a paradoxical negative effect on the treatment of OSAS, by contributing to the development of a facial pattern that is associated with OSAS (midface deficiency). Further, the potential iatrogenic creation of a midface deficient growth pattern as a side effect of long term CPAP use may contribute to the development of a Class III dental or skeletal pattern, creating a later need for orthodontic or orthognathic surgical treatment during or after the period of CPAP therapy, depending on the severity of the resulting malocclusion and the patient's perception of treatment need.

The primary objective of this study is, therefore, to assess the potential for increased midface deficiency and evaluate other characteristic craniofacial morphological patterns in children with OSA who are on long-term CPAP therapy. Lateral cephalometry was used to compare pediatric patients with OSA in two groups: a Study Group consisting of children on long term CPAP therapy (CPAP Group), and a Control group of age-matched children similarly diagnosed with OSA, but not using CPAP therapy (Control Group).

1.5 Problem statement

The potential iatrogenic orthopedic effects of long term PAP use via nasal mask delivery have not been adequately investigated. A viable theoretical explanation exists for the potential of long term nasal mask wear to lead to undesirable midface hypoplasia. A better understanding of the potential associations between long term CPAP therapy and craniofacial growth and development is required.

1.6 Research question

Is prolonged nasal mask use for PAP therapy during active craniofacial growth and development associated with midface hypoplasia associated in children with OSAS ?

1.7 Research Hypothesis

We hypothesize that there is a significant difference in craniofacial morphology between OSA patients on long term PAP therapy and untreated controls that may be attributable to prolonged nasal mask

wear during periods of active craniofacial growth and development. The primary difference is hypothesized to occur in the midface region as antero-posterior hypoplasia in the sagittal plane.

Null hypothesis: There is no difference between OSA patients on long term PAP therapy compared to non-PAP control group of OSA patients with regards to craniofacial morphology.

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Chapter 2 - Craniofacial Morphology in Children with Sleep-Disordered Breathing Syndromes:

A Systematic Review

2.1 Introduction

Obstructive sleep apnea syndrome (OSAS) is a form of sleep-disordered breathing (SDB) characterized by recurrent episodes of partial or complete airway obstruction during sleep. Both adults and children can be affected, however the prevalence, etiology, and pathophysiology of the disease is different between the two groups. The prevalence of OSA in children is reported in the range of 0.7-11%[1-4]. In contrast to adults, the most common cause of pediatric OSA is adenotonsillar hypertrophy[3, 5]. Several anatomic risk factors are associated with childhood OSA. These include macroglossia, mandibular and/or midface hypoplasia, and other craniofacial anomalies. Other risk factors include obesity, various syndromes affecting craniofacial growth and development (eg Down Syndrome, Pierre Robin sequence, Apert's syndrome, and Treacher Collins syndrome), and some neuromuscular disorders[4].

Subjective symptoms and clinical sequelae of OSA vary according to the severity of disease and patient-specific factors. The most common symptoms are chronic snoring, daytime fatigue and sleepiness, nocturnal enuresis, irritability and other behavioral and neurocognitive changes[6-8]. In children, these changes often present as poor academic performance and social adjustment problems[9]. Successful treatment of OSA has been associated with reversible improvement in these areas, with reported recurrence of these problems associated with recurrence of OSA[10]. In severe cases of untreated or poorly-controlled OSA more serious complications can occur, such as failure to thrive, cor pulmonale, pulmonary hypertension, and other significant cardiovascular complications[7].

The interrelationships between craniofacial form and physiologic function in the upper airway are central to current understanding of the etiology and treatment of upper airway resistance syndromes (UARS) in children. Cause-effect relationships between specific craniofacial growth patterns and the presence of sleep-disordered breathing conditions such as OSA in children have been the focus of much of the research in this area. Widely-held beliefs and assumptions about these complex relationships continue to underpin the majority of current mainstream treatments for both pediatric and adult OSA. Over the last 15 years, a growing body of published research has described specific patterns of craniofacial growth and development associated with sleep disordered breathing and other upper airway resistance syndromes[11-17].

It has been hypothesized that a change in respiratory mode to predominantly oral breathing associated with nasopharyngeal airway compromise due to adenotonsillar hypertrophy can alter the balance of pressures from the orofacial musculature on the underlying facial bones resulting in unfavourable craniofacial growth patterns in children with OSA. The term “adenoid facies” was coined to refer to a characteristic set of facial features often observed in individuals with upper airway obstruction and chronic mouth-breathing[14, 15, 18]. Indeed, a long-term change in mode of breathing or habitual mandibular posture very well may affect the resting equilibrium of forces exerted on the jaws and teeth by the perioral musculature [19]. However the level to which this equilibrium must be altered to affect significant skeletal or dental change remains unclear, as is the ability of a change in mode of breathing to reach that threshold consistently in the majority of growing children.

If a cause-effect relationship between upper airway resistance and altered craniofacial growth is assumed, it can be generally viewed from two opposing perspectives. First, the hypothesis that increased upper airway resistance or obstruction due to adenoid and/or tonsillar hypertrophy leads to the predominance of mouth-breathing as the primary mode of breathing due to nasopharyngeal airway obstruction. The resulting open-mouth posture leads to a series of chronic alterations in the musculo-

skeletal equilibrium of the lower face that ultimately lead to a more vertical mandibular growth pattern characterized by a long lower face, a more obtuse gonial angle, tendency towards anterior open bite and lip incompetence, narrow maxillary dental arch with posterior crossbite, and postero-inferior rotation of the mandible into the characteristic retrognathic long-face pattern. This is the more commonly-held view, and forms the basis of most current mainstream treatment protocols for children with upper airway resistance syndromes.

The opposite perspective on the cause-effect relationship between UARS such as OSA and craniofacial growth is one where an unfavorable underlying (genetically-predetermined) craniofacial growth pattern is viewed as an etiological contributor to the increased upper airway resistance rather than being caused by it. Under this hypothesis, the characteristic facial growth patterns observed in children with UARS are thought to be inherent phenotypic expressions of genetic profiles rather than the result of a change in mode of breathing to oral breathing at an early stage of development. Alternately, the presence of UARS is thought to be entirely independent of any specific craniofacial morphological patterns, and any presumed cause-effect associations between them largely anecdotal or theoretical.

It is quite possible that a combination of both theories may manifest simultaneously in many children with sleep-disordered breathing who are within the age range of peak lymphoid tissue growth (age 6-9), whereby lymphoid tissue hypertrophy combined with unfavorable underlying craniofacial morphology leads to symptomatic compromise of the upper airway during sleep with unknown relative contributions of the two factors to the etiology of the airway compromise.

This viewpoint is supported by at least two critical reviews of the literature published in 1996 and 1998 examining the associations between UARS and craniofacial morphology [17, 20], in which the strength of the evidence linking craniofacial morphology and OSAS is called into question. In these reviews by Vig and Miles et al, the authors conclude that there causal associations between craniofacial morphogical

patterns have not been established, and that treatment modalities based on these assumptions are not supported by the evidence. It has also been suggested that the observed improvement in mandibular growth magnitude and direction following tonsillectomy and adenoidectomy in children with OSA is related to increases in Growth Hormone levels due to the removal of the sleep disturbances and nocturnal hypoxia associated with OSA, rather than changes in mandibular posture or mode of breathing [21].

Over the last 13-15 years since the reviews mentioned above were published a large and growing number of studies have sought to further investigate form-function interactions in children with OSA and further develop current understanding of the craniofacial patterns most commonly observed in these children [11, 22-24]. The purpose of this systematic review is to consolidate the current knowledge of craniofacial morphological characteristics associated with upper airway resistance syndromes such as OSAS in children. Because of the significant differences in etiology and long-term impact on craniofacial morphology between pediatric and adult OSA, the focus of this review was limited to studies on pediatric patients.

2.2 Methods and Materials

The search methods used in this review included both electronic and manual searches of reference lists. Electronic database searches were conducted using a series of keywords and keyword combinations based on knowledge of the subject area controlled vocabulary and free text terms, consultation with a specialized health-sciences librarian, use of MESH subject headings, and reviews of reference lists in selected articles. Appropriate truncation and word combinations were used in each search. The electronic databases searched are listed below:

- Medline (Insert date range for each database)

- Pubmed
- Embase
- All EBM Reviews
- Scopus
- Web of Science

The specific search strategies, terms/combinations used, and number of results obtained in each electronic database search are given in Appendix 1. The major search terms used are listed below:

- Sleep Apnea (various spelling configurations)
- Obstructive Sleep Apnea (various spelling configurations)
- Skeletal
- Dental
- Craniofacial
- Nasal CPAP (Full words and abbreviated)
- Child
- Pediatric

Only studies that reported cephalometric findings in non-syndromic children with confirmed OSA were of interest. To identify these studies, the following selection criteria were applied to the retrieved articles:

- All subjects below 18 years of age.
- Polysomnography was performed to determine the presence and severity of UARS or OSAS in subjects or both subjects and Controls.
- Where appropriate for the study design, a comparison to an appropriate Control group or to commonly-accepted cephalometric normative data was conducted.

- All study samples had to exclude subjects with craniofacial syndromes such as Down's Syndrome, and could not have received orthodontic or orthognathic treatment prior to evaluation by the investigators.

These selection criteria were applied separately by the two different operators (MK and HA) to the retrieved abstracts in the electronic database search and later in the selected articles based on the potential abstracts. The first step of the selection process was based on reviews of the titles and abstracts of the retrieved entries. For citations where the title was insufficient to make a decision, the abstract was retrieved and reviewed. Where more information was necessary to assess compliance with the selection criteria, the entire article was retrieved and authors contacted if necessary.

The first stage of the selection process yielded a total of twenty-seven potentially suitable articles. The reference lists of these articles were then reviewed and the same process was applied to citation titles that appeared to potentially match the selection criteria. This process did not yield any additional articles over and above the twenty-seven initially identified in the first stage of the selection process. Discrepancies between the lists of articles selected by the two reviewers were resolved through discussion and comparison.

Once the twenty-seven selected articles were successfully retrieved in full-text format, they were reviewed in detail against the pre-determined selection criteria. Twelve articles were then eliminated due to the lack of polysomnographic confirmation of the presence of OSA, and a further six articles were eliminated due to the presence of adult age groups over 18 years of age. The remaining nine articles were deemed to have met the requirements of the four selection criteria. Discrepancies between the lists of articles selected by the two reviewers were resolved through discussion and comparison.

A qualitative assessment of the nine retrieved articles was conducted based on the degree to which they exhibited well-established and accepted requirements for clinical research in this area. The qualitative criteria for this assessment were:

- A control group: a group selected from the same patient pool or adequately-matched for gender, age, and BMI.
- Stated definitions of OSA with regards to polysomnographic findings.
- Measurement of evaluator reliability
- Evaluator blinding
- Definition of the cephalometric landmarks and angular/linear measurements used

Of the nine selected studies, five included a comparison between the study group and a Control group. In all five studies, age- and gender- matching were reported between the two groups, but not BMI. Two studies conducted cross-sectional evaluations using a single study group to assess correlations between cephalometric and polysomnographic data. One study used a sample of normative data from a different study for comparison to the study group, and one study performed longitudinal cephalometric and respiratory evaluations of study group subjects, with assessments before and after tonsillar/adenoid resection surgery for comparison. Eight of the nine selected studies stated the polysomnographic thresholds used to establish the diagnosis of OSA in study subjects. Six studies reported an assessment of evaluator reliability, two of which also reported a method of evaluator blinding. Various linear and angular measurements making up the cephalometric analysis used were reported in all nine studies.

2.3 Results

Outlines of the nine selected studies and their findings are given in Table2-1. There was general agreement among all of the studies about the types of craniofacial morphological characteristics associated with upper airway resistance syndromes. An aggregate list of the most commonly-reported findings across these studies is given below:

1. Narrow maxillary dental arch with high palatal vault and posterior crossbites
2. Longer lower anterior face height
3. Steeper (more obtuse) gonial angle (mandibular plane angle)
4. Posterior-inferior (clockwise) rotation of the mandible
5. Retrusive chin
6. Vertical growth pattern
7. Tendency towards anterior open bite and lip incompetence
8. Smaller pharyngeal airway spaces

In addition to these findings concerning the facial skeleton, several studies also reported shorter lower anterior base and more acute cranial base angle as morphological characteristics associated with UARS[25-27]. One study found no significant difference in mandibular size and shape between OSAS children and healthy controls based on 3-dimensional imaging of the mandible. However, the position of the mandible relative to the rest of the facial skeleton or the cranial base was not evaluated[28]. With the exception of this study, all studies relied on 2-dimensional traditional cephalometric radiography for morphological assessment of study subjects. The most frequently-used cephalometric measurements in the 9 studies selected in this review, along with the number of individual studies that used each measurement, are shown in Table 2-2.

Reference	Study Design	OSAS Group	Control Group	Cephalometric Findings
Schiffman 2004	Cross-sectional 3-D evaluation and comparison of Mandiblar shape and size	n=24 Mean age: 4.9+/-1.7 Mean AHI: 9.8+/-11.1	N=24 Mean age: 4.9+/-1.8 Mean AHI: 0.4+/-0.3	3-dimensional size and shape of analysis of the mandible showed no significant differences between the two groups. Position of the mandible relative to the facial skeleton or cranial base was not evaluated.
Agren 1998	Prospective evaluation of OSAS patients before and after T&A	n=20 Mean age: 6 Age range: 4-9	Age-matched healthy controls and T2 evaluation of OSAS group	OSAS/UARS group characterized by: - Higher frequency of narrow Maxillary dental arches and lateral cross-bites. - Reduction in vertical growth pattern of mandible to a more horizontal growth direction at 1 year post-T&A.
Lofstrand-Tidstrom 1999	Cross-sectional comparison between subjects and healthy controls	n=21 Mean age: 4.3 (4.0-4.9)	n=40 Mean age: 4.1 (3.9-4.7)	OSAS/UARS group characterized by: - Narrow Maxilla - Shorter lower dental arch - Lateral crossbites - Larger anterior face height - Posterior rotation of the Maxilla and Mandible - More acute cranial base angle
Kawashima 2000	Cross-sectional comparison between subjects and healthy controls	n=15 Japanese chidlren Mean age: 4.7 Age range: 3-5	n=30 Age-matched healthy controls	OSAS/UARS group characterized by: - Posteriorly positioned and posteriorly rotated mandible - Increased Gonial angle - Longer lower facial height - Greater mandibualr plane angle - Retrusive chin
Marino 2009	Cross-sectional comparison between subjects and normative data from separate study	n=21 Caucausian children Mean age: 4.56+/-0.6 Age range: 3.11-5.9	Sample of healthy age-matched controls obtained from another study (Tollaro 1996) Mean Age: 5.67	Normal Maxillary proportions and position in the OSAS/UARS group. However, differences characterizing the OSAS group included: - Retrognathic mandible in saggital plane - Strong posterior (clockwise) rotation of the mandible in relation to the anterior cranial base. - Increased lower anterior face height.
Juliano 2009	Cross-sectional comparison between mouth-breathing	n=15 Mean age: 9.5+/-1.8	n=12 Mean age: 10.3+/-1.4	Mouth-breathing (OSAS/UARS group) showed : - Increased anterior facial height

	and nose-breathing children.			- Greater clockwise inclination of the occlusal plane - Retruded mandible and steeper mandibular plane - Open bite tendency and lip incompetence - Reduced phayngeal airway spaces
Zettergren-Wijk 2006	Cross-sectional and longtudinal comparisons between study patients and healthy controls.	n=17 Mean age: 5.6	n=17 Mean age: 5.8 Healthy age- and gender-matched controls	<u>At baseline (T1), the following significant differences were identified in the OSAS/UARS group</u>: - Posteriorly positioned and inclined (clockwise) mandible - Increased lower anterior facial height - Reduced lower posterior facial height - Shorter anterior cranial base - Retroclined upper and lower incisors - Narrower nasopharyngeal airways <u>At 5-year post-treatment (T&A) follow-up</u>: Almost complete normalization of all cephalometric measures in th study group as compared to healthy controls, with the exception of length of the anterior cranial base and the nose, which remained shorter in the study group.
Ozdemir 2004	Cross-sectional evaluation of correlations between cephalometric variables and AHI scores in pediatric OSAS patients.	n=39 Mean age: 7.5+/-1.7 Age range: 4-12	None	Increased AHI scores (associated with increased severity of OSAS) were positively correlated with: - Decreased cranial base angle (Ba-S-N) - Increased gonial angle (Ar-Gn-Go) - Decreased length of mandibular plane (Gn-Go) - Decreased minimal posterior airway space (MPAS) Protrusion of the maxilla (SNA) and mandible (SNB) did not correlate with AHI scores.
Zucconi 1999	Cross-sectional comparison of cephalometric variables between OSAS patients and healthy controls	n=26 Mean age: 5.1+/-0.5 Age range: 4-7	n=26 Age-matched by categories (3-4.5, 4.6-6, >6)	OSAS group characterized by the following: - High angle face (Increased craniomandibular angle and inter-maxillary angle) - Increased gonial angle - Retrusion and clockwise rotation of the mandible - Vertical growth pattern - Increased size of the bony nasopharynx (Ba-S-PNS) - Higher prevalence of crossbite and labial incompetence

Table 2-1 Outlines of the nine studies selected for the Systematic Review

OSAS: Obstructive Sleep Apnea

UARS: Upper Airway Resistance Syndrome

Cephalometric measurement	Number of studies	Description
MP-SN	6	The angle formed between the Mandibular Plane and the Anterior Cranial base
SNA	5	Angle formed between Sella-Nasion-A Point
SNB	5	Angle formed between Sella-Nasion-B Point
ANB	5	Angle formed between A Point-Nasion-B Point
BaSN	4	Angle formed between Basion-Sella-Nasion
ArGoGn	4	Gonial angle of the mandible
SN-PP	3	Angle between the anterior cranial base (SN) and the Palatal Plane (ANS-PNS)
MP-PP	3	Angle between the Mandibular plane (Go-Gn) and the Palatal Plane (ANS-PNS)
Gn-Go (mm)	2	The linear distance (mm) between Gonion and Gnathion
Ba-S-PNS	2	Angle between Basion-Sella-Posterior Nasal Spine
L1-MP (deg)	2	Lower incisor inclination relative to Mandibular Plane
MPAS	2	Minimum Posterior Airway Space

TABLE 2-2 Number of studies incorporating the most commonly-used cephalometric variables

2.3.1 Pooled data

The cephalometric variables that appeared in three or more of the selected articles as shown in Table 2-1 were selected for pooling. This was a total of eight variables, including MP-SN, SNA, SNB, and ANB, which appeared most frequently in the selected articles. The cephalometric tracing methods in each article were reviewed to ensure that the same cephalometric landmarks were used across studies for

each of the variables being considered. A summary of the reported mean values for the eight cephalometric variables is given in Table 2-3.

	n	MP-SN	SNA	SNB	ANB	BaSN	ArGoGn	SN-PP	MP-PP
Lofstrand-Tidestrom 1999									
Study	21	36.1 (4.23)	82.5 (83.3)	77.4 (3.28)	5 (2.48)	126.6 (4.12)	132.6 (5.35)	5.8 (2.79)	30.5 (4.31)
Control	40	32.5 (2.85)	83.3 (2.5)	78.7 (2.38)	4.2 (1.59)	130.6 (4.33)	131.4 (4.72)	4.5 (1.56)	27.8 (3.34)
Marino 2009									
Study	21	39.11 (4.76)	79.63 (0.59)	74 (3.08)	5.55 (1.86)	132.32 (5.64)		6.71 (2.04)	
Control	100	39.11 (35.23)	79.63 (79.88)	76.35 (2.85)	3.53 (2.63)	131.56 (4.44)		7.94 (2.75)	
Juliano 2009									
Study	15	38.53 (5.63)	83.33 (3.99)	76.2 (4.04)	7.07 (2.46)				
Control	12	30.25 (7.21)	85.67 (5.26)	80.83 (5.25)	4.58 (1.44)				
Zucconi 1999									
Study	26	39.7 (5.1)	81.1 (3.4)	75.1 (3.9)	5.9 (1.9)				31.7 (5.3)
Control	26	34.7 (2.3)	80.8 (1.3)	76.1 (1.7)	4.8 (1.3)				20.1 (3.4)
Agren 1998									

Study	20	38.1*							34.2*
No Control Group	No control group								
Zettergren-Wijk 2006									
Study	17	38 (4.41)						4.2 (2.12)	
Control	17	33.5 (4.42)						6.7 (2.19)	
Ozdemir 2004									
Study	39		79.7 (1.2)	74.7 (1.4)	3.7 (7)	126.5 (2.6)	131 (3.4)		
No Control Group	No control group								
Kawashima 2000									
Study	15					134.8 (4.5)			
Control	30					134.9 (3.7)			
Schiffman 2004									
Study	24						115 (3)		
Control	24						115 (3)		

Table 2-3 Summary of the reported mean values for the eight most frequently-measured cephalometric variables in the selected articles.

** Standard Deviation not reported*

Standard Deviations given in brackets

Weighted sums of the individual means and standard deviations reported for each cephalometric measure were obtained using the reported sample sizes, and this was used to calculate pooled weighted mean values for each variable across all eight studies using the following formula :

$$\text{Weighted Mean} = \frac{\text{Sum of [mean value of given ceph variable x n]}}{\text{Total n across all studies reporting this variable}}$$

The mean differences between Study and Control groups were also pooled in a similar fashion to obtain a pooled mean difference for each variable across studies. The combined cephalometric data from the articles that reported these eight variables is summarized in Table 2-4.

	Pooled Study Group			**Pooled Control Group**			**Pooled Mean Difference**
	n	**Mean**	**St Dev**	**n**	**Mean**	**St Dev**	
MP-SN	120	38.31	4.01	195	34.14	2.77	4.17
SNA	122	80.91	2.35	178	81.17	2.74	0.26
SNB	122	75.31	2.87	178	77.14	2.74	1.83
ANB	122	5.13	3.69	178	3.94	2.12	1.19
BaSN	96	129.09	3.89	170	131.92	4.28	2.83
ArGoGn	84	126.83	3.77	84	125.25	4.83	1.58
SN-PP	59	5.66	1.72	157	6.93	2.15	1.27
MP-PP	67	32.07	3.41	66	24.77	3.36	7.30

Table 2-4 Summary of pooled data for the eight most frequently-reported variables in the selected articles*.

**All measurements angular, Means are given in degrees*

As demonstrated in Tables 2-2 and 2-3, the largest pooled datasets were the ones for the four variables MP-SN, SNA, SNB, and ANB. Of these four variables, only MP-SN appeared to differ significantly between Study and Control groups, with the pooled Study Group having a mean that is almost two standard deviations above that of the pooled control group suggesting a more anteriorly divergent growth pattern in Study patients (patients with upper airway problems).

The variable MP-PP, the angle between the Mandibular Plane and Palatal Plane, was also significantly different between the two groups, with the study group having a pooled mean that is more than two standard deviations higher that of the Control group. This further demonstrates a more divergent growth pattern in the study group (patients with upper airway problems) as shown by a steeper Mandibular Plane.

2.4 Discussion

To date, no single cephalometric analysis has been validated or is widely accepted as being the most appropriate for 2-dimensional evaluation of craniofacial form from an airway perspective. Neither the respiratory status nor the specific location of any potential obstruction in the upper airway can be reliably identified from a standard 2-dimensional lateral cephalogram[29]. However, cephalometric analysis and anthropometric measurements have been successfully used to distinguish OSAS patients from controls with relatively high accuracy. Lee et al reported an accuracy rate of 76.1% for direct clinical measurements of facial features, with sensitivity of 86.0% and specificity of 59.1%, and positive and negative predictive values of 78.4% and 70.9% respectively .[30, 31].

From the information compiled in this review a clear pattern emerges of the overall craniofacial morphologic pattern associated with pediatric OSA. An aggregate overview of the data describes a hyper-divergent growth pattern with a significant vertical component of growth in the lower face. However, results of meta-analysis of the cephalometric data reported in the selected studies should be interpreted with caution due to the variability in magnification/calibration of radiographic equipment between study, lack of standardization of measurements, and differences in study sample parameters.

It is noteworthy that the variables SNA, SNB, and ANB appeared not to be significantly different between the two pooled groups. The reliability of these measurements as indicators of antero-posterior projection of the Maxilla and Mandible is directly affected by the length of the Anterior Cranial Base, which has been reported to be significantly shorter in patients with OSA problems relative to normal controls[32, 33]. A tendency towards shorter anterior cranial bases in study patients could contribute to falsely normal SNA, SNB, and ANB values despite the presence of underlying maxillary or mandibular retrognathism.

Reports of reductions in the severity of these morphologic changes or even near-total normalization of the craniofacial growth pattern in the lower face following successful treatment of the UARS problem[15, 34-36] suggest that this unfavorable growth pattern is a reversible outcome of the craniofacial musculoskeletal imbalances associated with postural changes in response to UARS. These findings suggest direct cause-effect relationships between UARS and craniofacial growth changes, and were generally viewed as such by the authors[37-39].

However, confirmation of a causative relationship between OSA and craniofacial morphologic features cannot be obtained from these studies alone. Most of the studies were subject to various methodological deficiencies such as inconsistent reporting of operator reliability and blinding, inconsistent definitions of OSA status, and lack of an appropriate control group. Other factors affect the

strength of these conclusions, including the questionable relevance of static 2-dimensional measurements (lateral cephalometry) to the status of a dynamic structure like the upper airway, the lack of long-term follow up in most studies, and the lack of adequate exploration of alternative explanations for improvements in craniofacial growth and development following successful treatment of OSA and vice-versa. These alternate explanations include the role of Growth Hormone and other growth mediators in the growth and development of the lower face and the metabolic and cardiovascular implications of improving sleep and oxygenation parameters on craniofacial growth and development.

Further, the connection between mode of breathing and postural changes, which is a basic premise of the associations between OSA and craniofacial morphology, appears tenuous as predominant mouth-breathing does not appear to be necessarily abnormal or linked to nasal obstruction in humans[40]. Conversely, habitual open mouth posture as seen in benign lip incompetence is not necessarily indicative of a predominantly oral respiratory pattern[41, 42].

Nevertheless, the consistency of the general cephalometric patterns observed in pediatric patients with OSA and their clear distinction from normal craniofacial morphology is now fairly well-established. Whether these patterns are a cause, an effect, or neither with respect to OSA is still very much a matter of genuine debate, though successful treatment for OSA is currently being performed based on the assumption that these associations are present and significant.

Limitations of this review include the possibility that certain studies may have been missed in the literature search, though it is unlikely that enough studies fall in this category to affect the results of the review. Further, the selection process used was potentially susceptible to publication bias, with the recognition of the fact that studies showing negative outcomes or lack of a significant difference may be less likely to reach publication [43].

Despite methodological weaknesses in most of the studies examining the association between craniofacial morphology and obstructive sleep apnea in children, a fairly consistent pattern of distinctive cephalometric findings in pediatric OSA patients has been reported in the literature in recent years. Most of these findings are consistent with previous research in this area, and include downward-backward rotation of the mandible and a tendency towards vertical growth.

Etiologic connections between these morphologic patterns and upper airway resistance syndromes have not been clearly established. A deeper understanding of the pathophysiology of OSA and its relationship to craniofacial form and function is required in order to determine the nature and extent to which craniofacial morphologic patterns influence or are influenced by changes in upper airway function.

2.5 Conclusions

Several morphologic features were found to be commonly associated with airway problems in children, including increased vertical growth of the lower face and a more divergent growth pattern in children with upper airway resistance syndromes such as OSAS.

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CHAPTER 3 - The Association Between PAP Therapy and Craniofacial Growth and Development

3.1 Introduction

3.1.1 Obstructive Sleep Apnea Syndrome (OSAS)

Obstructive sleep apnea syndrome (OSAS) is a form of sleep-disordered breathing (SDB) characterized by recurrent episodes of partial or complete airway obstruction during sleep. The pathophysiology of OSA in any given patient will depend on the specific primary etiologic factor(s), but the overarching causative mechanism in non-centrally-mediated OSA is physical occlusion of the upper airway due to an anatomic obstruction. This obstruction can occur anywhere from the nares to the epiglottis, but most commonly appears to be a result of adenotonsillar hypertrophy, chronic inflammatory conditions (eg. allergic rhinitis) or pathologic changes (eg. nasal polyps, fibrosis) in the nasal mucosa, or unfavorable craniofacial skeletal morphology and growth patterns.

The current gold standard in the diagnosis of sleep-disordered breathing problems is overnight polysomnography (PSG). Despite its limitations, PSG still offers the most objective assessment of sleep architecture and physiology and remains the primary test in both the diagnosis of SDB problems and the evaluation of treatment response. Ambulatory sleep monitoring (eg. Overnight home oximetry) is also in widespread use as a helpful adjunct to PSG and clinical examination in the detection of SDB problems such as OSA. In patients with a high probability of OSA, home oximetry can be helpful in confirming the diagnosis [1]. Physical examination and detailed history recording with validated questionnaires are essential to identifying high-risk patients. The Epworth Sleepines Scale (ESS) and the Sleep Apnea Clinical

Score (SACS) can be used, with scores of >10 and >15 respectively being associated with higher probability of OSA [2].

Pediatric patients diagnosed with Obstructive Sleep Apnea Syndrome have several treatment options available. Depending on the primary etiologic factor, the treatment may involve surgical intervention, medical management, pharmacologic therapy, or a combinations thereof. The first-line surgical treatment for pediatric OSA is adenotonsillectomy, with a reasonably high success rate and significant improvement in quality of life post-operatively[3]. Other treatment options for OSA include dietary and lifestyle modification for weight loss and improved sleep patterns, positive airway pressure (PAP) therapy, oral appliances, pharmacologic management, and surgical advancement of the maxilla or mandible [3 4].

For patients who do not present with clinical evidence of adenotonsillar hypertrophy, are unresponsive to adenotonsillectomy, or where the procedure is contraindicated, medical management includes continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP) via a nasal mask as the second line of treatment[5 6]. Both CPAP and BiPAP supply external pressure to the upper airway to prevent its collapse during sleep. CPAP provides a continuous level of pressure, whereas BiPAP allows different pressure settings for inhalation and exhalation, making it more suitable for patients with neuromuscular disorders or who cannot tolerate CPAP[3].

In order for nasal mask-delivered CPAP or BiPAP devices to be effective, an airtight seal between the nasal mask flanges and the peri-nasal area must be achieved. A tight seal is obtained by ensuring adequate pressure and fit by the mask flanges against the facial skin using the supplied headgear strap(s) [7]. The pressure exerted by the mask on the soft tissues and underlying growing and remodeling bones of the midface may be a potential cause of mid-face hypoplasia in growing children who are on long term CPAP or BiPAP therapy during their peak growth years[8]. If such an association exists, it would

be safe to assume that the nature and magnitude of its impact would be directly related to the length of the CPAP therapy, patient compliance, the magnitude and direction of pressure exerted on various areas of the facial skeleton, and the timing of the initiation of PAP therapy in relation to the degree of skeletal and developmental maturation of the nasal-maxillary complex.

If long term use of PAP devices is shown to contribute to a midface hypoplastic growth pattern, an argument can be made that it is having a paradoxical negative effect on the treatment of OSAS, by contributing to the development of a facial pattern that is associated with OSAS (midface deficiency). Further, the potential iatrogenic creation of a midface deficient growth pattern as a side effect of long term PAP therapy may contribute to the development of a Class III (maxillary retrognathic) dental or skeletal pattern, creating a later need for orthodontic or orthognathic surgical treatment during or after the period of CPAP therapy, depending on the severity of the resulting malocclusion and the patient's perception of treatment need. This review aims to assess current knowledge of this potential risk through an examination of the literature covering the potential risk for iatrogenic midface deficiency as a result of long term PAP therapy in growing children.

3.1.2 Mechanism of action of headgear therapy and possible parallels with nasal CPAP therapy

Growth and development of the nasal-maxillary complex, and especially the Maxilla, is of critical importance to orthodontic diagnosis and treatment planning. The growth and downward-forward translation of the nasomaxillary complex occurs primarily at the sutures of the circum-maxillary and circum-nasal suture systems[9]. As new bone is formed at these sutures the flat bones of the maxilla grow larger in volume and are translated downward and forward away from the Frontal, Zygomatic, Sphenoid and other bones to which they are attached.

The direction and magnitude of this growth is what orthodontists aim to influence using protraction headgear devices in the treatment of skeletal class III malocclusions due to maxillary hypoplasia [10, 11]. Conversely, cervical or occipital headgear appliances placing posteriorly-directed traction force vectors on the maxillary dentition have been shown to produce skeletal effects at force levels as low as 500 grams [12]. The principle of the sustained application of forces above thresholds of bioactivity to effect skeletal change in the jaws is a well-established basic tenet of dentofacial orthopedics. This principle underpins the mechanism of action of a range of intraoral and extraoral devices used in modern clinical orthodontics to promote corrective skeletal and dentoalveolar changes in the maxilla and mandible; and is well-demonstrated in the use of orthodontic headgear to control maxillary anterior projection[13, 14 15].

The timing and duration of use of these orthopedic appliances in orthodontic treatment is roughly similar to the timing and duration of PAP therapy in pediatric patients with OSAS. When different, PAP therapy is also much more likely to be initiated much earlier in childhood than orthodontic-orthopedic appliance therapy, thereby potentially giving it a potentially greater impact on midfacial growth and development due to the earlier stage of craniofacial growth and development at which it is introduced.

Even though the PAP nasal mask exerts direct pressure on a different area of the maxilla than that on which orthodontic headgear acts, the anatomical structures involved are in close proximity and intimately connected. The dental anchorage units to which the headgear bow connects are attached to the maxillary bones via the maxilla alveolar process. This intermediary process does allow for some of posterior dental movement through biomechanical stimulation of periodontal bone-metabolic processes. However, the skeletal maxillary-retrusive effects of headgear therapy have also been clearly demonstrated [13 15]. Pressure exerted on the subnasal area from nasal masks or cannulas may have a similar effect by altering the equilibrium of forces exerted on the maxilla and other midfacial structures during growth.

3.2 Methods

A thorough review of the literature was conducted to consolidate current knowledge in this area. This review consisted of a series of electronic database searches using a series of keywords and keyword combinations based on knowledge of the subject area controlled vocabulary and free text terms, consultation with a specialized health-sciences librarian, use of MESH subject headings, and reviews of reference lists in selected articles. The electronic databases searched were Medline, PubMed, EMBASE, All EBM Reviews, Scopus, and Web of Science. The two selection criteria used to identify eligible articles for review were the requirement that the primary focus of the article be the effect of prolonged use of PAP therapy on craniofacial growth and development, and that the article be retrievable in full text form in either electronic or print format. These selection criteria were applied at both the initial and secondary stages of the literature search.

The electronic database searches were limited by age group to subjects under 18 years of age, with the assumption that individuals undergoing active growth would be potentially more affected than non-growing individuals or those for whom the period of peak growth (the pubertal growth spurt) has already passed. No other restrictions were placed on the type of publication, language, date of publication, or any other publication parameters. Two individual reviewers (MK and HA) assessed the search results of the database searches and independently applied the selection criteria to the retrieved results.

The keywords used in the electronic database searches are given in Table 3-1. Search terms were appropriately combined and truncated in each electronic database search according to the suggested protocols for each search engine interface.

Variable	Search Terms
Obstructive Sleep Apnea	sleep apnea sleep apnoea sleep apnea, obstructive sleep apnoea, obstructive obstructive sleep apnea obstructive sleep apnoea
Effects on craniofacial growth and skeletal/dental patterns	skeletal dental craniofacial, craniofacial*, craniofacial$
Nasal CPAP	continuous positive airway pressure CPAP nasal cpap nasal continuous positive airway pressure
Growing children	child, child$, child*, pediatric, pediatric$, pediatric*

TABLE 3-1 Search terms used to identify the variables of interest

3.3 Results

The results of the electronic database searches are given in Table 3-2. As shown, only one article met the selection criteria at the completion of the elimination process. During the search and selection process, it was noted that several articles did make vague and brief mention of the potentially deleterious effects of long term use of a nasal mask on the craniofacial growth of young children, though only the selected article held this topic as the primary focus of the publication.

Electronic Database	Results	Articles selected
Medline	39	0
Pubmed	37	1
Embase	34	0
All EBM Reviews		0
Scopus	56	1
Web of Science	30	1

TABLE 3-2 Summary of electronic database search results

The single article selected for this review was identified in three of the electronic searches conducted. The article was a case report by Li et al describing marked midface hypoplasia observed in a 15-year old patient who had been on CPAP therapy for a ten-year period. No other articles could be found specifically discussing associations between long term CPAP therapy and craniofacial growth and development. The first author of this case report was contacted and he confirmed that he was not aware of any other similar reports in the literature.

A secondary reference list search consisting of a manual review of the reference lists of the articles retrieved for this review and the single article selected for the review. The titles of the articles cited in these reference lists were evaluated for relevance to the topic of this review, and those that contained a desired combination of the search terms or otherwise appeared to be potentially suitable based on the selection criteria were retrieved and evaluated. This search did not yield any additional articles that met the selection criteria.

3.4 Discussion

In the single article selected for this review, the case reported by Li et al demonstrated profound midface hypoplasia apparently resulting from the chronic application of direct pressure to the perinasal structures by a nasal mask used to deliver CPAP therapy to a growing child with OSA. The patient involved had undergone nasal CPAP therapy for 10 years from age 5 to age 15. The authors indicated that the child's facial development was normal prior to the initiation of nasal CPAP therapy, though no initial cephalograms were discussed or published. The authors also cautioned that prolonged application of an undesirable orthopedic force, such as by use of a nasal CPAP headgear/facemask unit, to the malleable developing structures of the pediatric facial skeleton can have profound deleterious effects that can worsen a pre-existing problem. They suggested regular cephalometric evaluation of children on long-term CPAP, and presented the finding of midface hypoplasia as an often-observed though rarely-reported harmful side effect of long term PAP therapy.

Only one article, a case report, could be found that directly examined this issue, despite the presence of a strong biologic basis for the hypothesis that chronic direct external pressure applied to the midface can cause a headgear-like effect on midfacial growth and development. Orthodontists have not generally been involved in the management of patients with upper airway resistance problems until relatively recently [16 17 18]. However, orthodontists receive extensive specialized training in the radiographic and clinical evaluation of the anatomic and morphological characteristics of Maxilla in all three planes of space.

Orthodontists and dentists also routinely utilize various extraoral and intraoral orthopedic appliances aimed at altering maxillo-mandibular growth patterns. These devices operate by exerting biologically-compatible forces on the bones of the jaws and face either through direct pressure on the surface of the skin (eg. chin cup) or through attachments to individual teeth or groups of teeth (eg. orthodontic

headgear and fixed functional appliances). Most of these appliances have been extensively studied and reported on in the literature. This knowledge base and skill sets make orthodontists an invaluable member of any multidisciplinary team involved in the management of pediatric OSA patients.

A clear understanding of the pathophysiology of upper airway problems and the medical interventions available to treat them is essential to any orthodontist operating in this area of practice. These patients often present with complex malocclusions that require dental, orthopedic, or orthognathic treatment [19]. For patients on long-term CPAP therapy, successful orthodontic treatment can be more difficult due to the inability to effectively use traditional orthodontic devices such as reverse-pull headgear in conjunction with the PAP nasal mask apparatus. The nature and extent, if any, of anterior tooth movements in response to long term PAP therapy also remain unknown and can profoundly impact both the short-term success and long-term stability of orthodontic treatment outcomes.

The need for further investigation of the potential iatrogenic side effects of long term PAP therapy on craniofacial growth and development is clear. Both medical and dental practitioners involved in the management of pediatric sleep-disordered breathing disorders recognize the need to more clearly understand the potential for iatrogenic creation or worsening of midface hypoplasia as a result of long term PAP therapy.

3.5 Conclusions

The current literature on this topic, limited to just one case report, is clearly inadequate and warrants further research given the potentially significant implications to clinical practice in the multidisplinary management of growing children with OSAS.

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CHAPTER 4 – Craniofacial morphology in pediatric OSA patients on PAP therapy and untreated controls: A cross-sectional cephalometric comparison

4.1 Introduction

Obstructive sleep apnea syndrome (OSAS) is a form of sleep-disordered breathing (SDB) characterized by recurrent episodes of partial or complete airway obstruction during sleep. The prevalence of OSA in children is reported in the range of 0.7-11%[1-4]. In contrast to adults, the most common cause of pediatric OSA is adenotonsillar hypertrophy[3, 5]. Several anatomic risk factors are associated with childhood OSAS. These include macroglossia, mandibular and/or midface hypoplasia, and other craniofacial anomalies. Other risk factors include obesity, various syndromes affecting craniofacial growth and development (eg Down Syndrome, Pierre Robin sequence, Apert's syndrome, and Treacher Collins syndrome), and some neuromuscular disorders[4].

The pathophysiology of OSA in any given patient will depend on the specific primary etiologic factor(s), but the overarching causative mechanism in non-centrally-mediated OSA is physical occlusion of the upper airway due to an anatomic obstruction. This obstruction can occur anywhere from the nares to the epiglottis, but most commonly appears to be a result of adenotonsillar hypertrophy, chronic inflammatory conditions (eg. allergic rhinitis) or pathologic changes (eg. nasal polyps, fibrosis) in the nasal mucosa, or unfavorable craniofacial skeletal morphology and growth patterns.

Children diagnosed with Obstructive Sleep Apnea Syndrome have several treatment options available. Depending on the primary etiologic factor, the treatment may involve surgical intervention, medical management, orthopedic therapy, or combinations thereof. The first-line surgical treatment for pediatric OSA is adenotonsillectomy, with a very high success rate and significant improvement in quality of life

post-operatively[6]. Other surgical options include uvulopalatopharyngoplasty, and in severe, refractory cases, tracheostomy[7, 8]. Orthognathic surgical options include bimaxillary advancement and maxillary expansion and osseodistraction [8 9]. Pharmacologic management options include the use of topical or systemic corticosteroids for chronic nasal mucosal inflammation[10, 11].

However, for patients who do not present with clinical evidence of adenotonsillar hypertrophy, are unresponsive to adenotonsillectomy, or where surgical procedures are contraindicated, medical management may include continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP) via a nasal mask as the second line of treatment[12 13 14 6]. Both CPAP and BiPAP supply external pressure to the upper airway to prevent its collapse during sleep. CPAP provides a continuous level of pressure, whereas BiPAP allows different pressure settings for inhalation and exhalation, making it more suitable for some patients with neuromuscular disorders[6].

In order for nasal mask-delivered CPAP or BiPAP devices to be effective, an airtight seal between the nasal mask and the peri-nasal area must be achieved. A tight seal is obtained by ensuring adequate pressure and fit by the mask flanges against the facial skin using the supplied headgear strap(s). The pressure exerted by the mask on the soft tissues and underlying growing and remodeling bones of the midface may be a potential cause of mid-face retrusion in growing children who are on long term CPAP or BiPAP therapy during their peak growth years[15]. If such an association exists, it would be safe to assume that its magnitude and impact would be directly related to the length of the CPAP therapy, patient compliance, the magnitude and direction of pressure exerted on various areas of the face, and the timing of the initiation of treatment in relation to the degree of skeletal and developmental maturation of the nasal-maxillary complex.

As mentioned earlier, midface hypoplasia is one of the anatomic risk factors for OSAS. The relative contribution of midface hypoplasia to the etiology of upper airway resistance is variable, and is most

prominent in the presence of syndromes with craniosynostosis such as Apert's syndrome, Crouzon's disease, Pfieffer's syndrome, and achondroplasia**.** In cases where midface hypoplasia is thought to be a major contributor to the etiology of upper airway resistance, orthodontic maxillary expansion and/or protraction using surgical or non-surgical means may be curative[16, 17]**.** The orthodontic diagnosis in these cases is based on clinical and radiographic observation of maxillary antero-posterior hypoplasia and transverse constriction, and a straight or concave facial profile. Suspected Sleep-disordered breathing (SDB) disorders are confirmed thorough review of the relevant history including, consultation with a sleep medicine specialist, and polysomnography or ambulatory sleep monitoring.

The potential iatrogenic orthopedic effects of long term PAP use via nasal mask delivery have not been adequately investigated. A viable theoretical explanation exists for the potential of long term nasal mask wear to lead to undesirable midface hypoplasia. A better understanding of the potential interactions between long term PAP therapy and craniofacial growth and development is required before nasal mask-delivered PAP therapy can safely be used on growing children from an orthopedic perspective.

The primary question the authors sought to investigate in this study is whether long term CPAP use was associated with any identifiable cephalometric differences, primarily in the midface area, as compared to untreated controls. The underlying theory behind this question is that the sustained application of external forces to the midface on a long term basis by the tightly strapped PAP mask to the peri-nasal area of the face may negatively affect the anterio-posterior growth of the nasomaxillary complex with long term use during the period of active growth and development.

To investigate this issue, the authors conducted a cross-sectional comparison of lateral cephalometric measurements between two groups of OSA patients; a group who have been prescribed CPAP therapy (CPAP Group) and a group of untreated controls (Control Group).

Null Hypothesis

The Null hypothesis states that there is no difference in the craniofacial morphological pattern in the nasal-maxillary complex in the sagittal plane between growing children with OSAS who are on long-term CPAP therapy vs. those who are not as measured with lateral cephalometric radiography.

4.2 Methods

Participants in this study were recruited from the patient pool of the Pediatric Sleep Medicine Program at the Stollery Children's Hospital in Edmonton, Alberta, Canada. All potentially eligible participants were fully informed of the intent and procedures of the study and participation was completely voluntary with no incentives provided to encourage participation or discourage rejection.

4.2.1 Ethics approval and study procedures

A complete application for ethics approval was submitted to the University of Alberta Human Research Ethics Board (HREB). Formal HREB Ethics approval was granted on August 7th 2009 (Study ID: Pro00005700).

Eligible patients and their legal guardians who agreed to consider participation in the study were given an Information Sheet/Consent Form (Appendix C). Upon review of the information provided and answering any questions, the Informed Consent portion of the form was completed by each patient's legal guardian. Pediatric assent forms were also provided and explained to all patients below 18 years age (Appendix D).

4.2.2 Patient population

With the exception of CPAP status, the same selection criteria were used for both the Study and Control groups. These selection criteria are listed in Table 4-1. The Control Group consisted primarily of patients with residual OSA following Tonsil or Adenoid removal that required PAP therapy but had not yet started it, or patients whose residual OSA was not severe enough to require the use of PAP therapy at follow-up. TABLE 4-7 PAP compliance and duration

Common criteria	**Study Group**
• Age 6 – 18 years • Diagnosed with Obstructive Sleep Apnea Syndrome by a qualified sleep medicine specialist (based on standardized polysomnographic, clinical, and other diagnostic criteria) • No previous or current orthodontic treatment • No previous orthognathic surgery • No contraindication for diagnostic radiography	• Has used CPAP for no less than 6 hours per night for a period of 6 consecutive months or more between the ages 6 – 18* **This criterion is based on commonly accepted thresholds in the orthodontic literature for the manifestation of a skeletal effect from a functional orthopedic appliance intended for maxillary retraction such as high-pull headgear.* **Control Group** • No history of CPAP use at any point in the past • Age- and gender- matched to Study Group

TABLE 4-1 Selection criteria participation in the study

Patients were assessed for suitability for inclusion in the study as they consecutively present to the Sleep Medicine Program on referral from other practitioners or on self-referral. Those who were found to meet the inclusion criteria were then asked if they would like to participate in the study and directed accordingly.

4.2.3 Region of interest

The region of interest is the nasal-maxillary complex, also referred to as the "midface". For the purposes of this study, this region is described circumscribed by four lines in the midsagittal plane. The anatomical landmarks demarcating these lines are the cephalometric landmarks Nasion (N) and A-point (the most anterior point of the maxillary apical base) anteriorly, and the Sella Turcica (S) and the Posterior Nasal Spine (PNS) posteriorly. The main variable to be considered in the comparison is the antero-posterior projection of the midface in the sagittal plane. Other regions of interest included the anterior cranial base, the malar regions of the face, and the dentoalvealor arches.

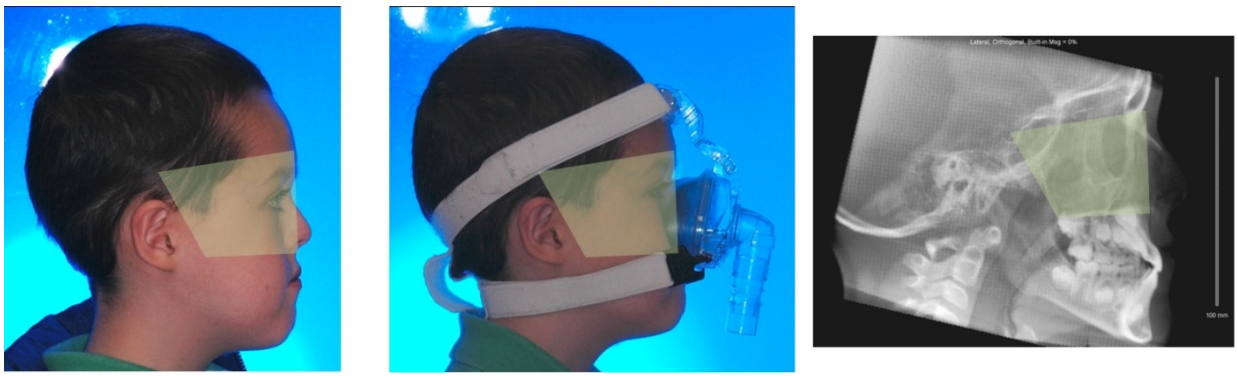

FIGURE 4-1 - Primary region of interest (light green shading)

4.2.4 Data acquisition and cephalometric analysis

All participants answered a set of standardized medical/dental history questions and received a full extraoral/intraoral standardized orthodontic clinical examination. The information collected during the examination was documented on a customized Data Collection Form (Appendix E) and tabulated appropriately with blinding of the operators to the identity of all participants and the groups to which they belong.

All participants also received 3-dimensional radiographic examination using Cone Beam Volumetric Imaging by means of an i-CAT machine *(Imaging Sciences International, Hatfield, PA, USA)* using the full Field of View (FOV) setting of 13 cm. The images were obtained in the DICOM3 format, and were processed using Dolphin 3D software *(Dolphin Imaging Solutions, Chatsworth, CA, USA)* to produce two-dimensional lateral cephalometric and panoramic images using a standardized imaging protocol.

All lateral cephalometric images were traced by the same operator (MK). To reduce the effect of operator measurement error, tracings were carried out three separate times in random order of patients and the values for each tracing were entered into an electronic spreadsheet *(Microsoft Excel, Microsoft Office 2010, Microsoft Corporation, Redmond, WA, USA)*. Mean values for each cephalometric variable from the three tracings per image were obtained and compared in the final statistical analysis. Blinding of the evaluator to the identity of patients and study groups to which the images belonged was maintained throughout the tracing process by means of a coding system.

The cephalometric analysis used in this study was based on a combination of the most-commonly used variables used in the relevant literature (See section 2.1) and specifically-selected measurements describing the antero-posterior projection of the midface region in the sagittal plane. A listing and description of the variables that constituted the cephalometric analysis used in this study is shown in Figure 4-2 and Table 4-4.

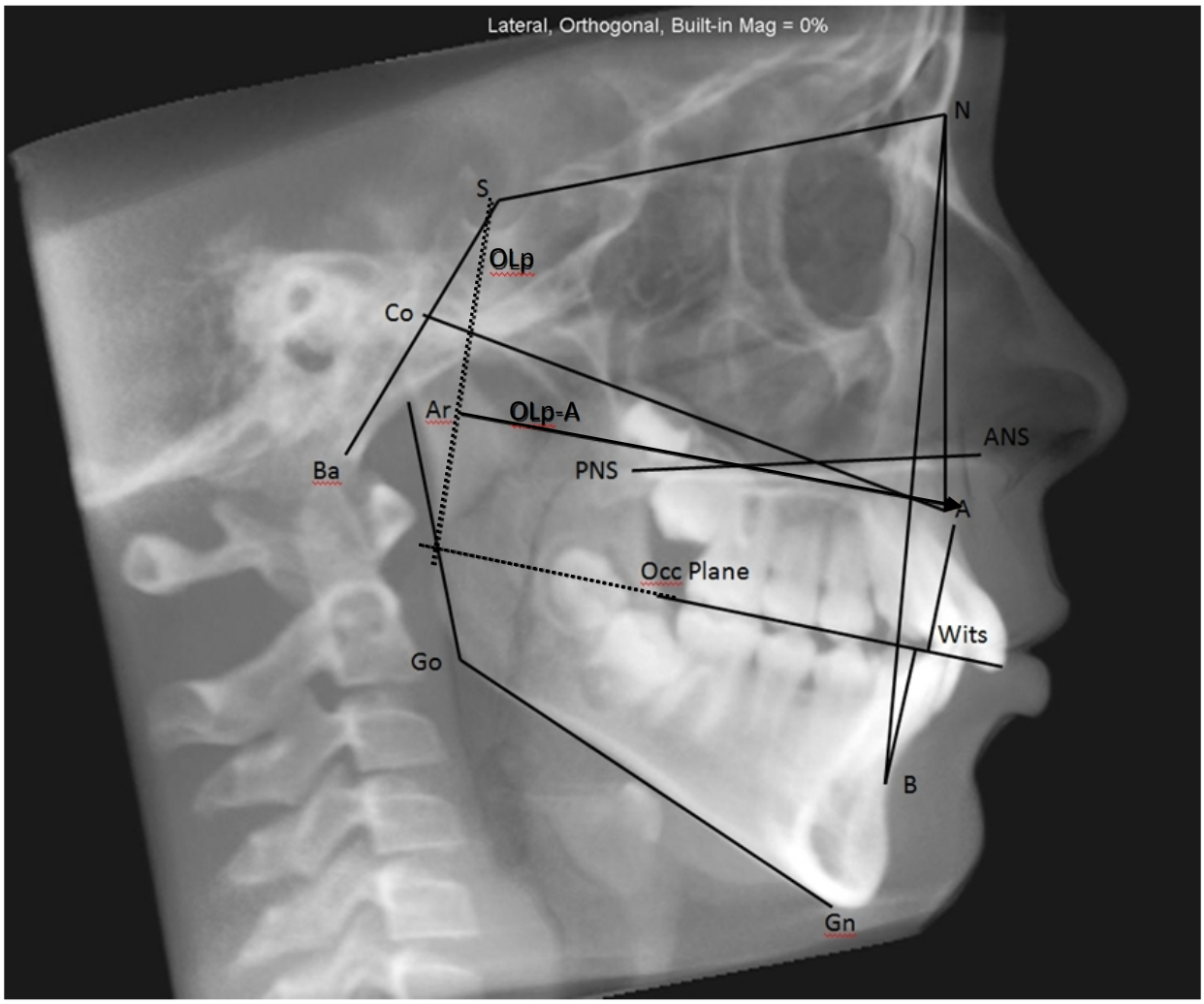

FIGURE 4-2 Lateral Cephalometric linear and angular landmarks

Cranial Base	
S-N (mm)	Length of Anterior Cranial Base
BaSN	Angle of flexure of Cranial Base
Maxilla/Midface	
SNA	Sella-Nasian-A Point: Maxillary A-P projection

PP-SN	Palatal Plane-SN (angle): Vertical inclination of palate relative to cranial base.
Co-ANS (mm)	Condylion-ANS (mm): Maxillary A-P projection
ANS-PNS (mm)	Anterior Nasal Spine – Post. Nasal Spine (mm): Length of Palate
U1-PP	Angulation of Upper incisor to palatal plane
A-NPerp (mm)	A point – Perpendicular to Frankfort Horizontal at N Point: Maxillary projection
OLp-A	The linear distance between A-Point and a line drawn perpendicular to the Occlusal Plane at Sella (OLp)
Mandible	
SNB	Sella-Nasion-Basion: Madibular A-P projection
ArGoMe	Articulare-Gonion-Menton (angle): Angle of mandible
Go-Me (mm)	Gonion-Menton (mm): Length of mandibular body
Maxilla-Mandible	
ANB	A point-Nasion-B Point (angle): relative position of mandible to maxilla
Wits analysis (mm)	Distance between perpendiculars to occlusal plane at A and B points

TABLE 4-2 Cephalometric analysis variables

4.2.5 Statistical Analysis

As previously mentioned, each lateral cephalometric image was traced by the same operator (MK) three separate times. After Intra-operator reliability was evaluated for all variables, the final comparison between the CPAP group and the Control group was conducted using mean values of the three measurements of each variable. All statistical analyses were performed using SPSS 16.0 software (SPSS Inc. Chicago, Ill, USA).

Given the nature of the sample and the collected information, a non-parametric statistical comparison of the two groups as two independent samples was selected. A Man-Whitney U-test is appropriate for

this time of comparison and was used as the primary statistical test in this study. A comparison using parametric statistical methods (t-test) was also conducted as an adjunctive analysis.

Additionally, multivariate linear regression analysis and Pearson's correlation analysis were conducted to assess potential associations between length of time in PAP therapy (months), compliance with PAP therapy, and variance in cephalometric variables.

4.3 Results

4.3.1 Study Sample

All subjects had had either tonsillectomy or adenoidectomy or both at the time of evaluation. Those whose OSA symptoms sufficiently improved following surgical removal of hyperplastic adenoid tissue and did not require further therapy, were allocated to the Control Group. Those who continued to exhibit residual OSA following tonsilloadenoidectomy and required nocturnal noninvasive ventilatory support (CPAP or BiPAP) were allocated to the CPAP group.

A total of 34 consecutive patients were recruited in this study. 21 patients were recruited in the OSAS group and 13 in the Control Group. The final number of patients recruited in the OSAS group was larger than the CPAP group due to the larger number of unusable datasets that were obtained in this group. As unusable datasets were encountered in either group, additional subjects were recruited in that group to to replace those datasets. Datasets were deemed unusable when the imaging obtained was not of diagnostic quality due to poor patient cooperation or technical difficulties with imaging hardware or software. Datasets were also discarded when a patient was recruited into the study and later found to have a Craniofacial syndrome, disqualifying them from the study. The number of datasets in each of these categories is shown in Table 4-2.

	CPAP Group	Control Group
	n=21	n=13
No imaging		1 (patient too apprehensive)
Poor imaging	7	1
Craniofacial syndromes	2 (1 Downs syndrome, 1 Dwarfism)	
Sub-totals	9	2
Grand total	**11**	

TABLE 4-3 Unusable datasets eliminated from the final analysis

Elimination of the unusable datasets resulted in a final study sample of 23 patients; 12 CPAP users and and 11 Controls. A demographic summary of this study sample is provided Table 4-4.

	CPAP Group	Control Group
	n=12	n=11
Gender	Males: 10 Females: 2	Males: 5 Females: 6
Mean age (years)	Males: 9.8 Females: 7.2 **Overall: 9.3**	Males: 8.6 Females: 10.5 **Overall: 9.6**

TABLE 4-4 Basic demographics of final study sample

The age and gender distributions were evaluated for compatibility between the two groups. There was no statistically significant difference in age between the two groups (p=0.814). The gender distribution, however, was clearly different between the two groups with a Male:Female ratio of 5:1 in the CPAP group and 5:6 in the Control group. This discrepancy was taken into account in the statistical comparison as explained in Section 4.3.2

4.3.2 Duration of PAP therapy

The duration of prescribed PAP therapy (months) was available for ten of the twelve patients in the CPAP group. At the time of clinical assessment, the number of months that patients had been prescribed PAP therapy ranged from 10.1 to 86.0, with a mean of 35.7 and standard deviation of 25.8. Table 4-5 shows the ages of PAP group subjects at the time PAP therapy was prescribed, and the age and number of months in PAP therapy at the time of evaluation in this study (T0).

	Age at PAP start (years)	**Age at T0 (years)**	**Duration of PAP therapy at T0 (years)**
1	6.1	7.1	1.01
2	5.3	8.3	3.03
3	1.2	6.2	4.98
4	6.2	8.4	2.23

5	9.0	10.9	2.08
6	10.3	11.6	1.35
7	8.0	15.2	7.17
8	5.1	6.8	1.68
9	8.9	9.7	0.84
10	3.7	9.1	5.43
Mean (SD)	**6.4 (2.7)**	**9.3 (2.7)**	**2.98 (2.15)**

TABLE 4-5 Age timeframe and duration of PAP treatment of CPAP group

As shown in the table above, the patient who had been on PAP therapy the longest at the time of the evaluation was initiated on therapy at the age of eight years and had been in therapy for eighty-six months at the time of evaluation. The youngest patient in the PAP group was 6.2 years old at T0 and had been on PAP therapy for 59.7 months.

4.3.3 Adherence to PAP therapy

Limited data on patient compliance with PAP therapy was available for subjects in the PAP group. This consisted of subjective reporting of the frequency and duration of PAP use by patients and parents as well as objective measurements of actual use obtained from electronic recording devices integrated into PAP units used by some of the subjects in this group. Several parents reported periods of disuse or irregular use of the CPAP mask. It was not possible to reliably verify the frequency or duration of PAP use for all PAP patients for the duration of the prescribed therapy due to equipment and staffing limitations.

ID	Months	Duration	S-N	BaSN	SNA	PP-SN	Co-ANS	ANS-	U1-PP

For the eight subjects for whom objective compliance data was available, the agreement between the objectively-recorded and subjectively-reported compliance data for any given patient varied widely. Subjective compliance over-reported actual compliance in most cases. The available compliance data for these eight subjects is given in Table 4-6.

	Subjective Compliance (hours / night)	**Objective Compliance (hours / night)**	**% agreement** (objective/subjective x 100)
1	8	8.4	104.4
2	10	10.5	105.0
3	7	2.5	35.7
4	6	2.9	48.3
5	9	9.5	105.6
6	10	1.1	11.0
7	9	4.5	50.0
8	10.5	8.0	76.2
Mean (SD)	**8.7 (1.6)**	**5.9 (3.6)**	**67.0 (36.2)**

TABLE 4-6 PAP compliance subjective reports and objective measurements

Individual cephalometric data is provided for the patients for whom both compliance and duration data was available is provided in TABLE 4-7.

	PAP at T0	(month)						PNS	
SS001	12.1	12.1	60.0	122.3	83.1	-0.7	76.7	46.5	87.5
SS003	36.4	36.4	67.3	124.0	82.1	12.0	76.7	48.4	100.2
LE118	59.7	59.7	58.4	121.7	83.6	0.3	74.9	42.5	108.5
SS009	26.7	26.7	64.8	138.2	78.0	8.5	82.7	44.8	104.4
SS012	24.9	24.9	58.8	141.1	78.9	10.6	78.1	40.8	114.2
SS014	86	86	66.0	129.0	85.2	7.6	89.0	50.0	118.7
SS016	20.2	20.2	62.2	123.9	82.2	5.5	72.6	38.6	94.4
SS018	10.1	10.1	60.0	125.9	84.2	6.7	73.4	45.7	104.3
			ANperp	**SNB**	**ArGoMe**	**GoMe**	**ANB**	**Wits**	**OLp-A**
SS001	12.1	12.1	2.8	80.1	130.0	62.3	2.9	-5.1	68.8
SS003	36.4	36.4	3.0	82.7	131.2	63.6	0.9	-5.4	64.1
LE118	59.7	59.7	4.2	75.1	120.4	72.0	2.0	-0.8	68.9
SS009	26.7	26.7	1.8	76.2	104.6	72.2	2.7	1.3	60.3
SS012	24.9	24.9	6.0	82.4	128.6	63.1	-0.1	-3.9	63.7
SS014	86	86	0.3	83.4	136.0	60.6	-1.2	-6.7	66.9
SS016	20.2	20.2	5.8	81.4	129.2	49.2	2.7	-5.1	69.7
SS018	10.1	10.1	2.9	84.7	122.0	66.8	-1.1	-8.1	68.3

TABLE 4-7 PAP compliance and duration

4.3.4 Intra-operator reliability

The three repetitions of the cephalometric measurements were designated M1, M2, and M3, and were conducted at least one week apart. The data from these three separate iterations of the cephalometric tracings were compared to assess intra-operator reliability using Intraclass Correlation Coefficient (ICC). The intra-class correlation coefficients were generally very high for all cephalometric variables, ranging from 0.704 (ANS-PNS) to 0.970 (ANperp) for single-measure comparisons.

The 95% confidence intervals were also lowest for ANS-PNS and highest for ANperp (0.505-0.849 and 0.941-0.986 respectively). The ICC tables for each variable showing ICC and Confidence Intervals are given in Table 4-7. Intra-operator reliability was deemed high enough to sufficiently reduce any potential impact of measurement error on the analysis in this study.

	Intra-Class Correlation	95% Confidence Interval	
		Lower Bound	Upper Bound
SN	.968	.937	.985
BaSN	.950	.903	.977
SNA	.942	.888	.973
PP-SN	.935	.875	.969
CoANS	.856	.738	.930
ANS-PNS	.704	.505	.849
U1-PP	.907	.826	.956
ANperp	.970	.941	.986
OLp-A	.924	.873	.964
SNB	.910	.832	.958
ArGoME	.735	.549	.866
GoMe	.909	.828	.957
ANB	.957	.903	.982
Wits	.936	.838	.974

Table 4-8 Intra-operator reliability demonstrated using Intraclass Correlation Coefficients

4.3.5 Cephalometric Analysis

The raw data of the cephalometric values obtained from the Study and Control groups are given in Appendix F**.** A summary of this data is provided Table 4-6 showing the Mean and Standard Deviation of the cephalometric variables measured in each study group:

	CPAP		Control	
n	n=12 10 males, 2 female Mean age: 9.3		n=11 5 males, 6 females Mean age: 9.6	
	Mean	*S.D.*	*Mean*	*S.D.*
S-N (mm)	61.5	3.4	64.0	3.7
BaSN (deg)	131.1	8.4	131.3	4.0
SNA (deg)	81.5	3.0	80.5	3.8
PP-SN (mm)	7.2	4.1	6.2	3.7
Co-ANS (mm)	78.4	5.8	79.7	5.0
ANS-PNS (mm)	44.9	4.5	45.6	3.0
U1-PP (mm)	105.1	9.3	106.4	9.1
ANperp (mm)	2.7	2.1	0.6	4.8
OLp-A (mm)	66.8	5.1	68.6	3.9
SNB (deg)	79.3	3.7	77.2	4.7
ArGoMe (deg)	123.8	8.9	129.5	8.4
GoMe (mm)	63.3	8.0	61.2	7.7
ANB (deg)	1.8	2.2	2.6	3.2
Wits (mm)	-2.2	3.9	-1.5	2.7

TABLE 4-9 Mean and standard deviation of cephalometric values

Descriptive statistical summaries were obtained for the dataset. These summaries include boxplots, histograms, and scatterplots of the variables in each group, and are given in Appendix H. Some potential outliers were noted in the variables PP-SN, CoANS, ANperp, and ArGoMe.

The sample data did not appear to be normally distributed, and the sample size was relatively small with several relatively large standard deviations for some variables. Given the nature of the sample and the small sample size, a non-parametric Mann-Whitney U-Test was selected as the primary statistical instrument of comparison. This test showed no significant differences between the two groups in any of the cephalometric variables. The lowest p-value in this test was obtained for SN (p=0.124), and the highest was for GoMe (p=0.951). The results of this test are given in Table 4-9.

	SN	BaSN	SNA	PP_SN	CoANS	ANS_PNS	U1_PP	ANperp	OLp-A	SNB	ArGoMe	GoMe	ANB	Wits
p-value	.124	.712	.479	.406	.460	.667	.622	.157	.196	.218	.242	.951	.389	.689

Table 4-10 Mann-Whitney U-Test comparing Study and Control groups for each cephalometric variable

To investigate the potential impact of the difference in gender distribution between the two groups (M:F Ratio 5:1 in CPAP group, 5:6 in Control group). The Mann-Whitney U-Test was repeated separately for each gender in the two groups. In the comparison of males there was no significant difference in any of the cephalometric variables (lowest p-value: SNA, p=0.050 / highest p-value: Wits, p=1 approximately). Similar results were obtained in the comparison of females, with no significant differences found in any of the cephalometric variables compared (lower p-value: SN, p=0.071 / highest p-value: PP-SN, ANB, and Wits, p=1 approximately). With these finding, the difference in gender distributions between the two groups was determined not to have a significant impact on the outcome of the overall comparison.

As an additional exploratory exercise, a parametric test was conducted to compare the two groups. The primary statistical instruments of comparison is the non-parametric test described above, however an Independent-Samples T-Test was also conducted comparing the two groups (Table 4-10). With equal variances were both assumed and not assumed, no significant differences between the two groups were found in any of the cephalometric variables in this test. The comparison with the lowest p-value was SN (p=0.107) and the highest was BaSN (p=0.931). The Independent-Samples t-Test was repeated with outliers removed for each of the variables in which outliers were identified. This did not change the outcome of the comparison, with no significant differences found between the two Study Groups with respect to these four variables (p-Value range: p=0.07 ANperp – p=0.841 PP-SN)

	CPAP			**Control**			**Mean**	**95% Conf. Interval**		**p-**
	Mean	*S.D.*	*Range*	*Mean*	*S.D.*	*Range*	**Diff.***	*Lower Bound*	*Upper Bound*	**value**
SN	61.5	3.4	55.1 – 67.3	64.0	3.7	58.1 -70.4	-2.49	-5.3481	0.7542	.107
BaSN	131.5	8.4	121.0 – 143.4	131.3	4.0	125.8 – 139.2	-0.24	-5.4517	5.6396	.931
SNA	81.5	3.0	75.7 - 86.2	80.5	3.8	75.1 – 86.0	1.06	-1.5745	4.1623	.461
PP-SN	7.2	4.1	-1.4 – 12.3	6.2	3.7	-0.1 – 13.3	0.91	-2.4446	4.3567	.583
CoANS	78.4	5.8	71.3 – 91.7	79.7	5.0	72.3 – 89.8	-1.28	-5.7043	2.8603	.578
ANS-PNS	44.9	4.5	37.9 – 51.7	45.6	3.0	41.6 – 50.1	-0.69	-4.1335	1.4578	.672
U1-PP	105.1	9.3	87.2 – 121.0	106.4	9.1	88.0 – 116.5	-1.32	-9.1966	4.8042	.735
ANperp	2.7	2.1	-1.1 – 6.7	0.6	4.8	-9.7 – 8.2	2.10	-1.1573	5.0346	.187
OLp-A	66.8	5.1	58.5 – 76.0	68.6	3.9	65.0 – 76.2	-1.80	-5.7188	2.1127	.349
SNB	79.3	3.7	72.7 – 83.7	77.2	4.7	68.7 – 81.9	2.06	-1.7227	5.7000	.255
ArGoMe	123.8	8.9	102.3 – 134.0	129.5	8.4	119.1 – 147.1	-5.68	-12.7723	2.6511	.130
GoMe	63.3	8.0	48.9 – 72.7	61.2	7.7	49.1 – 75.5	2.13	-5.1076	8.0591	.524

ANB	1.8	2.2	-1.5 – 5.3	2.6	3.2	-3.4 – 6.4	-0.76	-3.0726	1.4998	.511
Wits	-2.2	3.9	-8.4 – 2.6	-1.5	2.7	-6.5 – 2.3	-0.69	-3.3952	2.3436	.624

Table 4-11 Independent-Samples T-Test

Multivariate linear regression analysis showed no significant association between variance in the number of months of PAP therapy and cephalometric variables (p=0.364). Pearson's correlations between the duration of prescribed PAP therapy and cephalometric variables were also weak, ranging from -0.07 (PP_SN) to 0.568 (U1_PP). A similar pattern was also found when objective compliance data was evaluated against cephalometric variables, with multivariate regression showing no significant association (p=0.148) and Pearson's correlations ranging from 0.078 (Co_ANS) to 0.579 (SNA). Pearson's correlation values relating cephalometric variables to number of months in PAP therapy and compliance data (hours per night) are provided in Table 4-11

	Pearson's Correlations	
	PAP therapy duration (Months)	**Compliance with PAP therapy (Hours per night)**
SN	0.350	-0.466
BaSN	-0.137	-0.177
SNA	0.427	0.579
PP-SN	-0.077	-0.485
CoANS	0.562	0.078
ANS-PNS	0.491	0.475
U1-PP	0.568	0.101
ANperp	-0.458	0.383

OLp-A	0.406	-0.090
SNB	0.402	-0.472
ArGoMe	0.183	0.269
GoMe	-0.484	-0.099
ANB	0.174	-0.102
Wits	0.041	-0.383

Table 4-12 Pearson's Correlation values relating PAP compliance and treatment duration to Cephalometric variables.

4.4 Discussion

The use of CPAP and BiPAP therapy in pediatric patients as long-term therapy for Obstructive Sleep Apnea (OSA) is a relatively recent phenomenon first reported in 1980 [18]. However it has been in widespread use for the treatment of adult OSA for decades[14]. Unlike adults, the primary etiologic factor for OSA in children is adenotonsillar enlargement, hence the gold standard treatment of tonsillectomy and adenoidectomy. The need for adequate management of cases that do not adequately respond to surgical resection of hyperplastic lymphoid tissue or are not suitable candidates for surgery, gave rise to the use of PAP therapy in children, along with other treatment modalities such as orthodontic interventions and anti-inflammatory pharmacologic management.

4.4.1 Orthodontic-orthopedic manipulation of midface growth

The craniofacial skeleton in the growing child is responsive to changing functional demands and environmental factors. Orthopedic modification of facial bones through the sustained application of near-constant forces over prolonged periods of time has long been a mainstay of orthodontic and

dentofacial orthopedic therapy[19]. The successful use of CPAP therapy requires the application of such forces to the midface area, which prompts concern about the potential side effects this might have on the anterio-posterior skeletal development in that area.

Orthodontic cervical headgear (CHG) can be effectively used to restrict anterior maxillary growth, reduce maxillary anterior displacement, and reduce effective maxillary length [20]. The nature of the changes achieved by different configurations of orthodontic devices used to reduce maxillary projection varies depending on the type of appliances used and the direction of force application [21 22]. Dentoalveolar changes tend to be greater than skeletal changes with headgear, however orthopedic change demonstrated as measurable reduction in midfacial anterior projection at the skeletal level is also consistently achieved with extraoral traction for class II correction [23-25]

Wear of CHG for 12 hours or more per day for 12-18 months using an average force of 450 grams per side is capable of producing significant cephalometric changes consistent with maxillary retraction[22].. Unlike CHG, which is typically dentally-anchored attaching to fixed appliances bonded to posterior teeth, the nasal mask used to deliver PAP therapy applies direct external pressure to the midface area at the level of the maxillary apical base. The magnitude of force applied by the headgear straps is based on the threshold of required to produce dentoalveolar and orthopedic change, while nasal mask straps are adjusted to produce an airtight fit of the mask to the face that is tolerable to the patient regardless of force level.

The actual force level required to obtain an airtight seal will vary depending on the type of nasal mask used, facial morphology and adaptability to non-customized masks, and other factors. It is likely that these force levels would typically far exceed those used in CHG therapy. However, the daily duration of wear of PAP nasal masks would typically be far shorter than the prescribed daily interval of wear of orthodontic headgear due to the fact that PAP therapy is only required during sleep, while orthodontic

headgear must also be worn during waking hours (minimum total of 12-14 hours per day) to be effective.

Further, compliance with CHG wear is reported around 55-65% [26] of the prescribed daily duration, or about 7-8 hours. In contrast, pediatric adherence to PAP therapy is reported at an average of 5.3 hours per night [27]. In both cases, subjective patient or parent reporting of compliance consistently significantly overestimated the number of hours of daily wear of the orthodontic appliance or nasal mask. Compliance with CHG may be higher than nasal mask therapy partially due to the circumscribed period of time required to achieve the desired treatment effect with CHG (12-18 months) as compared to the more open-ended timeframe of PAP therapy.

This study sought to examine the potential for midface hypoplasia in response to long term PAP therapy by comparing two groups of children with obstructive sleep apnea: one comprised of long term CPAP users, and the other of untreated controls. The results of this study showed no significant differences between the two groups as identified by lateral cephalometry. While there is a viable theoretical explanation for iatrogentic midface deficiency in response to prolonged CPAP therapy in the growing child, only one case report making this connection has been published to date[15]. Unfortunately, in both this study and the case report by Li et al, objective assessment of patients' exposure to the intervention (compliance with CPAP) was not available, making it difficult to judge the potential relative contribution of CPAP use to clinically-observed midface deficiency.

Both maxillary deficiency and mandibular retrognathism have been linked to OSA as both etiologic factors as well as sequelae of prolonged mouth breathing during growth years [28] [29, 30] [16] [31]. As discussed in the next section, both study groups exhibited a pattern of absolute bimaxillary retrognathism relative to normative data. This finding further complicates efforts to discern the craniofacial morphological effects, if any, that are specifically attributable to long term PAP therapy.

4.4.2 Comparisons to normative data

During the data collection phase of this study, it was noted that the facial appearance and craniofacial morphological patterns of many of the participants were considerably different from normal patterns. While it was shown in the statistical analysis that the two groups did not differ significantly from one another, it was interesting to note that both groups did show significant differences from normative data on four important cephalometric variables as shown in Table 4-12. In this cursory comparison of the two study groups to normative values for the 13 variables considered in this study, the patients in both groups are shown to be significantly deficient in the A-P dimension in relation to the norm with regards to Anterior Cranial Base, and Maxillary and Mandibular forward projection. The normative data obtained for this comparison was selected from published normative data collected from subjects of similar race, age, and gender profiles[35-37]. A possible weakness of this comparison is the inherent variation in distortion/magnification between different cephalometric equipment models used in the various studies.

Of particular interest, is the comparison of the Anterior Cranial Base in the study groups relative to normative data. Both groups showed mean SN(mm) that were over two standard deviations below the norm (CPAP: 61.6, Control: 64.0, Norm: 72.1). This is consistent with the findings of three of the studies indentified in the literature review for this study [32] [33] [34]. This significant finding has the potential to affect the usefulness of other linear and angular cephalometric measurements that rely on Sella and Nasion (such as SNA, SNB, and ANperp) as indicators of antero-posterior projection of the Maxilla and Mandible. A shortened cranial base makes it more difficult to reliably evaluate absolute A-P projection of the lower face in the sagittal plane.

	CPAP n=12		Control n = 11		Norm			p-value	p-value
	Mean	S.D.	Mean	S.D.	Mean	S.D.	n	CPAP-Norm	CTRL-Norm
SN	61.5	3.4	64	3.7	70.8	2.9	42	0.0000	0.0000
BaSN	131.5	8.4	131.3	4	134.9	5.4	39	0.0845	0.0775
SNA	81.5	3.0	80.5	3.8	80.1	3.7	39	0.2392	0.7350
PP-SN	7.2	4.1	6.2	3.7	6.7	2.8	42	0.6370	0.6483
CoANS	78.4	5.8	79.7	5	88.5	4.0	42	0.0000	0.0000
ANS-PNS	44.9	4.5	45.6	3	48.1	2.1	42	0.0010	0.0112
U1-PP	105.1	9.3	106.4	9.1	109.0	5.4	39	0.0938	0.2750
ANperp	2.7	2.1	0.6	4.8	-3.3	3.1	39	0.0000	0.0011
OLp-A	66.8	5.1	68.6	3.9	79.0	3.7	86	0.0000	0.0000
SNB	63.3	3.7	77.2	4.7	77.5	3.1	39	0.0000	0.7844
ArGoMe	123.8	8.9	129.5	8.4	123.4	5.3	39	0.8431	0.0095
GoMe	63.3	8.0	61.2	7.7	73.0	3.8	42	0.0000	0.0000
ANB	1.8	2.2	2.6	3.2	2.6	2.1	39	0.3357	0.9503
Wits	-2.2	3.9	-1.5	2.7	-1.0	2.1	39	0.1599	0.5513

Table 4-13 Comparisons to Normative Data

[a] *Thilander et al 2005 [35] – sample of 42 Swedish Caucasian children of average age 9.5-11.2 years*

[b] *Obloj et al 2008 [36] – sample of 34 Polish Caucasian children of average age 10.4 years*

[c] *Wu et al 2010 [37] – sample of 86 British Caucasian children of average age 12.4 years*

The two study groups (CPAP and Control) followed a very similar pattern of differences from normative cephalometric values. SN was significantly lower than normal in both groups (p=0.00), as was CoANS (p=0.00). The CPAP group was also significantly different from normal for ANS-PNS, ANperp, OLp-A, SNB, ArGoMe, and GoMe (p=0.00 for all), in a pattern consistent with bimaxillary retrusion and a more vertical growth pattern. A similar of significant differences was observed for the Control group (Table 4-

13), with the exception of SNB which was not significantly different from normal in the Control group. ArGoMe was also significantly different from normal in the CPAP group but not in the Control group.

Another cephalometric measurement proposed by Pancherz [38, 39] measures maxillary projection independently of the cranial base. This measurement, OLp-A, is the linear distance (mm) from A-point to a line perpendicular to the Occlusal plane through Sella. In comparison to means of normative data reported by Wu et al for Caucasian subjects of similar age/gender distributions to the subjects in this study, both groups were significantly lower than normal (p=0.00). This is another indication that, when cranial base variability is removed from consideration, OSA patients demonstrate significant midface retrusion relative to normal counterparts.

Cephalometric measurements that use the anterior cranial base as a reference for A-P projection of the maxilla and mandible (SNA, SNB, and ANB) showed no differences between the study groups and normative data. It was in absolute measurements of jaw size and A-P projection that differences were found. This further supports the notion that the shorter cranial base observed in OSA patients in this study and previously reported in other studies may, in fact, influence its reliability as a reference line for measuring forward projection of the lower face in OSA patients. For example, when investigating the presence of absolute maxillary deficiency in the sagittal plane, a false negative is given when it is related to a shortened anterior cranial base.

An in-depth comparison between OSA patients and normative data was not the focus of this study, but this cursory comparison does provide interesting perspective on the general pattern of differences between OSA patients and normal healthy children with regards to craniofacial morphology.

Several important restrictions of this study limit the strength of conclusions from this study. The small sample size diminishes the power of the conclusions and is associated with an increased chance of Type II error. Future research in this area should address these limitations to the extent possible in order to

gain a fuller understanding of any potential associations between long term PAP use and craniofacial morphology. Several important cephalometric findings were noted among study patients in relation to normative data. These findings were bimaxillary retrognathism and shorter anterior cranial base, and are consistent with previous studies.

4.5 Conclusions

Within this study sample, no significant differences were found in craniofacial morphology between OSA children who are on long term PAP therapy and untreated controls as measured with lateral cephalometry.

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CHAPTER 5 - General Discussion

5.1 Implications for clinical practice

The complex interactions between craniofacial form and upper airway function remain relatively poorly understood. The potential interactions of therapeutic modalities such as PAP therapy with craniofacial growth and development are even less clear. Orthodontists recognize the profound impact long term habits can have in shaping and molding the hard and soft tissues of the lower face. A classic example is the typical pattern of mandibular retrognathism, maxillary prognathism, and anterior open bite observed in prolonged thumb-sucking [1]. This principle of the sustained application of forces above thresholds of bioactivity over a prolonged period of time is a major underpinning of the mechanism of action of functional orthopedic appliances used in orthodontics to promote corrective skeletal and dentoalveolar changes in the treatment of malocclusion[2, 3].

The same principle is theoretically applicable to the use of nasal mask-delivered PAP therapy. The risk of iatrogenic midface hypoplasia as a result of long term nasal mask use is biologically quite plausible, and often anecdotally discussed among practitioners in the area of sleep medicine. A case report by Li et al demonstrated this finding in a patient who had been using PAP therapy for ten years from age 5 to 15 [4], and highlighted the fact that this risk remains markedly underreported in the literature despite suspected widespread clinical observation.

The present study found no significant cephalometric differences between children with OSA who are on long term PAP therapy, and other OSA children not requiring PAP. Several explanations are possible for this finding, including the shorter daily interval of wear of PAP masks compared to orthopedic devices such as orthodontic headgear, the more variable compliance associate with PAP therapy, and the possibility of an inherently different underlying craniofacial growth pattern in children with refractory OSA requiring PAP therapy and their less-severely affected counterparts.

Despite the lack of clear evidence corroborating this potential side effect of long term nasal mask use, it is advisable for clinicians to remain aware of the potential for iatrogenic midface hypoplasia in young patients who rely on PAP therapy for adequate ventilation during sleep, and to monitor their craniofacial growth and development on a regular basis. Consultation with an orthodontic specialist can prove very helpful in this regard. Proper mask fitting and strap adjustment can also help mitigate the potential impact on midface projection [5].

5.2 Strengths and limitations of this study

Based on a systematic review of the literature, only one article – a case report by Li et al[4] – specifically focused on the potential of long term CPAP therapy to lead to midface hypoplasia. To the authors' knowledge, this is the first study to directly compare craniofacial morphology in OSA children on CPAP therapy with untreated controls using lateral cephalometry. All participants in this study had PSG-confirmed obstructive sleep apnea and had undergone tonsillectomy and/or adenoidectomy at least 6 months prior to the study. None had previous orthodontic, orthopedic, or surgical-orthognathic treatment at the time of assessment, and patients with craniofacial developmental syndromes, such as Down syndrome, were excluded from the analysis. These criteria allowed for the elimination of as many confounding variables as possible from the study sample.

Reports on the side effects of CPAP therapy have been largely limited to soft tissue irritation due to pressure on perinasal skin or drying of the nasal or pharyngeal mucosa. Compliance is often limited by these two factors as well as difficulty in initial acceptance and tolerance of the mask during sleep [5]. Proper fitting of the nasal mask, heated humidification, and parental cooperation can help improve compliance [6]. As with any home-administered medical intervention, compliance with CPAP therapy is critical to its clinical effectiveness. However, few studies have objectively assessed overall compliance,

including frequency and duration of use, probably due to technical restrictions, and funding or staffing limitations.

The magnitude of orthopedic change caused by externally-applied forces (such as orthodontic headgear and other orthopedic devices) is entirely dependent on the duration and frequency of use of the device. The limited available data on PAP compliance in the CPAP group restricts the ability to draw conclusions on the potential effect of CPAP therapy on skeletal midface growth and development. Future prospective studies in this area should collect objective compliance data systematically and frequently.

Another limitation is the variability in mask types and sizes, and the inability to measure the level of force exerted by the masks on the midface area to generate an adequate airtight seal. A properly-sized and fitted mask can reduce the amount of pressure needed to generate an airtight seal [7]. The quality of the mask fit and the areas of contact with the face were not assessed in this study.

Finally the limited sample size, variable ages and stages of craniofacial development at which the participants began CPAP therapy, and Inherent variability in craniofacial morphology relative to the severity of OSA, all complicate efforts to discern the effects on craniofacial development, if any, that are primarily attributable to long term CPAP therapy.

5.3 Future research

Objective quantification of the frequency and duration of CPAP use should be enhanced through the use of advanced recording/logging upgrades to PAP devices, as well as specialized training for those involved in home care for PAP patients. Direct measurement of the forces exerted by the CPAP mask on the midface is also possible through the use of spring-loaded gauges and pressure transducers. Future

investigations into the potential side effects of CPAP therapy on craniofacial growth and development can incorporate these objective assessments to quantify exposure to the suspected causative agent.

Longitudinal assessments of patients starting with pre-CPAP baseline lateral cephalometric assessments followed by sequential assessments at regular intervals with superimposition can help locate specific changes in various regions of the facial skeleton over time. Comparisons can then be made to longitudinal normative data or to untreated healthy controls as well as to OSA patients who do not require CPAP therapy. These prospective cephalometric investigations, when combined with accurate quantitative evaluation of CPAP compliance, can yield valuable insight into the true orthopedic effects, if any, of long term CPAP use.

Beyond traditional two-dimensional radiography, Cone Beam Computed Tomography (CBCT) can be used to create 3-dimensional models of regions of interest within the facial skeleton for comparison between CPAP users and non-users [8]. Validated 3-dimensional cephalometric analysis can also be performed to enhance the understanding of craniofacial morphological differences in all three dimensions. CBCT can also be used to perform segmental volumetric assessments of the upper airway, which can be compared between the two groups [9].

Other imaging modalities such as 3-dimensional photogrammetry and laser scanning can also be used to describe surface topographical patterns in children with OSA [10]. These can then be related back to cephalometric patterns to gain an understanding of soft tissue relationships to underlying skeletal structures in these patients. Surface topography “maps” can be compared between CPAP users and untreated controls to investigate potential long term soft tissue changes in three dimensions.

In brief, children with OSA who are on CPAP therapy can be compared to non-CPAP users in much the same ways as OSA children in general have been compared to healthy controls in previous studies. There is now a reasonably large body of scientific literature examining cephalometric patterns and

differences between children with various sleep disordered breathing conditions (primarily OSA) and healthy controls. As CPAP gains broader acceptance as mainstream therapy for pediatric OSA, and as inter-disciplinary collaboration becomes more established between investigators in various areas of expertise, it is anticipated that the potential iatrogenic effects of prolonged CPAP therapy will be much more thoroughly investigated in future studies.

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Appendix A – Electronic Database Search Terms and Strategies

Medline (1950 – Present)

#	Keywords / Search Strategy	Results
1	sleep apnea {Including Related Terms}	1157
2	sleep apnoea {Including Related Terms}	536
3	sleep apnea, obstructive {Including Related Terms}	640
4	sleep apnoea, obstructive {Including Related Terms}	1063
5	obstructive sleep apnea {Including Related Terms}	734
6	obstructive sleep apnoea {Including Related Terms}	1063
7	**1 OR 2 OR 3 OR 4 OR 5 OR 6**	**2108**
8	skeletal* {Including Related Terms}	617
9	dental* {Including Related Terms}	2791
10	craniofacial* {Including Related Terms}	616
11	**8 OR 9 OR 10**	**4011**
12	continuous positive airway pressure {Including Related Terms}	531
13	CPAP {Including Related Terms}	531
14	nasal cpap {Including Related Terms}	553
15	nasal continuous positive airway pressure {Including Related Terms}	342
16	**12 OR 13 OR 14 OR 15**	**982**
17	child* {Including Related Terms}	3633
18	pediatric* {Including Related Terms}	753
19	**17 OR 18**	**4386**
20	**7 AND 11 AND 16 AND 19**	**32**

PubMed (Restricted)		
#	**Keywords / Search Strategy**	**Results**
1	sleep apnea	19223
2	sleep apnoea	19223
3	sleep apnea, obstructive	11276
4	sleep apnoea, obstructive	11187
5	obstructive sleep apnea	11588
6	obstructive sleep apnoea	11588
7	**(((((#1) OR (#2)) OR (#3)) OR (#4)) OR (#5)) OR (#6)**	**19223**
8	skeletal$	163479
9	dental$	346889
10	craniofacial$	17357
11	**((#9) OR (#10)) OR (#11)**	**519333**
12	continuous positive airway pressure	4954
13	CPAP	3380
14	nasal CPAP	1142
15	nasal continuous positive airway pressure	4954
16	**(((#12) OR (#13)) OR (#14)) OR (#15)**	5887
17	child$	1383798
18	pediatric$	166169
19	**(#17) OR (#18)**	**1438487**
20	**(((#7) AND (#11)) AND (#16)) AND (#19)**	**37**

EMBASE – 1980 to 2009 Week 7		
#	**Keywords / Search Strategy**	**Results**
1	sleep apnea {Including Related Terms}	5223
2	sleep apnoea {Including Related Terms}	512
3	sleep apnea, obstructive {Including Related Terms}	2846
4	sleep apnoea, obstructive {Including Related Terms}	510

5	obstructive sleep apnea {Including Related Terms}	2758
6	obstructive sleep apnoea {Including Related Terms}	510
7	**1 OR 2 OR 3 OR 4 OR 5 OR 6**	**5430**
8	skeletal* {Including Related Terms}	752
9	dental* {Including Related Terms}	6220
10	craniofacial* {Including Related Terms}	1798
11	**8 OR 9 OR 10**	**8758**
12	continuous positive airway pressure {Including Related Terms}	1497
13	CPAP {Including Related Terms}	1497
14	nasal cpap {Including Related Terms}	586
15	nasal continuous positive airway pressure {Including Related Terms}	260
16	**12 OR 13 OR 14 OR 15**	**1608**
17	child* {Including Related Terms}	98278
18	pediatric* {Including Related Terms}	20170
19	**17 OR 18**	**118448**
20	**7 AND 11 AND 16 AND 19**	**30**

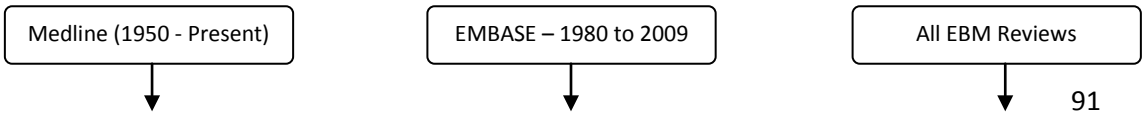
All EBM Reviews - Cochrane DSR, ACP Journal Club, DARE, CCTR, CMR, HTA, and NHSEED		
#	**Keywords / Search Strategy**	**Results**
1	sleep apnea {Including Related Terms}	260
2	sleep apnoea {Including Related Terms}	663
3	sleep apnea, obstructive {Including Related Terms}	716
4	sleep apnoea, obstructive {Including Related Terms}	516
5	obstructive sleep apnea {Including Related Terms}	231
6	obstructive sleep apnoea {Including Related Terms}	518
7	**1 OR 2 OR 3 OR 4 OR 5 OR 6**	**1320**
8	skeletal* {Including Related Terms}	734
9	dental* {Including Related Terms}	592
10	craniofacial* {Including Related Terms}	144
11	**8 OR 9 OR 10**	**1457**
12	continuous positive airway pressure {Including Related Terms}	235
13	CPAP {Including Related Terms}	235
14	nasal cpap {Including Related Terms}	443
15	nasal continuous positive airway pressure {Including Related Terms}	127
16	**12 OR 13 OR 14 OR 15**	**587**
17	child* {Including Related Terms}	11525
18	pediatric* {Including Related Terms}	1927
19	**17 OR 18**	**13443**
20	**7 AND 11 AND 16 AND 19**	**48**

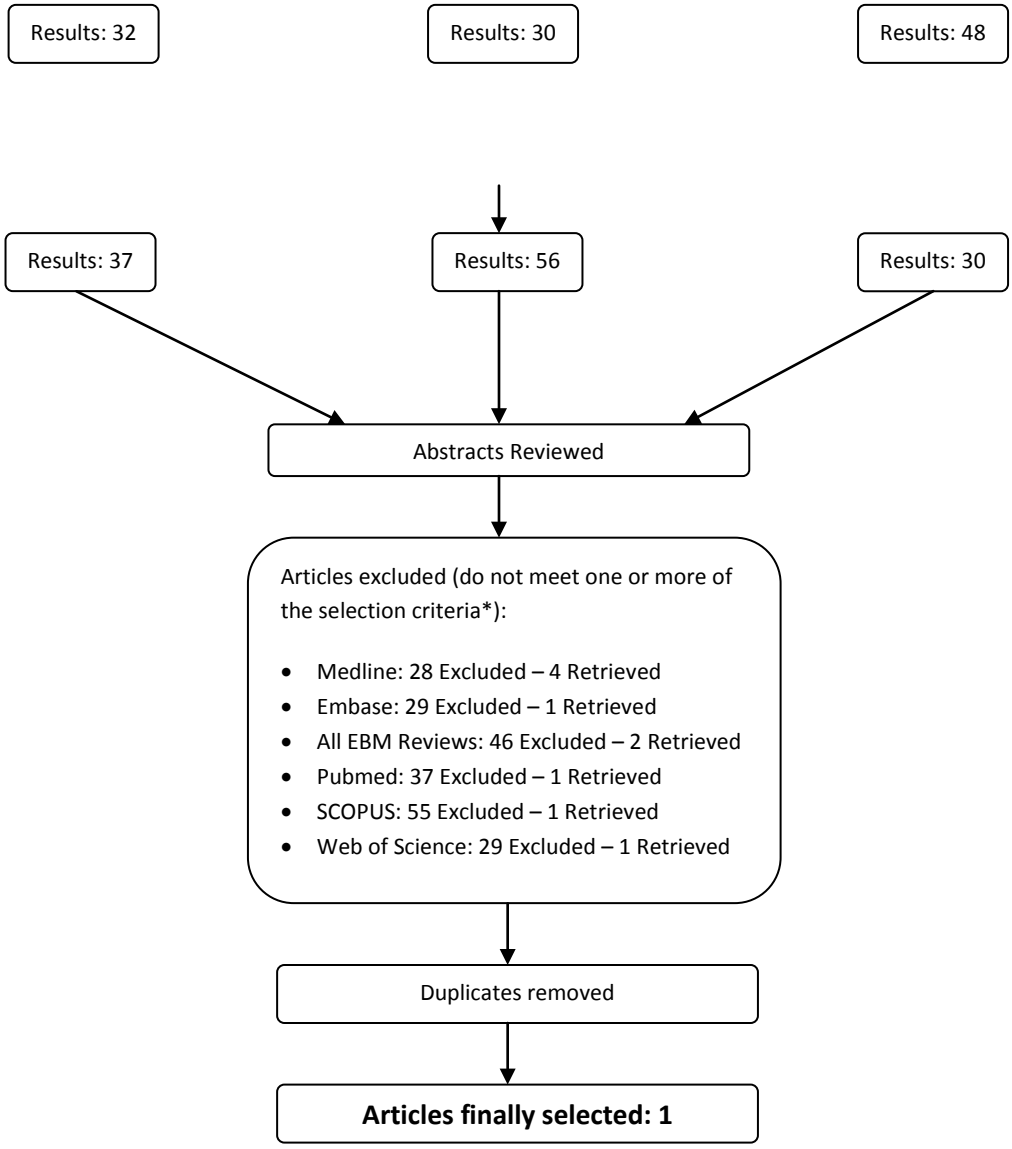
SCOPUS		
#	Keywords / Search Strategy	Results
1	TITLE-ABS-KEY(sleep apnea)	24,041
2	TITLE-ABS-KEY(sleep apnoea)	3,677
3	TITLE-ABS-KEY(sleep apnea,obstructive)	12,774
4	TITLE-ABS-KEY(sleep apnoea,obstructive)	2,456

5	TITLE-ABS-KEY(obstructive sleep apnea)	12,774
6	TITLE-ABS-KEY(obstructive sleep apnoea)	2,456
7	**(TITLE-ABS-KEY(sleep apnea)) OR (TITLE-ABS-KEY(sleep apnoea)) OR (TITLE-ABS-KEY(sleep apnea,obstructive)) OR (TITLE-ABS-KEY(sleep apnoea,obstructive)) OR (TITLE-ABS-KEY(obstructive sleep apnea)) OR (TITLE-ABS-KEY(obstructive sleep apnoea))**	**24,575**
8	TITLE-ABS-KEY(skeletal*)	194,032
9	TITLE-ABS-KEY(dental*)	320,628
10	TITLE-ABS-KEY(craniofacial*)	21,345
11	**(TITLE-ABS-KEY(skeletal*)) OR (TITLE-ABS-KEY(dental*)) OR (TITLE-ABS-KEY(craniofacial*))**	**529,065**
12	TITLE-ABS-KEY(continuous positive airway pressure)	5,733
13	TITLE-ABS-KEY(cpap)	4,174
14	TITLE-ABS-KEY(nasal cpap)	1,385
15	TITLE-ABS-KEY(nasal continuous positive airway pressure)	1,944
16	**(TITLE-ABS-KEY(continuous positive airway pressure)) OR (TITLE-ABS-KEY(cpap)) OR (TITLE-ABS-KEY(nasal cpap)) OR (TITLE-ABS-KEY(nasal continuous positive airway pressure))**	**7,005**
17	TITLE-ABS-KEY(child*)	1,783,244
18	TITLE-ABS-KEY(pediatric*)	197,508
19	**(TITLE-ABS-KEY(child*)) OR (TITLE-ABS-KEY(pediatric*))**	**1,827,562**
20	**((TITLE-ABS-KEY(sleep apnea)) OR (TITLE-ABS-KEY(sleep apnoea)) OR (TITLE-ABS-KEY(sleep apnea,obstructive)) OR (TITLE-ABS-KEY(sleep apnoea,obstructive)) OR (TITLE-ABS-KEY(obstructive sleep apnea)) OR (TITLE-ABS-KEY(obstructive sleep apnoea))) AND ((TITLE-ABS-KEY(skeletal*)) OR (TITLE-ABS-KEY(dental*)) OR (TITLE-ABS-KEY(craniofacial*))) AND ((TITLE-ABS-KEY(continuous positive airway pressure)) OR (TITLE-ABS-KEY(cpap)) OR (TITLE-ABS-KEY(nasal cpap)) OR (TITLE-ABS-KEY(nasal continuous positive airway pressure))) AND ((TITLE-ABS-KEY(child*)) OR (TITLE-ABS-KEY(pediatric*)))**	**56**

Web of Science (ISI Web of Knowledge)		
#	**Keywords / Search Strategy**	**Results**
1	Topic=(sleep apnea) OR Topic=(sleep apnoea) OR Topic=(sleep apnea, obstructive) OR Topic=(sleep apnoea, obstructive) OR Topic=(obstructive sleep apnea) OR Topic=(obstructive sleep apnoea) *Databases=SCI-EXPANDED, SSCI, A&HCI Timespan=All Years*	17256
2	Topic=(skeletal*) OR Topic=(dental*) OR Topic=(craniofacial*) *Databases=SCI-EXPANDED, SSCI, A&HCI Timespan=All Years*	>100,000
3	Topic=(continuous positive airway pressure) OR Topic=(CPAP) OR Topic=(nasal cpap) OR Topic=(nasal continuous positive airway pressure) *Databases=SCI-EXPANDED, SSCI, A&HCI Timespan=All Years*	5274
4	Topic=(child*) OR Topic=(pediatric*) *Databases=SCI-EXPANDED, SSCI, A&HCI Timespan=All Years*	>100,000
5	**#1 AND #2 AND #3 AND #4** *Databases=SCI-EXPANDED, SSCI, A&HCI Timespan=All Years*	**30**

APPENDIX B – Flow Diagram of Literature Search and Selection Criteria





*Selection Criteria:

- Main focus of article is the effect of long term use of n-CPAP on craniofacial growth and development patterns.
- No restrictions on type of study, language, date of publication, or other restrictions.

Study Title	The Association Between Nasal Continuous Positive Airway Pressure and Craniofacial Growth and Development		
Co-Investigator	Dr. Mohammed Korayem	Phone: (780) 492-4469	e-mail: korayem@ualberta.ca
Principal Investigator	Dr. Carlos Flores-Mir	Phone: (780) 492-4469	e-mail: cf1@ualberta.ca
Research Committee Members	Dr. Paul Major Dr. Manisha Witmans Dr. Giseon Heo		

Study Information

You are invited to participate in a research study currently being conducted by the Department of Dentistry Graduate Orthodontic Program at the University of Alberta Faculty of Medicine and Dentistry. The main goal of this study is to find the associations (relationships) between long-term use of Continuous Positive Airway Pressure (CPAP) devices and the growth and development of facial structures.

1. STUDY METHODS

Should you chose to participate in this study, you will be asked to present to the Graduate Orthodontic Clinic at the Department of Dentistry for the following assessments:

a. Orthodontic Clinical Exam: An assessment of dental and facial structures conducted by a licensed dentist.
b. 3-Dimensional Surface Photography: A set of digital cameras will be used to take a series of photographs to create a 3-dimensional digital image of the face and surrounding structures through computer software.
c. 3-Dimensional Volumetric Radiographic Imaging: A special type of x-ray machine, specifically developed for facial imaging, will be used. The radiation exposure from this technique is comparable to the standard set of x-ray images taken for an orthodontic treatment (braces).

All significant findings noted from the examinations above will be reported to you and your parent (guardian). The information gathered from these examinations will then be analyzed to obtain the potential associations between long-term CPAP use and craniofacial growth and development.

Personal information collected will include age, gender, ethnic background, duration of CPAP use to date, frequency of CPAP use, and number of hours per night. In addition, relevant medical history information from your health records at Capital Health facilities may be collected. All data collected and analyzed may be used for presentation at scientific conferences or publication in scientific literature but no personal information or personal identifiers will be used in those cases.

2. RISKS AND BENEFITS

Apart from the minimal risk associated with 3-dimensional radiographic imaging, there are no other known risks associated with any procedures associated with this study. Benefits to the participant include the ability to obtain a full orthodontic and radiographic examination and report of findings at no cost to the participant. Potential benefits to the scientific community and broader society also exist from the knowledge generated by this study. These benefits will not be applicable to you but to future children with a similar condition as yours.

3. CONFIDENTIALITY

All personal and clinical data collected in this study will remain confidential and secure at all times. Only authorized personnel associated with this study will be allowed access to information on a need-to-know basis.

4. RIGHTS AND RESPONSIBILITIES

All potential participants in this study maintain the following rights at all times:

- To decline to participate for any reason(s). The reason(s) do not have to be disclosed.
- To withdraw from the study at any time for any reason(s), and to be provided with treatment thereafter.
- To have any data collected withdrawn from the study and not included in the analysis.
- To the maintenance of privacy, anonymity, autonomy, and confidentiality of information.
- To disclosure of any actual or apparent conflict of interest on the part of any of the researchers.
- To receive a report of any significant clinical and/or radiographic findings observed during the assessments conducted as part of this study.

All participants in this study agree to accept the following responsibilities:

- To present promptly for appointment(s) at the Pediatric Sleep Medicine Program, Home Ventilation Clinic, Graduate Orthodontic Clinic, and other appointments as prescribed by the research team.
- To provide adequate notice (minimum of 48 hours) for the cancellation or re-scheduling of appointments.
- To fully reveal to the best of their ability any pertinent information sought by the researchers.
- To accurately and completely fill out all required paperwork associated with the study.
- To comply with instructions provided by the researchers to assist in the conduct of the study.
- To ensure that they understand the nature of the study, their involvement within, and to ask any questions or request any clarification or information they may need.

5. CONTACT NAMES AND TELEPHONE NUMBERS

If you have any concerns regarding your rights as a study participant, you may contact the Chairperson of the Department of Dentistry of the University of Alberta, at (780) 492-3312 or the Human Research Ethics Board, at (780) 492-0724.

Please contact any of the individuals identified below if you have any questions or concerns about the study at any time:

Principal Investigator(s): Dr. Carlos Flores-Mir (780) 492-7409

Study Title	The Association Between Nasal Continuous Positive Airway Pressure and Craniofacial Growth and Development		
Co-Investigator	Dr. Mohammed Korayem	Phone: (780) 492-4469	e-mail: korayem@ualberta.ca
Principal Investigator	Dr. Carlos Flores-Mir	Phone: (780) 492-4469	e-mail: cf1@ualberta.ca
Research Committee Members	Dr. Paul Major Dr. Manisha Witmans Dr. Giseon Heo	Dr. Cheryl Cable Dr. Carina Majaesic	

Informed Consent

	Yes	**No**
Have you read and understood the information provided in this form?	☐	☐
Do you understand that your child has been asked to participate in a research study?	☐	☐
Do you understand the benefits and risks involved in taking part in this research study?	☐	☐
Do you understand that you are free to withdraw your child from the stud at any time, without having to give a reason, and without affecting your child's future medical care?	☐	☐
Do you understand who will have access to your child's records including personally identifiable health information	☐	☐
Have you had an opportunity to ask questions and discuss this study to your satisfaction?	☐	☐

Participant's Name (Child's name) _____

I agree for my child to take part in this study: YES ☐ NO ☐

Signature of Parent or Guardian _____ Date _____

(Printed Name) _____

Signature of Witness _____ Date _____

Signature of Investigator or Designee _____ Date _____

University of Alberta
Faculty of Medicine and Dentistry
Department of Dentistry
Graduate Orthodontics Program

Information Sheet

Study Title	The Association Between Nasal Continuous Positive Airway Pressure and Craniofacial Growth and Development		
Co-Investigator	Dr. Mohammed Korayem	Phone: (780) 492-4469	e-mail: korayem@ualberta.ca
Principal Investigator	Dr. Carlos Flores-Mir	Phone: (780) 492-4469	e-mail: cf1@ualberta.ca
Research Committee Members	Dr. Paul Major Dr. Manisha Witmans Dr. Giseon Heo		

Study Information

You are invited to participate in a research study currently being conducted by the Department of Dentistry Graduate Orthodontic Program at the University of Alberta Faculty of Medicine and Dentistry. The main goal of this study is to find the associations (relationships) between long-term use of Continuous Positive Airway Pressure (CPAP) devices and the growth and development of facial structures.

6. STUDY METHODS

Should you chose to participate in this study, you will be asked to present to the Graduate Orthodontic Clinic at the Department of Dentistry for the following assessments:

d. Orthodontic Clinical Exam: An assessment of dental and facial structures conducted by a licensed dentist.
e. 3-Dimensional Surface Photography: A set of digital cameras will be used to take a series of photographs to create a 3-dimensional digital image of the face and surrounding structures through computer software.
f. 3-Dimensional Volumetric Radiographic Imaging: A special type of x-ray machine, specifically developed for facial imaging, will be used. The radiation exposure from this technique is comparable to the standard set of x-ray images taken for an orthodontic treatment (braces).

All significant findings noted from the examinations above will be reported to you and your parent (guardian). The information gathered from these examinations will then be analyzed to obtain the potential associations between long-term CPAP use and craniofacial growth and development.

Personal information collected will include age, gender, ethnic background, duration of CPAP use to date, frequency of CPAP use, and number of hours per night. In addition, relevant medical history information from your health records at Capital Health facilities may be collected. All data collected and analyzed may be used for presentation at scientific conferences or publication in scientific literature but no personal information or personal identifiers will be used in those cases.

7. RISKS AND BENEFITS

Apart from the minimal risk associated with 3-dimensional radiographic imaging, there are no other known risks associated with any procedures associated with this study. Benefits to the participant include the ability to obtain a full orthodontic and radiographic examination and report of findings at no cost to the participant. Potential benefits to the scientific community and broader society also exist from the knowledge generated by this study. These benefits will not be applicable to you but to future children with a similar condition as yours.

8. CONFIDENTIALITY

All personal and clinical data collected in this study will remain confidential and secure at all times. Only authorized personnel associated with this study will be allowed access to information on a need-to-know basis.

9. RIGHTS AND RESPONSIBILITIES

All potential participants in this study maintain the following rights at all times:

- To decline to participate for any reason(s). The reason(s) do not have to be disclosed.
- To withdraw from the study at any time for any reason(s), and to be provided with treatment thereafter.
- To have any data collected withdrawn from the study and not included in the analysis.
- To the maintenance of privacy, anonymity, autonomy, and confidentiality of information.
- To disclosure of any actual or apparent conflict of interest on the part of any of the researchers.
- To receive a report of any significant clinical and/or radiographic findings observed during the assessments conducted as part of this study.

All participants in this study agree to accept the following responsibilities:

- To present promptly for appointment(s) at the Pediatric Sleep Medicine Program, Home Ventilation Clinic, Graduate Orthodontic Clinic, and other appointments as prescribed by the research team.
- To provide adequate notice (minimum of 48 hours) for the cancellation or re-scheduling of appointments.
- To fully reveal to the best of their ability any pertinent information sought by the researchers.
- To accurately and completely fill out all required paperwork associated with the study.
- To comply with instructions provided by the researchers to assist in the conduct of the study.
- To ensure that they understand the nature of the study, their involvement within, and to ask any questions or request any clarification or information they may need.

10. CONTACT NAMES AND TELEPHONE NUMBERS

If you have any concerns regarding your rights as a study participant, you may contact the Chairperson of the Department of Dentistry of the University of Alberta, at (780) 492-3312 or the Human Research Ethics Board, at (780) 492-0724.

Please contact any of the individuals identified below if you have any questions or concerns about the study at any time:

Principal Investigator(s): Dr. Carlos Flores-Mir (780) 492-7409

Study Title	The Association Between Nasal Continuous Positive Airway Pressure and Craniofacial Growth and Development		
Co-Investigator	Dr. Mohammed Korayem	Phone: (780) 492-4469	e-mail: korayem@ualberta.ca
Principal Investigator	Dr. Carlos Flores-Mir	Phone: (780) 492-4469	e-mail: cf1@ualberta.ca
Research Committee Members	Dr. Paul Major Dr. Manisha Witmans Dr. Giseon Heo	Dr. Cheryl Cable Dr. Carina Majaesic	

Informed Consent

	Yes	**No**
Have you read and understood the information provided in this form?	☐	☐
Do you understand that your child has been asked to participate in a research study?	☐	☐
Do you understand the benefits and risks involved in taking part in this research study?	☐	☐
Do you understand that you are free to withdraw your child from the stud at any time, without having to give a reason, and without affecting your child's future medical care?	☐	☐
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Participant's Name (Child's name) _____

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Signature of Parent or Guardian _____ Date _____

(Printed Name) _____

Signature of Witness _____ Date _____

Signature of Investigator or Designee _____ Date _____

University of Alberta
Faculty of Medicine and Dentistry
Department of Dentistry
Graduate Orthodontics Program

Information Sheet

Study Title	The Association Between Nasal Continuous Positive Airway Pressure and Craniofacial Growth and Development		
Co-Investigator	Dr. Mohammed Korayem	Phone: (780) 492-4469	e-mail: korayem@ualberta.ca
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- To have any data collected withdrawn from the study and not included in the analysis.
- To the maintenance of privacy, anonymity, autonomy, and confidentiality of information.
- To disclosure of any actual or apparent conflict of interest on the part of any of the researchers.
- To receive a report of any significant clinical and/or radiographic findings observed during the assessments conducted as part of this study.

All participants in this study agree to accept the following responsibilities:

- To present promptly for appointment(s) at the Pediatric Sleep Medicine Program, Home Ventilation Clinic, Graduate Orthodontic Clinic, and other appointments as prescribed by the research team.
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- To fully reveal to the best of their ability any pertinent information sought by the researchers.
- To accurately and completely fill out all required paperwork associated with the study.
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Principal Investigator(s): Dr. Carlos Flores-Mir (780) 492-7409

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Principal Investigator	Dr. Carlos Flores-Mir	Phone: (780) 492-4469	e-mail: cf1@ualberta.ca
Research Committee Members	Dr. Paul Major Dr. Manisha Witmans Dr. Giseon Heo	Dr. Cheryl Cable Dr. Carina Majaesic	

Informed Consent

	Yes	**No**
Have you read and understood the information provided in this form?	☐	☐
Do you understand that your child has been asked to participate in a research study?	☐	☐
Do you understand the benefits and risks involved in taking part in this research study?	☐	☐
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Participant's Name (Child's name) _____

I agree for my child to take part in this study: YES ☐ NO ☐

Signature of Parent or Guardian _____ Date _____

(Printed Name) _____

Signature of Witness _____ Date _____

Signature of Investigator or Designee _____ Date _____

	S-N					BaSN					SNA					PP-SN				
	M1	*M2*	*M3*	**SD**	**MEAN**	*M1*	*M2*	*M3*	**SD**	**MEAN**	*M1*	*M2*	*M3*	**SD**	**MEAN**	*M1*	*M2*	*M3*	**SD**	**MEAN**
CPAP	60.0	59.0	60.0	0.6	59.7	122.3	120.3	120.3	1.2	121.0	83.1	83.1	82.1	0.6	82.8	-0.7	-1.7	-1.7	0.6	-1.4
CPAP	67.3	67.3	67.3	0.0	67.3	124.0	121.0	125.0	2.1	123.3	82.1	82.1	81.1	0.6	81.8	12.0	12.0	13.0	0.6	12.3
CPAP	58.4	58.4	59.4	0.6	58.7	121.7	121.7	119.7	1.2	121.0	83.6	84.6	83.6	0.6	83.9	0.3	1.3	2.3	1.0	1.3
CPAP	64.8	63.8	63.8	0.6	64.1	138.2	137.2	137.2	0.6	137.5	78.0	79.0	77.0	1.0	78.0	8.5	10.5	8.5	1.2	9.2
CPAP	55.1	56.1	54.1	1.0	55.1	134.0	132.0	133.0	1.0	133.0	79.9	78.9	78.9	0.6	79.2	13.3	11.3	11.3	1.2	12.0
CPAP	58.8	57.8	57.8	0.6	58.1	141.1	144.1	140.1	2.1	141.8	78.9	79.9	78.9	0.6	79.2	10.6	8.6	10.6	1.2	9.9
CPAP	60.6	61.6	60.6	0.6	60.9	141.8	139.8	142.8	1.5	141.5	82.3	83.3	81.3	1.0	82.3	10.0	11.0	10.0	0.6	10.3
CPAP	66.0	65.0	65.0	0.6	65.3	129.0	128.0	131.0	1.5	129.3	85.2	86.2	87.2	1.0	86.2	7.6	9.6	7.6	1.2	8.3
CPAP	62.2	62.2	63.2	0.6	62.5	123.9	122.9	122.9	0.6	123.2	82.2	81.2	81.2	0.6	81.5	5.5	5.5	6.5	0.6	5.8
CPAP	60.0	61.0	60.0	0.6	60.3	125.9	126.9	126.9	0.6	126.6	84.2	85.2	83.2	1.0	84.2	6.7	4.7	6.7	1.2	6.0
CPAP	62.0	61.0	63.0	1.0	62.0	131.6	131.6	130.6	0.6	131.3	83.6	84.6	82.6	1.0	83.6	5.3	7.3	3.3	2.0	5.3
CPAP	63.6	63.6	64.6	0.6	63.9	144.1	141.1	145.1	2.1	143.4	75.7	74.7	76.7	1.0	75.7	7.1	7.1	6.1	0.6	6.8
Mean	**61.6**	**61.4**	**61.6**	**0.6**	**61.5**	**131.5**	**130.6**	**131.2**	**1.2**	**131.1**	**81.6**	**81.9**	**81.2**	**0.8**	**81.5**	**7.2**	**7.3**	**7.0**	**1.0**	**7.2**
StDev	**3.5**	**3.2**	**3.6**		**3.4**	**8.2**	**8.4**	**8.7**		**8.4**	**2.8**	**3.3**	**3.0**		**3.0**	**4.2**	**4.2**	**4.2**		**4.1**
CTRL	66.4	67.4	65.4	1.0	66.4	137.5	140.5	139.5	1.5	139.2	78.8	78.8	77.8	0.6	78.5	8.8	7.8	9.8	1.0	8.8
CTRL	58.4	57.4	58.4	0.6	58.1	134.2	137.2	133.2	2.1	134.9	77.3	78.3	78.3	0.6	78.0	12.6	13.6	13.6	0.6	13.3
CTRL	65.9	65.9	66.9	0.6	66.2	134.6	131.6	135.6	2.1	133.9	75.1	76.1	74.1	1.0	75.1	7.8	8.8	8.8	0.6	8.5
CTRL	61.4	62.4	62.4	0.6	62.1	130.7	128.7	128.7	1.2	129.4	81.8	82.8	82.8	0.6	82.5	3.5	4.5	2.5	1.0	3.5
CTRL	63.6	64.6	64.6	0.6	64.3	130.7	129.7	132.7	1.5	131.0	80.4	81.4	81.4	0.6	81.1	8.9	7.9	7.9	0.6	8.2
CTRL	60.9	60.9	60.9	0.0	60.9	127.4	127.4	125.4	1.2	126.7	83.4	83.4	85.4	1.2	84.1	4.6	2.6	5.6	1.5	4.3
CTRL	60.7	61.7	59.7	1.0	60.7	127.3	126.3	128.3	1.0	127.3	79.1	78.1	81.1	1.5	79.4	2.2	3.2	3.2	0.6	2.9
CTRL	68.5	69.5	68.5	0.6	68.8	126.8	124.8	125.8	1.0	125.8	75.5	75.5	75.5	0.0	75.5	5.7	7.7	4.7	1.5	6.0
CTRL	70.1	71.1	70.1	0.6	70.4	133.2	133.2	132.2	0.6	132.9	85.7	86.7	84.7	1.0	85.7	0.6	0.6	-1.4	1.2	-0.1
CTRL	63.3	62.3	64.3	1.0	63.3	130.1	127.1	132.1	2.5	129.8	86.3	86.3	85.3	0.6	86.0	4.9	4.9	3.9	0.6	4.6
CTRL	63.3	62.3	62.3	0.6	62.6	132.6	132.6	135.6	1.7	133.6	79.6	78.6	79.6	0.6	79.3	8.9	7.9	8.9	0.6	8.6
Mean	**63.9**	**64.1**	**64.0**	**0.6**	**64.0**	**131.4**	**130.8**	**131.7**	**1.5**	**131.3**	**80.3**	**80.5**	**80.5**	**0.7**	**80.5**	**6.2**	**6.3**	**6.1**	**0.9**	**6.2**

StDev	**3.6**	**4.0**	**3.6**		**3.7**	**3.4**	**4.8**	**4.4**		**4.0**	**3.7**	**3.8**	**3.9**		**3.8**	**3.5**	**3.6**	**4.2**		**3.7**

APPENDIX F - Cephalometric variables (raw data)

	Co-ANS					**ANS-PNS**					**U1-PP**				
	M1	*M2*	*M3*	**SD**	**MEAN**	*M1*	*M2*	*M3*	**SD**	**MEAN**	*M1*	*M2*	*M3*	**SD**	**MEAN**
CPAP	76.7	81.7	75.7	3.2	78.0	46.5	47.5	52.5	3.2	48.8	87.5	89.5	84.5	2.5	87.2
CPAP	76.7	73.7	73.7	1.7	74.7	48.4	52.4	51.4	2.1	50.7	100.2	105.2	102.2	2.5	102.5
CPAP	74.9	73.9	77.9	2.1	75.6	42.5	38.5	41.5	2.1	40.8	108.5	114.5	109.5	3.2	110.8
CPAP	82.7	86.7	83.7	2.1	84.4	44.8	41.8	45.8	2.1	44.1	104.4	102.4	99.4	2.5	102.1
CPAP	73.9	76.9	74.9	1.5	75.2	37.9	40.9	34.9	3.0	37.9	102.4	106.4	106.4	2.3	105.1
CPAP	78.1	80.1	79.1	1.0	79.1	40.8	40.8	43.8	1.7	41.8	114.2	114.2	112.2	1.2	113.5
CPAP	80.1	84.1	82.1	2.0	82.1	43.7	38.7	44.7	3.2	42.4	110.5	115.5	112.5	2.5	112.8
CPAP	89.0	93.0	93.0	2.3	91.7	50.0	53.0	52.0	1.5	51.7	118.7	120.7	123.7	2.5	121.0
CPAP	72.6	72.6	68.6	2.3	71.3	38.6	39.6	41.6	1.5	39.9	94.4	94.4	88.4	3.5	92.4
CPAP	73.4	69.4	70.4	2.1	71.1	45.7	42.7	48.7	3.0	45.7	104.3	103.3	110.3	3.8	106.0
CPAP	78.2	76.2	78.2	1.2	77.5	48.4	52.4	46.4	3.1	49.1	106.7	109.7	104.7	2.5	107.0
CPAP	81.4	78.4	81.4	1.7	80.4	45.7	44.7	47.7	1.5	46.0	101.7	96.7	102.7	3.2	100.4
Mean	**78.1**	**78.9**	**78.2**	**1.9**	**78.4**	**44.4**	**44.4**	**45.9**	**2.3**	**44.9**	**104.5**	**106.0**	**104.7**	**2.7**	**105.1**
StDev	**4.7**	**6.7**	**6.5**		**5.8**	**3.9**	**5.5**	**5.1**		**4.5**	**8.4**	**9.4**	**10.6**		**9.3**
CTRL	83.9	88.9	86.9	2.5	86.6	47.8	47.8	46.8	0.6	47.5	113.9	113.9	113.9	0.0	113.9
CTRL	74.3	79.3	78.3	2.6	77.3	46.2	47.2	46.2	0.6	46.5	103.4	101.4	97.4	3.1	100.7
CTRL	81.2	77.2	80.2	2.1	79.5	47.5	42.5	44.5	2.5	44.8	99.5	94.5	95.5	2.6	96.5
CTRL	77.7	77.7	77.7	0.0	77.7	42.9	40.9	40.9	1.2	41.6	114.2	111.2	119.2	4.0	114.9
CTRL	81.0	77.0	83.0	3.1	80.3	46.3	48.3	44.3	2.0	46.3	115.8	119.8	113.8	3.1	116.5
CTRL	77.2	80.2	80.2	1.7	79.2	45.3	48.3	46.3	1.5	46.6	107.8	108.8	110.8	1.5	109.1
CTRL	71.3	76.3	69.3	3.6	72.3	42.4	37.4	42.4	2.9	40.7	90.3	89.3	84.3	3.2	88.0
CTRL	80.9	78.9	77.9	1.5	79.2	47.8	51.8	45.8	3.1	48.5	110.0	113.0	109.0	2.1	110.7
CTRL	89.8	88.8	90.8	1.0	89.8	48.8	51.8	49.8	1.5	50.1	105.1	99.1	109.1	5.0	104.4
CTRL	83.2	80.2	80.2	1.7	81.2	46.1	51.1	44.1	3.6	47.1	101.4	99.4	101.4	1.2	100.7
CTRL	74.7	75.7	70.7	2.6	73.7	42.2	40.2	43.2	1.5	41.9	111.8	116.8	115.8	2.6	114.8

Mean	**79.6**	**80.0**	**79.6**	**2.0**	**79.7**	**45.8**	**46.1**	**44.9**	**1.9**	**45.6**	**106.7**	**106.1**	**106.4**	**2.6**	**106.4**
StDev	**5.2**	**4.6**	**6.2**		**5.0**	**2.3**	**5.0**	**2.4**		**3.0**	**7.7**	**9.9**	**10.5**		**9.1**

	ANperp					**SNB**					**ArGoMe**				
	M1	*M2*	*M3*	**SD**	**MEAN**	*M1*	*M2*	*M3*	**SD**	**MEAN**	*M1*	*M2*	*M3*	**SD**	**MEAN**
CPAP	2.8	2.8	1.8	0.6	2.5	80.1	82.1	78.1	2.0	80.1	130.0	139.0	133.0	4.6	134.0
CPAP	3.8	2.8	2.8	0.6	3.1	76.8	76.8	76.8	0.0	76.8	125.6	134.6	130.6	4.5	130.3
CPAP	3.0	4.0	4.0	0.6	3.7	82.7	80.7	83.7	1.5	82.4	131.2	122.2	141.2	9.5	131.5
CPAP	4.2	5.2	3.2	1.0	4.2	75.1	77.1	73.1	2.0	75.1	120.4	127.4	111.4	8.0	119.7
CPAP	-0.4	-1.4	-1.4	0.6	-1.1	74.7	76.7	73.7	1.5	75.0	126.3	125.3	124.3	1.0	125.3
CPAP	1.8	2.8	0.8	1.0	1.8	76.2	78.2	78.2	1.2	77.5	104.6	98.6	103.6	3.2	102.3
CPAP	6.0	7.0	7.0	0.6	6.7	82.4	81.4	81.4	0.6	81.7	128.6	124.6	120.6	4.0	124.6
CPAP	0.6	0.6	0.6	0.0	0.6	83.4	81.4	84.4	1.5	83.1	120.5	112.5	114.5	4.2	115.8
CPAP	0.3	1.3	1.3	0.6	1.0	83.4	81.4	82.4	1.0	82.4	136.0	133.0	129.0	3.5	132.7
CPAP	5.8	5.8	4.8	0.6	5.5	81.4	79.4	81.4	1.2	80.7	129.2	120.2	134.2	7.1	127.9
CPAP	2.9	2.9	3.9	0.6	3.2	84.7	82.7	83.7	1.0	83.7	122.0	116.0	123.0	3.8	120.3
CPAP	1.3	1.3	2.3	0.6	1.6	73.4	73.4	71.4	1.2	72.7	116.8	126.8	120.8	5.0	121.5
Mean	**2.7**	**2.9**	**2.6**	**0.6**	**2.7**	**79.5**	**79.3**	**79.0**	**1.2**	**79.3**	**124.3**	**123.4**	**123.9**	**4.9**	**123.8**
StDev	**2.1**	**2.3**	**2.2**		**2.1**	**4.0**	**2.8**	**4.5**		**3.7**	**8.2**	**10.8**	**10.6**		**8.9**
CTRL	-0.8	-0.8	0.2	0.6	-0.5	79.2	78.2	80.2	1.0	79.2	132.6	143.6	127.6	8.2	134.6
CTRL	6.2	5.2	6.2	0.6	5.9	72.5	72.5	72.5	0.0	72.5	128.2	133.2	132.2	2.6	131.2
CTRL	-3.5	-4.5	-4.5	0.6	-4.2	69.7	67.7	68.7	1.0	68.7	150.8	148.8	141.8	4.7	147.1
CTRL	0.0	1.0	1.0	0.6	0.7	81.3	83.3	79.3	2.0	81.3	125.8	130.8	123.8	3.6	126.8
CTRL	1.3	1.3	2.3	0.6	1.6	74.0	73.0	74.0	0.6	73.7	128.9	136.9	131.9	4.0	132.6
CTRL	3.0	4.0	2.0	1.0	3.0	79.5	78.5	77.5	1.0	78.5	122.1	118.1	117.1	2.6	119.1
CTRL	-1.3	-1.3	-2.3	0.6	-1.6	82.2	83.2	80.2	1.5	81.9	125.2	122.2	119.2	3.0	122.2
CTRL	-9.0	-10.0	-10.0	0.6	-9.7	75.7	73.7	73.7	1.2	74.4	115.3	124.3	118.3	4.6	119.3
CTRL	3.8	2.8	2.8	0.6	3.1	83.5	81.5	84.5	1.5	83.2	130.6	128.6	123.6	3.6	127.6
CTRL	8.2	9.2	7.2	1.0	8.2	81.2	80.2	83.2	1.5	81.5	122.9	123.9	131.9	4.9	126.2
CTRL	0.2	0.2	1.2	0.6	0.5	74.1	73.1	76.1	1.5	74.4	140.2	130.2	143.2	6.8	137.9
Mean	**0.7**	**0.6**	**0.6**	**0.7**	**0.6**	**77.5**	**76.8**	**77.3**	**1.2**	**77.2**	**129.3**	**131.0**	**128.2**	**4.4**	**129.5**

StDev	**4.7**	**5.1**	**4.8**		**4.8**	**4.5**	**5.1**	**4.8**		**4.7**	**9.6**	**9.3**	**8.9**		**8.4**

	GoMe					ANB					Wits				
	M1	*M2*	*M3*	**SD**	**MEAN**	*M1*	*M2*	*M3*	**SD**	**MEAN**	*M1*	*M2*	*M3*	**SD**	**MEAN**
CPAP	62.3	61.3	63.3	1.0	62.3	2.9	2.9	2.9	0.0	2.9	-5.1	-5.1	-6.1	0.6	-5.4
CPAP	52.0	54.0	53.0	1.0	53.0	5.3	5.3	5.3	0.0	5.3	2.4	1.4	1.4	0.6	1.7
CPAP	63.6	61.6	61.6	1.2	62.3	0.9	-0.1	-0.1	0.6	0.2	-5.4	-3.4	-4.4	1.0	-4.4
CPAP	72.0	77.0	69.0	4.0	72.7	2.0	2.0	2.0	0.0	2.0	-0.8	-0.8	-1.8	0.6	-1.1
CPAP	57.8	58.8	59.8	1.0	58.8	5.2	5.2	4.2	0.6	4.9	2.3	4.3	1.3	1.5	2.6
CPAP	72.2	71.2	72.2	0.6	71.9	2.7	3.7	2.7	0.6	3.0	1.3	3.3	2.3	1.0	2.3
CPAP	63.1	64.1	62.1	1.0	63.1	-0.1	0.9	-0.1	0.6	0.2	-3.9	-1.9	-4.9	1.5	-3.6
CPAP	75.0	78.0	79.0	2.1	77.3	1.8	0.8	1.8	0.6	1.5	-0.5	0.5	-0.5	0.6	-0.2
CPAP	60.6	60.6	63.6	1.7	61.6	-1.2	-1.2	-2.2	0.6	-1.5	-6.7	-5.7	-6.7	0.6	-6.4
CPAP	49.2	51.2	46.2	2.5	48.9	2.7	1.7	2.7	0.6	2.4	-5.1	-5.1	-5.1	0.0	-5.1
CPAP	66.8	64.8	67.8	1.5	66.5	-1.1	-1.1	-2.1	0.6	-1.4	-8.1	-8.1	-9.1	0.6	-8.4
CPAP	61.0	62.0	62.0	0.6	61.7	2.3	3.3	1.3	1.0	2.3	1.8	2.8	1.8	0.6	2.1
Mean	**63.0**	**63.7**	**63.3**	**1.5**	**63.3**	**2.0**	**2.0**	**1.5**	**0.5**	**1.8**	**-2.3**	**-1.5**	**-2.7**	**0.8**	**-2.2**
StDev	**7.8**	**8.2**	**8.5**		**8.0**	**2.1**	**2.2**	**2.3**		**2.2**	**3.8**	**4.0**	**3.9**		**3.9**
CTRL	64.8	69.8	60.8	4.5	65.1	-0.4	-1.4	-1.4	0.6	-1.1	-3.0	-1.0	-4.0	1.5	-2.7
CTRL	55.8	51.8	51.8	2.3	53.1	4.8	3.8	3.8	0.6	4.1	-1.9	-0.9	-1.9	0.6	-1.6
CTRL	51.6	54.6	53.6	1.5	53.3	5.4	4.4	4.4	0.6	4.7	1.6	2.6	2.6	0.6	2.3
CTRL	64.2	61.2	66.2	2.5	63.9	0.5	1.5	0.5	0.6	0.8	-4.0	-2.0	-3.0	1.0	-3.0
CTRL	64.0	64.0	62.0	1.2	63.3	6.4	6.4	6.4	0.0	6.4	2.6	1.6	1.6	0.6	1.9
CTRL	62.7	61.7	66.7	2.6	63.7	3.9	4.9	3.9	0.6	4.2	-0.5	1.5	0.5	1.0	0.5
CTRL	57.1	55.1	53.1	2.0	55.1	-3.1	-3.1	-4.1	0.6	-3.4	-6.8	-5.8	-6.8	0.6	-6.5
CTRL	67.9	62.9	70.9	4.0	67.2	-0.2	-0.2	-1.2	0.6	-0.5	-3.4	-4.4	-3.4	0.6	-3.7
CTRL	74.2	80.2	72.2	4.2	75.5	2.2	2.2	2.2	0.0	2.2	-2.9	-3.9	-2.9	0.6	-3.2
CTRL	64.7	61.7	65.7	2.1	64.0	5.1	6.1	5.1	0.6	5.4	-0.7	1.3	0.3	1.0	0.3
CTRL	49.4	52.4	45.4	3.5	49.1	5.5	6.5	4.5	1.0	5.5	-0.7	0.3	-0.7	0.6	-0.4
Mean	**61.5**	**61.4**	**60.8**	**2.8**	**61.2**	**2.7**	**2.8**	**2.2**	**0.5**	**2.6**	**-1.8**	**-1.0**	**-1.6**	**0.8**	**-1.5**
StDev	**7.3**	**8.3**	**8.7**		**7.7**	**3.1**	**3.3**	**3.3**		**3.2**	**2.6**	**2.8**	**2.8**		**2.7**

APPENDIX G - Intra-Operator Reliability Analysis

S-N

Intraclass Correlation Coefficient

	Intraclass Correlation[a]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.968[b]	.937	.985	87.214	22	44	.000
Average Measures	.989[c]	.978	.995	87.214	22	44	.000

Two-way mixed effects model where people effects are random and measures effects are fixed.

a. Type A intraclass correlation coefficients using an absolute agreement definition.

b. The estimator is the same, whether the interaction effect is present or not.

c. This estimate is computed assuming the interaction effect is absent, because it is not estimable otherwise.

BaSN

Intraclass Correlation Coefficient

	Intraclass Correlation[a]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.950[b]	.903	.977	60.880	22	44	.000
Average Measures	.983[c]	.966	.992	60.880	22	44	.000

Two-way mixed effects model where people effects are random and measures effects are fixed.

a. Type A intraclass correlation coefficients using an absolute agreement definition.

b. The estimator is the same, whether the interaction effect is present or not.

c. This estimate is computed assuming the interaction effect is absent, because it is not estimable otherwise.

SNA

Intraclass Correlation Coefficient

	Intraclass Correlation[a]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.942[b]	.888	.973	50.241	22	44	.000
Average Measures	.980[c]	.960	.991	50.241	22	44	.000

Two-way mixed effects model where people effects are random and measures effects are fixed.

a. Type A intraclass correlation coefficients using an absolute agreement definition.

Intraclass Correlation Coefficient

	Intraclass Correlation[a]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.942[b]	.888	.973	50.241	22	44	.000
Average Measures	.980[c]	.960	.991	50.241	22	44	.000

Two-way mixed effects model where people effects are random and measures effects are fixed.

a. Type A intraclass correlation coefficients using an absolute agreement definition.

b. The estimator is the same, whether the interaction effect is present or not.

c. This estimate is computed assuming the interaction effect is absent, because it is not estimable otherwise

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PP-SN

Intraclass Correlation Coefficient

	Intraclass Correlation[a]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.935[b]	.875	.969	42.569	22	44	.000
Average Measures	.977[c]	.955	.990	42.569	22	44	.000

Two-way mixed effects model where people effects are random and measures effects are fixed.

a. Type A intraclass correlation coefficients using an absolute agreement definition.

b. The estimator is the same, whether the interaction effect is present or not.

c. This estimate is computed assuming the interaction effect is absent, because it is not estimable otherwise.

CoANS

Intraclass Correlation Coefficient

	Intraclass Correlation[a]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.856[b]	.738	.930	18.453	22	44	.000
Average Measures	.947[c]	.894	.976	18.453	22	44	.000

Two-way mixed effects model where people effects are random and measures effects are fixed.

a. Type A intraclass correlation coefficients using an absolute agreement definition.

b. The estimator is the same, whether the interaction effect is present or not.

Intraclass Correlation Coefficient

	Intraclass Correlation[a]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.856[b]	.738	.930	18.453	22	44	.000
Average Measures	.947[c]	.894	.976	18.453	22	44	.000

Two-way mixed effects model where people effects are random and measures effects are fixed.

a. Type A intraclass correlation coefficients using an absolute agreement definition.

c. This estimate is computed assuming the interaction effect is absent, because it is not estimable otherwise.

ANS-PNS

Intraclass Correlation Coefficient

	Intraclass Correlation[a]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.704[b]	.505	.849	7.880	22	44	.000
Average Measures	.877[c]	.754	.944	7.880	22	44	.000

Two-way mixed effects model where people effects are random and measures effects are fixed.

a. Type A intraclass correlation coefficients using an absolute agreement definition.

b. The estimator is the same, whether the interaction effect is present or not.

c. This estimate is computed assuming the interaction effect is absent, because it is not estimable otherwise.

U1-PP

Intraclass Correlation Coefficient

	Intraclass Correlation[a]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.907[b]	.826	.956	29.434	22	44	.000
Average Measures	.967[c]	.934	.985	29.434	22	44	.000

Two-way mixed effects model where people effects are random and measures effects are fixed.

a. Type A intraclass correlation coefficients using an absolute agreement definition.

b. The estimator is the same, whether the interaction effect is present or not.

Intraclass Correlation Coefficient

	Intraclass Correlation[a]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.907[b]	.826	.956	29.434	22	44	.000
Average Measures	.967[c]	.934	.985	29.434	22	44	.000

Two-way mixed effects model where people effects are random and measures effects are fixed.

a. Type A intraclass correlation coefficients using an absolute agreement definition.

c. This estimate is computed assuming the interaction effect is absent, because it is not estimable otherwise.

ANperp

Intraclass Correlation Coefficient

	Intraclass Correlation[a]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.970[b]	.941	.986	95.193	22	44	.000
Average Measures	.990[c]	.979	.995	95.193	22	44	.000

Two-way mixed effects model where people effects are random and measures effects are fixed.

a. Type A intraclass correlation coefficients using an absolute agreement definition.

b. The estimator is the same, whether the interaction effect is present or not.

c. This estimate is computed assuming the interaction effect is absent, because it is not estimable otherwise.

SNB

Intraclass Correlation Coefficient

	Intraclass Correlation[a]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.910[b]	.832	.958	31.340	22	44	.000
Average Measures	.968[c]	.937	.985	31.340	22	44	.000

Two-way mixed effects model where people effects are random and measures effects are fixed.

a. Type A intraclass correlation coefficients using an absolute agreement definition.

b. The estimator is the same, whether the interaction effect is present or not.

c. This estimate is computed assuming the interaction effect is absent, because it is not estimable otherwise.

ArGoMe

Intraclass Correlation Coefficient

	Intraclass Correlation[a]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.735[b]	.549	.866	9.044	22	44	.000
Average Measures	.893[c]	.785	.951	9.044	22	44	.000

Two-way mixed effects model where people effects are random and measures effects are fixed.

a. Type A intraclass correlation coefficients using an absolute agreement definition.

b. The estimator is the same, whether the interaction effect is present or not.

c. This estimate is computed assuming the interaction effect is absent, because it is not estimable otherwise.

GoMe

Intraclass Correlation Coefficient

	Intraclass Correlation[a]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.909[b]	.828	.957	29.877	22	44	.000
Average Measures	.968[c]	.935	.985	29.877	22	44	.000

Two-way mixed effects model where people effects are random and measures effects are fixed.

a. Type A intraclass correlation coefficients using an absolute agreement definition.

b. The estimator is the same, whether the interaction effect is present or not.

c. This estimate is computed assuming the interaction effect is absent, because it is not estimable otherwise.

ANB

Intraclass Correlation Coefficient

	Intraclass Correlation[a]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.957[b]	.903	.982	87.909	22	44	.000
Average Measures	.985[c]	.965	.994	87.909	22	44	.000

Two-way mixed effects model where people effects are random and measures effects are fixed.

a. Type A intraclass correlation coefficients using an absolute agreement definition.

b. The estimator is the same, whether the interaction effect is present or not.

c. This estimate is computed assuming the interaction effect is absent, because it is not estimable otherwise.

Wits

Intraclass Correlation Coefficient

	Intraclass Correlation[a]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.936[b]	.838	.974	66.062	22	44	.000
Average Measures	.978[c]	.939	.991	66.062	22	44	.000

Two-way mixed effects model where people effects are random and measures effects are fixed.

a. Type A intraclass correlation coefficients using an absolute agreement definition.

b. The estimator is the same, whether the interaction effect is present or not.

c. This estimate is computed assuming the interaction effect is absent, because it is not estimable otherwise.

APPENDIX H – Descriptive Statistics

Tests of Normality

		Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Group	Statistic	df	Sig.	Statistic	df	Sig.
SN	0	.094	12	.200*	.993	12	1.000
	1	.119	11	.200*	.976	11	.939

BaSN	0	.157	12	.200*	.905	12	.182
	1	.113	11	.200*	.962	11	.791
SNA	0	.162	12	.200*	.965	12	.854
	1	.158	11	.200*	.944	11	.566
PP_SN	0	.160	12	.200*	.935	12	.433
	1	.157	11	.200*	.965	11	.828
CoANS	0	.120	12	.200*	.935	12	.433
	1	.202	11	.200*	.930	11	.416
ANS_PNS	0	.140	12	.200*	.959	12	.768
	1	.228	11	.115	.922	11	.335
U1_PP	0	.140	12	.200*	.975	12	.953
	1	.163	11	.200*	.914	11	.269
ANperp	0	.084	12	.200*	.992	12	1.000
	1	.140	11	.200*	.963	11	.809
SNB	0	.172	12	.200*	.913	12	.233
	1	.179	11	.200*	.927	11	.379
ArGoMe	0	.154	12	.200*	.903	12	.171
	1	.135	11	.200*	.948	11	.619
GoMe	0	.179	12	.200*	.958	12	.759
	1	.243	11	.068	.927	11	.377
ANB	0	.126	12	.200*	.950	12	.642
	1	.229	11	.112	.919	11	.307

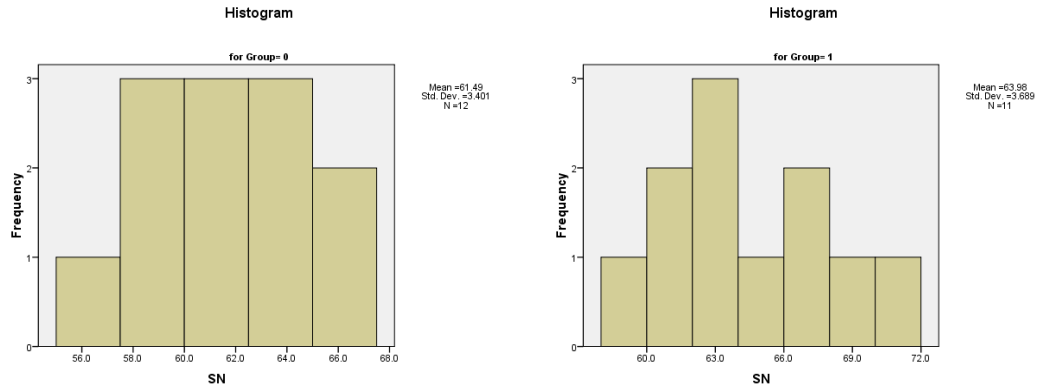
Wits	0	.175	12	.200*	.912	12	.226
	1	.133	11	.200*	.961	11	.789

a. Lilliefors Significance Correction

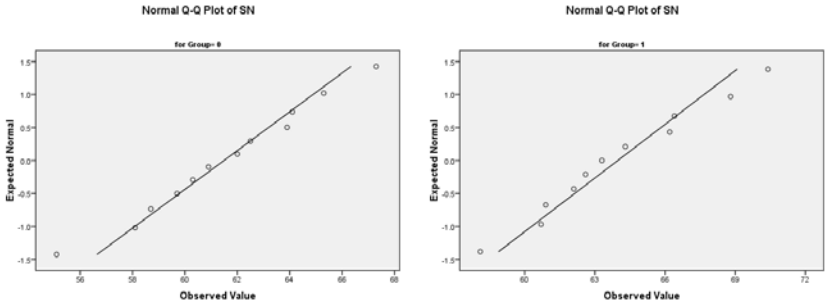
*. This is a lower bound of the true significance.

SN

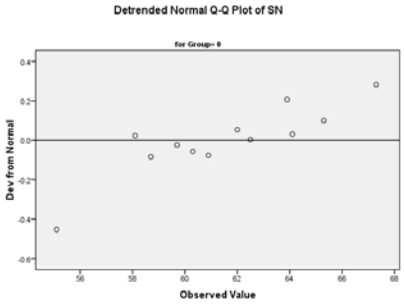
Histograms

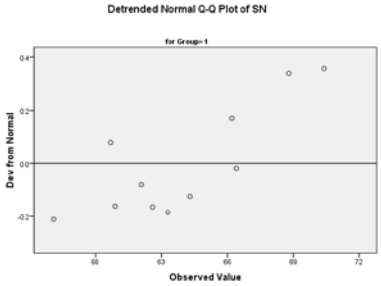


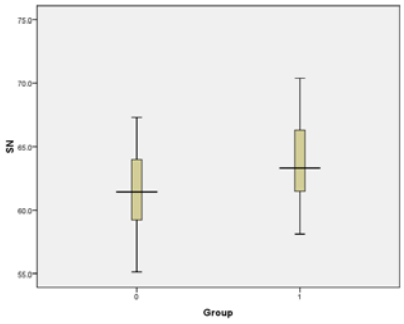
Normal Q-Q Plots



Detrended Normal Q-Q Plots

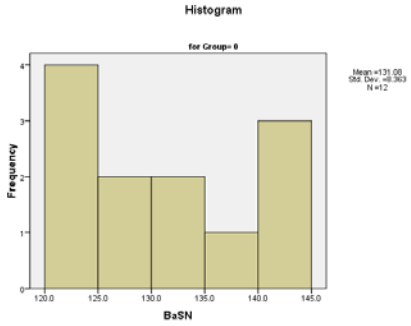


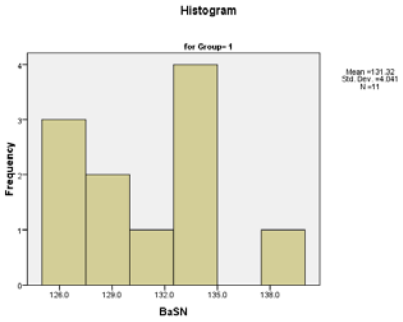




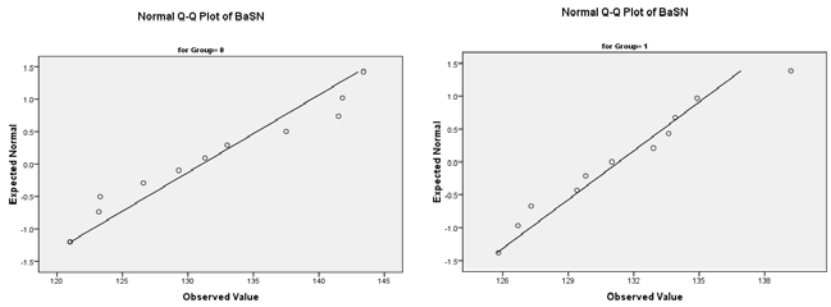
BaSN

Histograms





Normal Q-Q Plots



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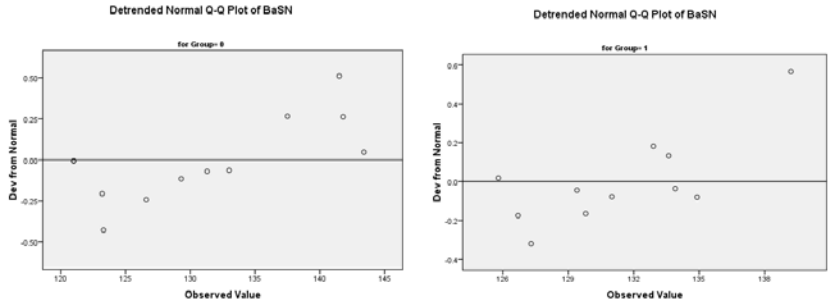

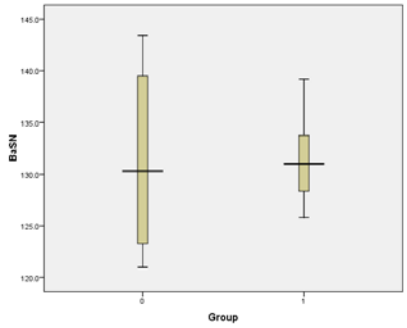

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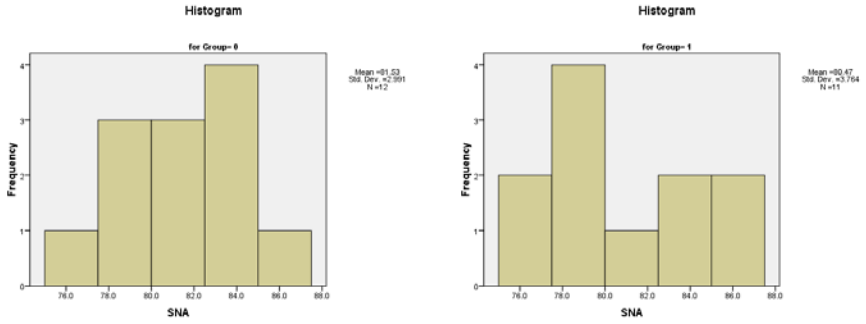
Histograms



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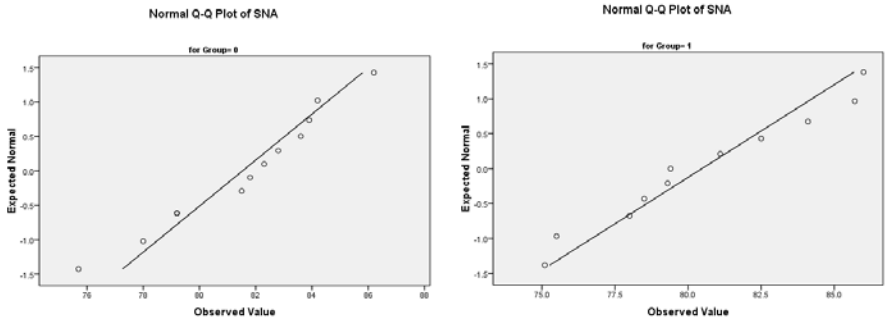

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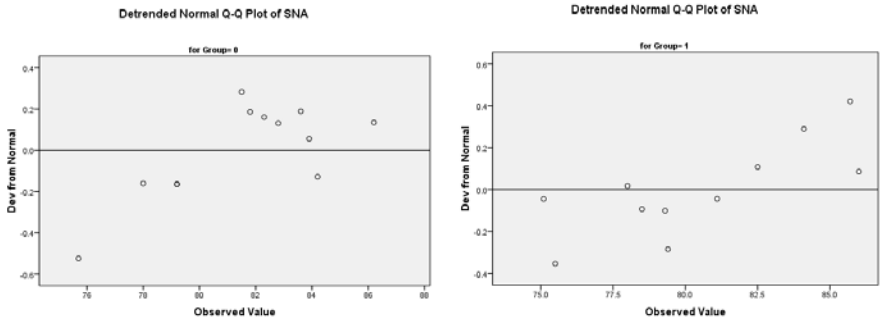
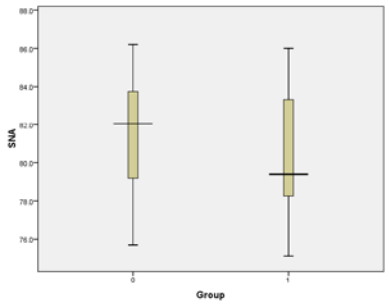
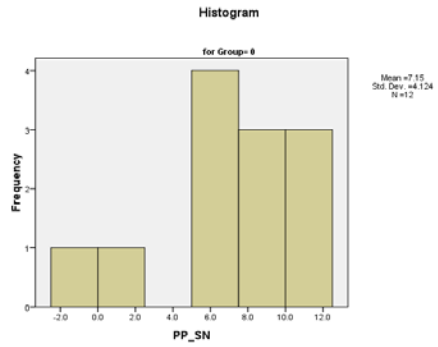
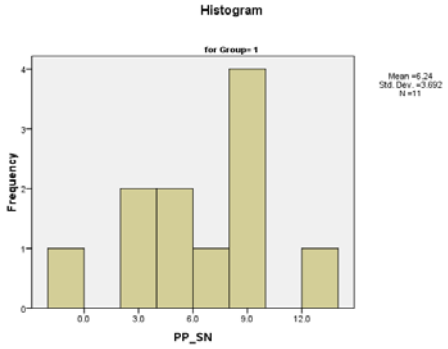




PP_SN

Histograms





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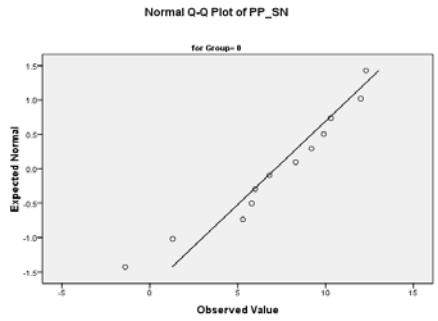

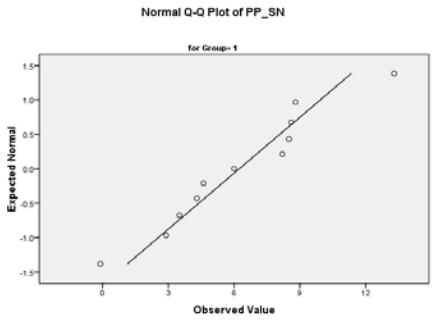

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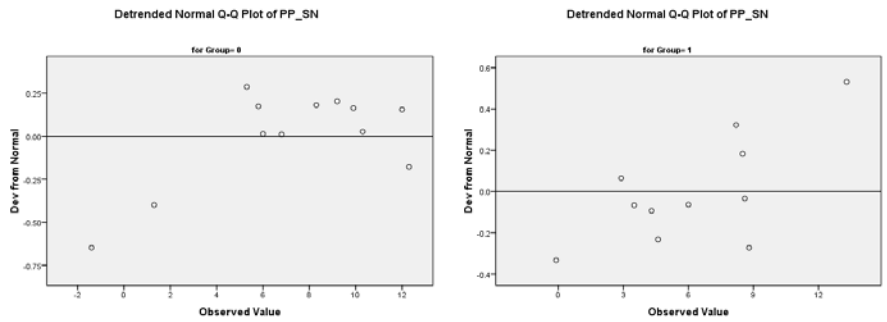
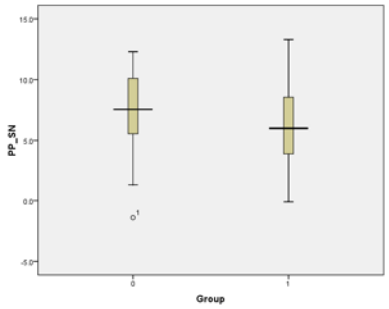
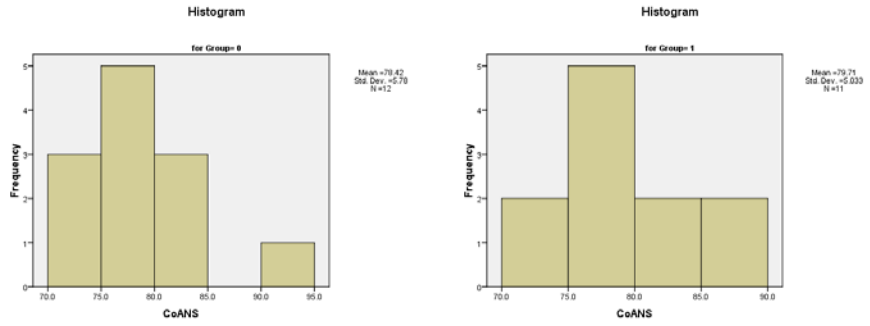




CoANS

Histograms



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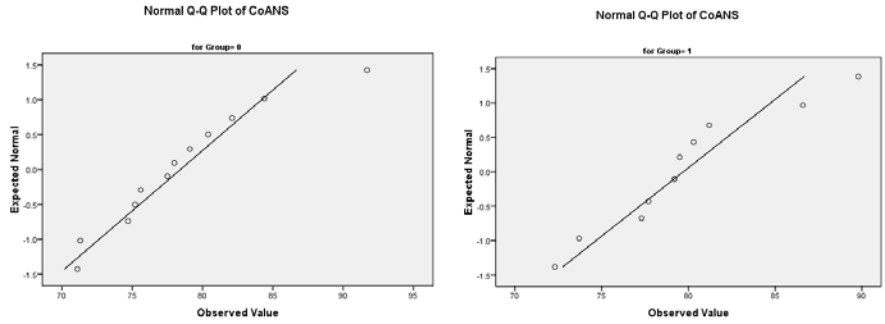

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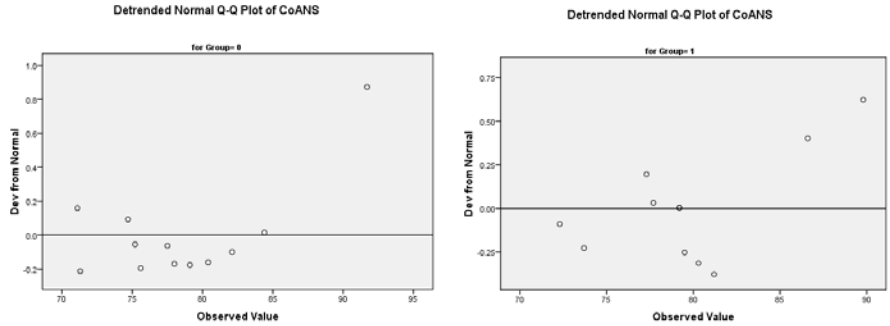
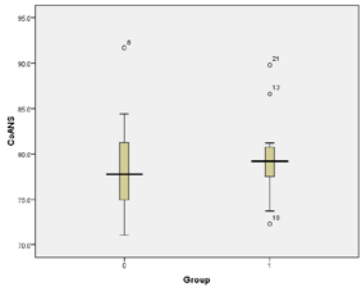
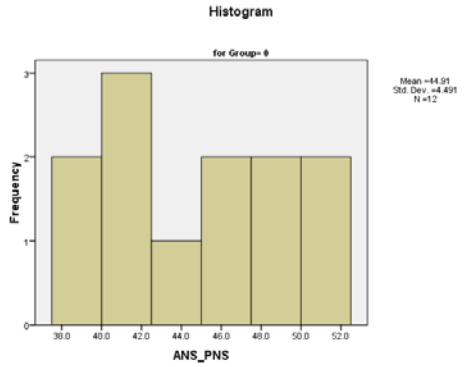
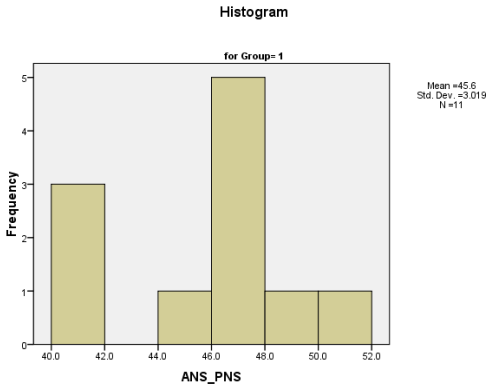




ANS_PNS

Histograms





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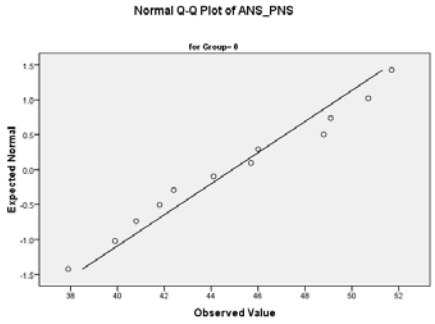

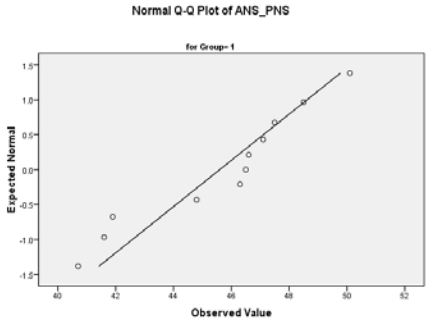

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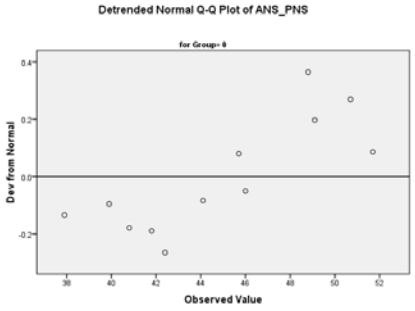
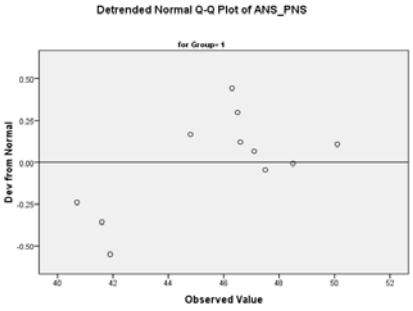
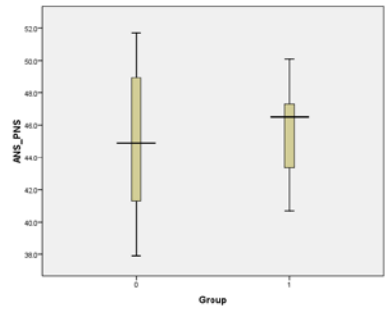
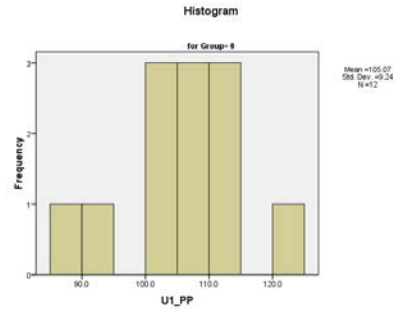


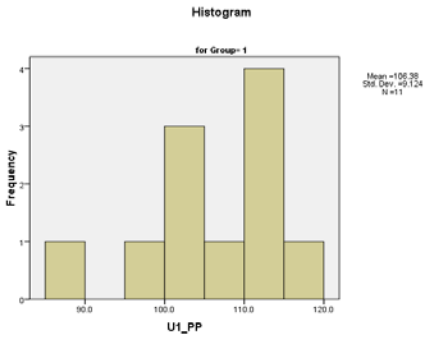




U1_PP

Histograms





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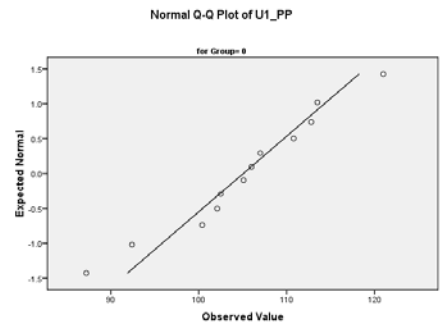

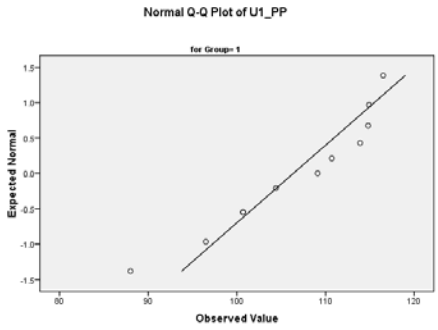

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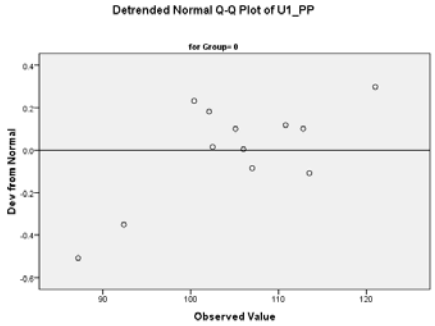
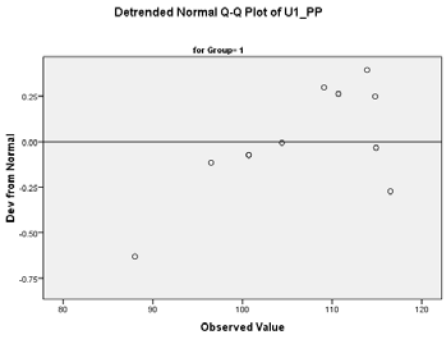
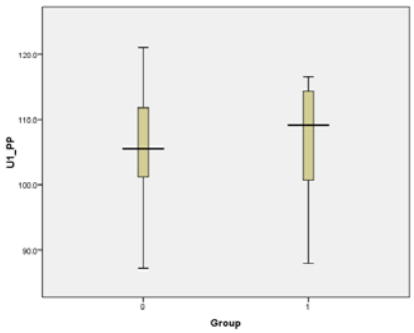
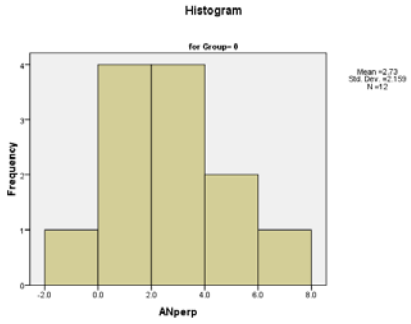


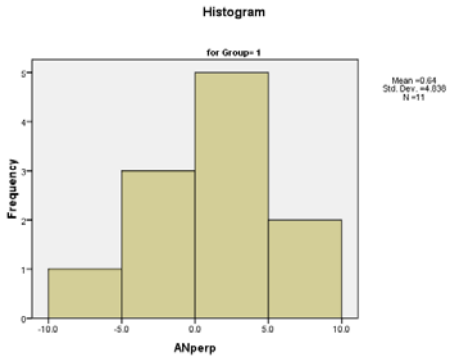




ANperp

Histograms





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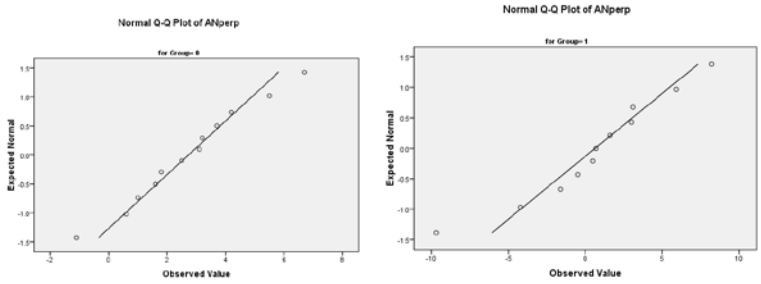

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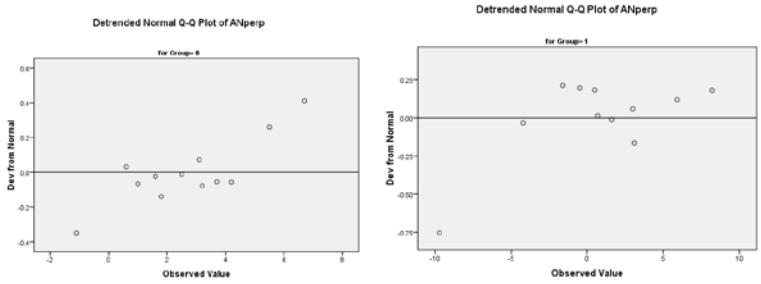
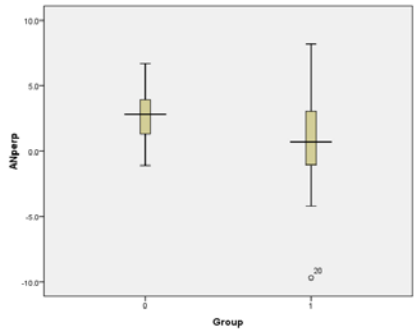
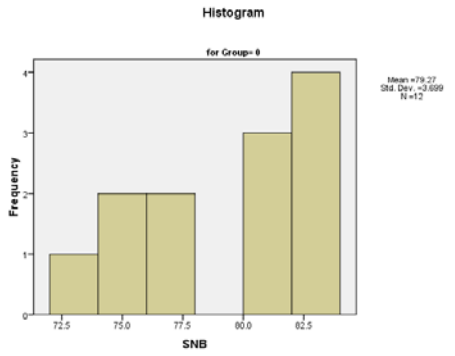
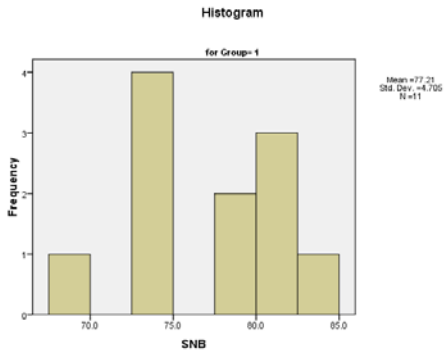




SNB

Histograms





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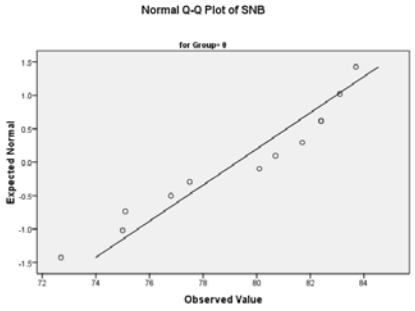

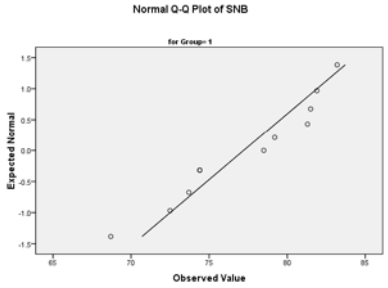

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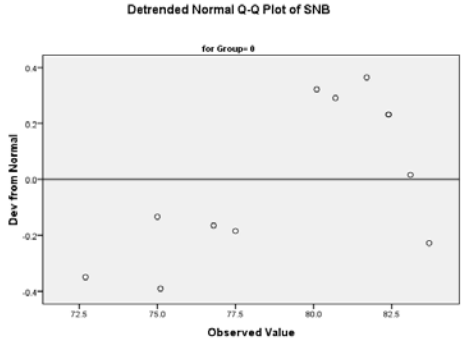
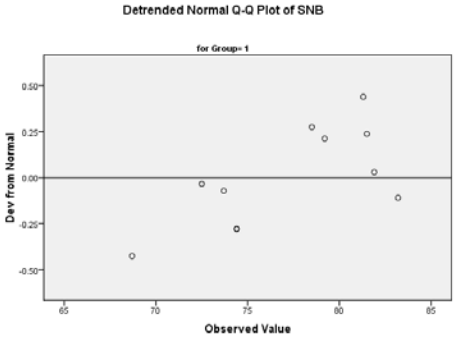
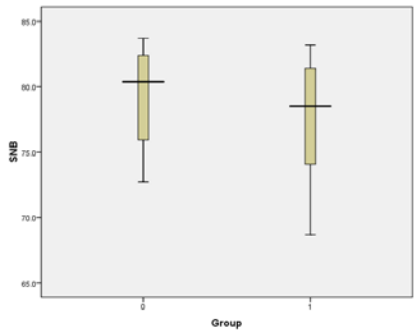
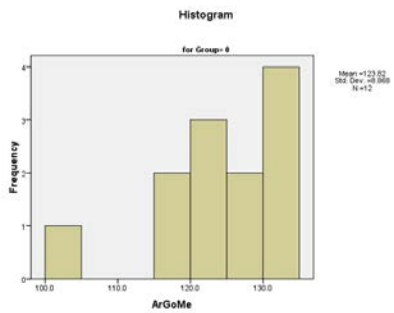


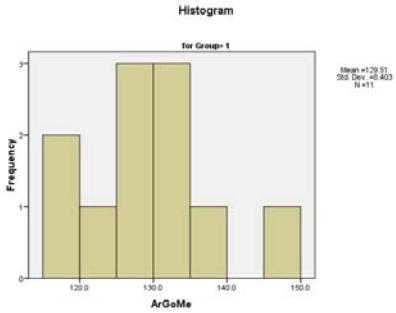




ArGoMe

Histograms





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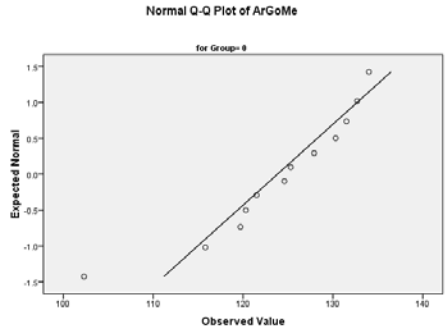

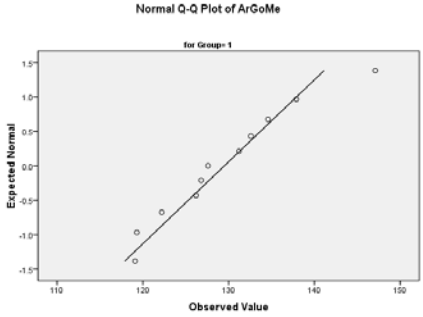

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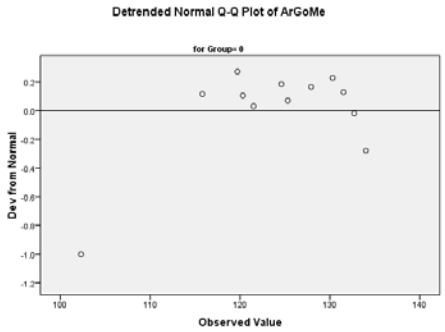
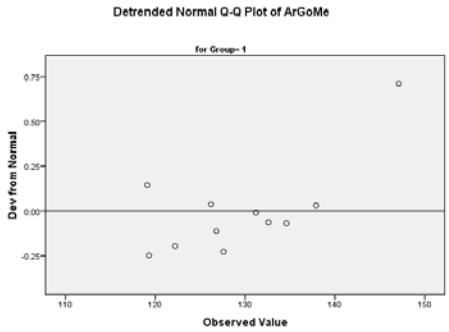
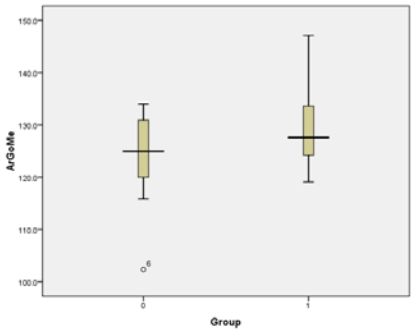
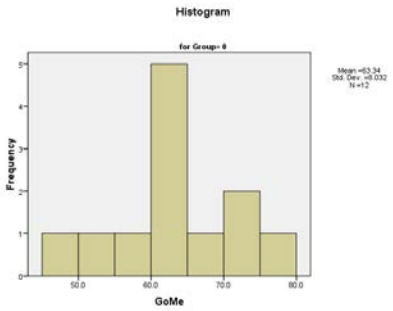


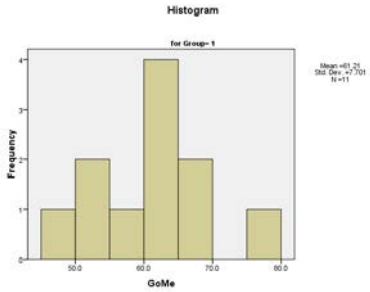




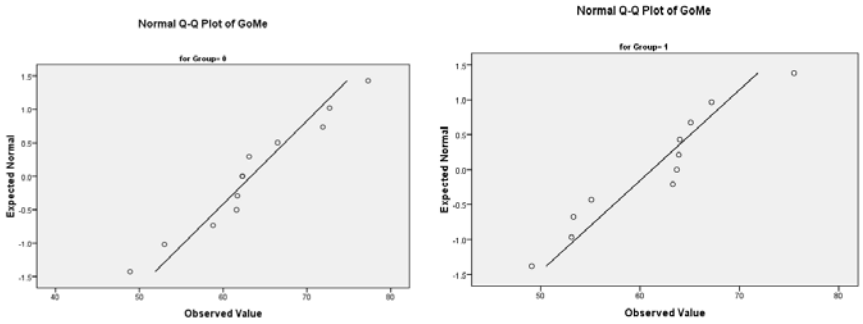
GoMe

Histograms





Normal Q-Q Plots



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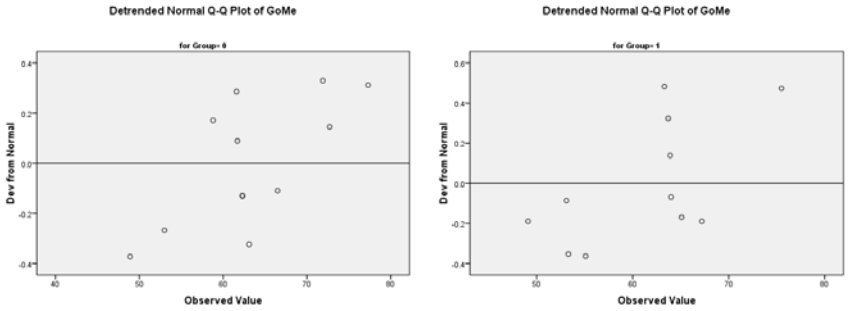
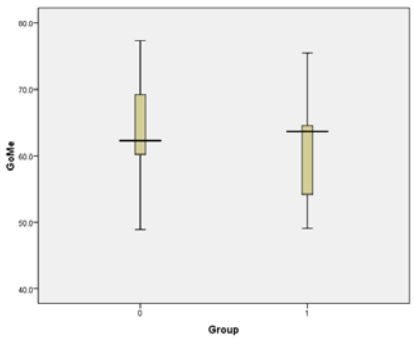
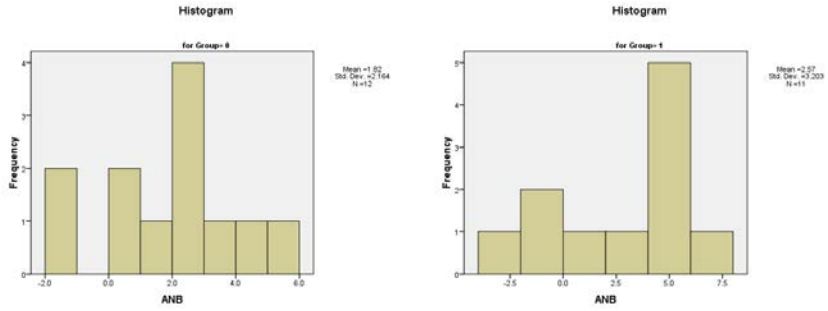


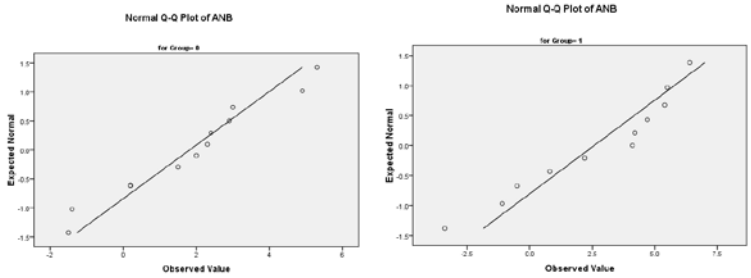


ANB

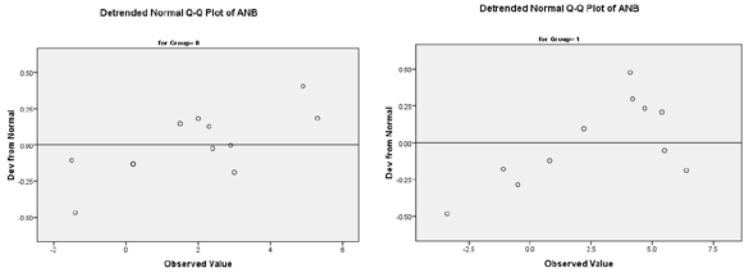
Histograms

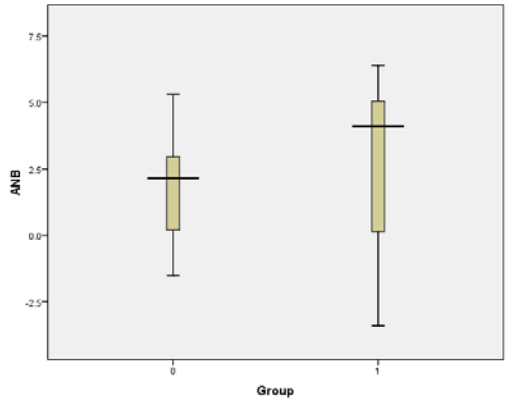


Normal Q-Q Plots



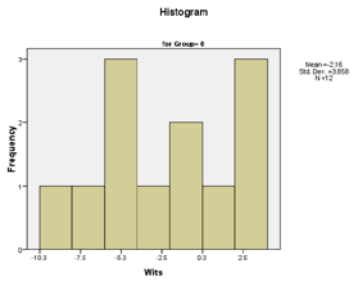
Detrended Normal Q-Q Plots

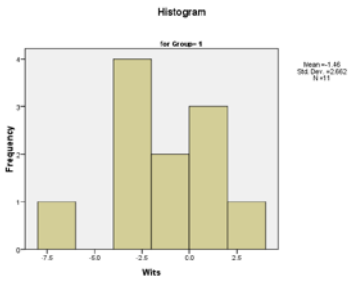




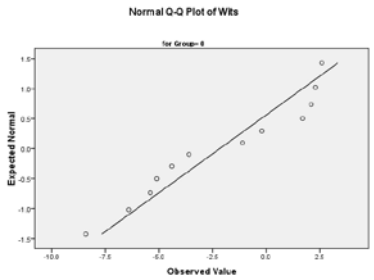
Wits

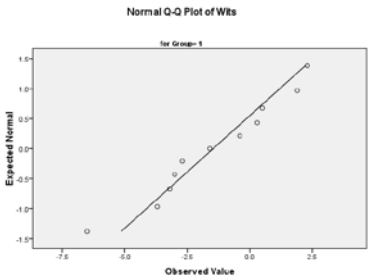
Histograms



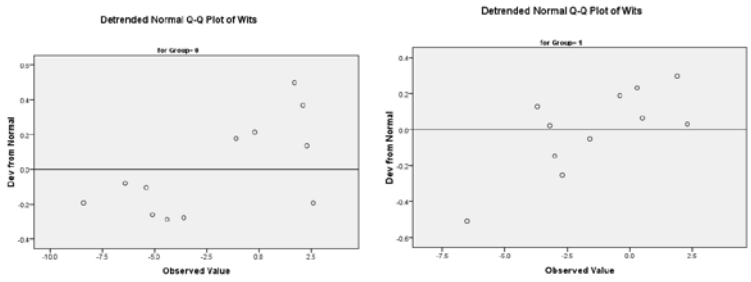


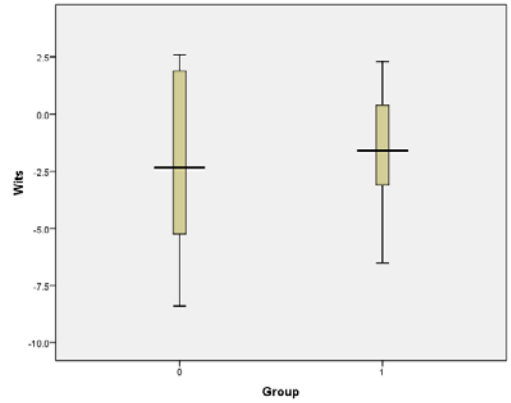
Normal Q-Q Plots





Detrended Normal Q-Q Plots





APPENDIX I - Statistical Analysis

Independent-Samples T-Test

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
SN	Equal variances assumed	.095	.762	-1.685	21	.107	-2.4902	1.4781	-5.5640	.5837
	Equal variances not assumed			-1.679	20.398	.109	-2.4902	1.4835	-5.5809	.6006
BaSN	Equal variances assumed	7.488	.012	-.087	21	.931	-.2432	2.7818	-6.0282	5.5419
	Equal variances not assumed			-.090	16.165	.929	-.2432	2.7042	-5.9712	5.4848
SNA	Equal variances assumed	.997	.330	.751	21	.461	1.0606	1.4114	-1.8746	3.9958
	Equal variances not assumed			.744	19.109	.466	1.0606	1.4260	-1.9229	4.0441
PP_SN	Equal variances assumed	.063	.805	.558	21	.583	.9136	1.6380	-2.4927	4.3200
	Equal variances not assumed			.561	20.992	.581	.9136	1.6298	-2.4757	4.3030
CoANS	Equal variances assumed	.282	.601	-.566	21	.578	-1.2841	2.2696	-6.0039	3.4357
	Equal variances not assumed			-.569	20.954	.575	-1.2841	2.2554	-5.9750	3.4069
ANS_PNS	Equal variances assumed	2.692	.116	-.429	21	.672	-.6917	1.6117	-4.0433	2.6600

	Equal variances not assumed			-.437	19.347	.667	-.6917	1.5842	-4.0034	2.6201
U1_PP	Equal variances assumed	.123	.729	-.343	21	.735	-1.3152	3.8339	-9.2881	6.6578
	Equal variances not assumed			-.343	20.871	.735	-1.3152	3.8317	-9.2865	6.6562
ANperp	Equal variances assumed	2.884	.104	1.363	21	.187	2.0970	1.5387	-1.1028	5.2968
	Equal variances not assumed			1.322	13.574	.208	2.0970	1.5863	-1.3153	5.5092
SNB	Equal variances assumed	1.322	.263	1.171	21	.255	2.0576	1.7566	-1.5955	5.7107
	Equal variances not assumed			1.159	18.999	.261	2.0576	1.7756	-1.6588	5.7740
ArGoMe	Equal variances assumed	.001	.975	-1.574	21	.130	-5.6841	3.6106	-13.1928	1.8246
	Equal variances not assumed			-1.578	20.971	.130	-5.6841	3.6018	-13.1750	1.8069
GoMe	Equal variances assumed	.038	.847	.649	21	.524	2.1326	3.2879	-4.7049	8.9701
	Equal variances not assumed			.650	20.949	.523	2.1326	3.2816	-4.6929	8.9580
ANB	Equal variances assumed	3.157	.090	-.669	21	.511	-.7561	1.1307	-3.1076	1.5955
	Equal variances not assumed			-.657	17.355	.520	-.7561	1.1502	-3.1789	1.6668
Wits	Equal variances assumed	4.028	.058	-.498	21	.624	-.6947	1.3951	-3.5960	2.2066
	Equal variances not assumed			-.506	19.583	.618	-.6947	1.3728	-3.5621	2.1727

PP-SN

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
PP_SN	Equal variances assumed	.041	.841	1.100	20	.285	1.6727	1.5210	-1.5000	4.8455
	Equal variances not assumed			1.100	19.987	.285	1.6727	1.5210	-1.5002	4.8456

CoANS

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
Co_ANS	Equal variances assumed	.209	.653	-1.923	17	.071	-3.5080	1.8242	-7.3566	.3407
	Equal variances not assumed			-1.821	11.996	.094	-3.5080	1.9264	-7.7055	.6896

A

Nperp

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
ANperp	Equal variances assumed	3.475	.077	.790	20	.439	.9650	1.2217	-1.5835	3.5135
	Equal variances not assumed			.753	13.758	.464	.9650	1.2823	-1.7899	3.7199

ArGoMe

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
ArGoMe	Equal variances assumed	1.005	.328	-.977	20	.340	-3.2727	3.3512	-10.2632	3.7178

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
ArGoMe	Equal variances assumed	1.005	.328	-.977	20	.340	-3.2727	3.3512	-10.2632	3.7178
	Equal variances not assumed			-.977	16.282	.343	-3.2727	3.3512	-10.3670	3.8215

Mann-Whitney U-Test

Test Statistics[b]

	SN	BaSN	SNA	PP_SN	CoANS	ANS_PNS	U1_PP	ANperp	SNB	ArGoMe	GoMe	ANB	Wits
Mann-Whitney U	41.000	60.000	54.500	52.500	54.000	59.000	58.000	43.000	46.000	47.000	65.000	52.000	59.500
Wilcoxon W	119.000	138.000	120.500	118.500	132.000	137.000	136.000	109.000	112.000	125.000	143.000	130.000	137.500
Z	-1.539	-.369	-.708	-.831	-.739	-.431	-.492	-1.416	-1.232	-1.169	-.062	-.862	-.400
Asymp. Sig. (2-tailed)	.124	.712	.479	.406	.460	.667	.622	.157	.218	.242	.951	.389	.689
Exact Sig. [2*(1-tailed Sig.)]	.134[a]	.740[a]	.487[a]	.413[a]	.487[a]	.695[a]	.651[a]	.169[a]	.235[a]	.260[a]	.976[a]	.413[a]	.695[a]

a. Not corrected for ties.

b. Grouping Variable: Group