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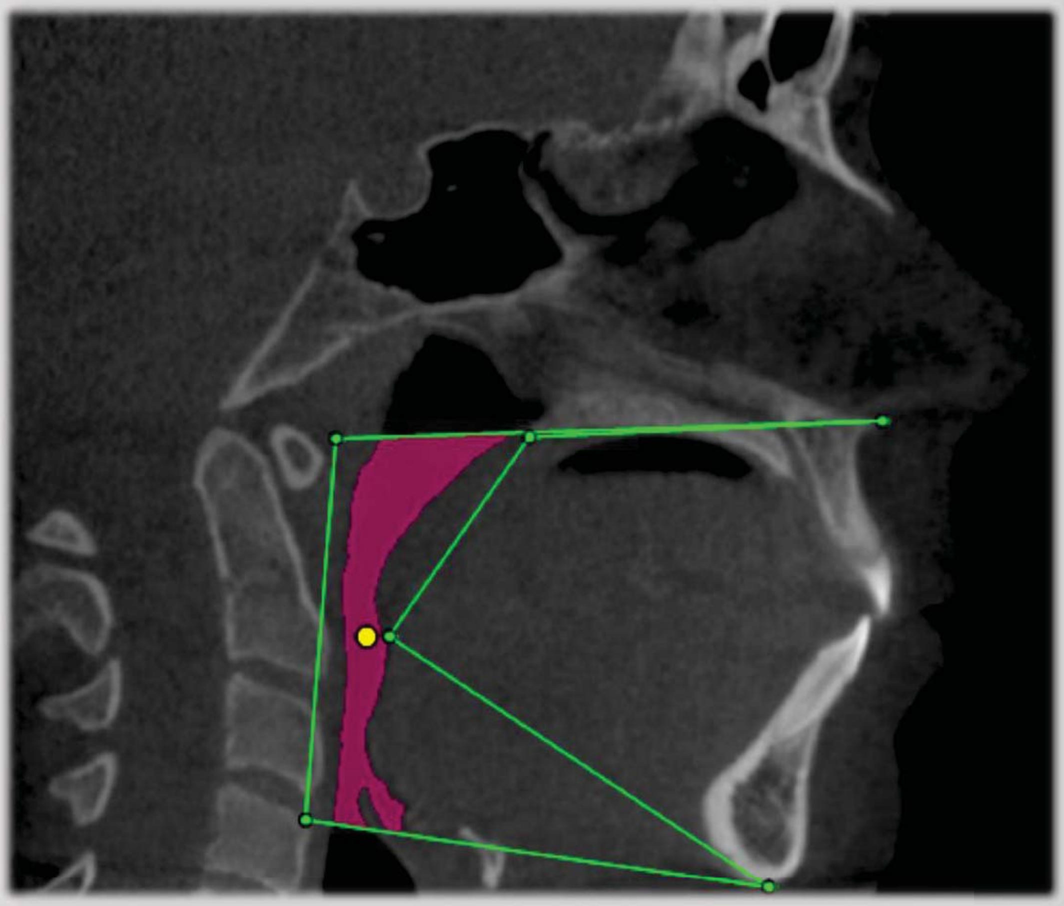
JAMES COOK UNIVERSITY
AUSTRALIA

3-D pharyngeal airway related to facial morphology, upper cervical vertebral column morphology and skeletal maturation in children: a pilot study



Seerone Anandarajah

3-D pharyngeal airway related to facial morphology, upper cervical vertebral column morphology and skeletal maturation in children: a pilot study

A thesis submitted as partial fulfilment of the requirements for the degree of Doctor of Clinical Dentistry (Orthodontics)

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June 2015

College of Medicine and Dentistry

JAMES COOK UNIVERSITY
AUSTRALIA

Table of contents

Declaration

I, Seerone Anandarajah, do solemnly and sincerely declare that this research project has not been accepted for the award of any other degree or diploma in any other university. To the best of my belief, it contains no material published, except where due reference is made in the text. I give consent for this copy of my thesis, when deposited in the University Library, to be made available for loan and photocopy.

___________________________________ __________________

Seerone Anandarajah Date

Declaration of ethics

This research presented and reported in this thesis was conducted in accordance with the National Health and Medical Research Council (NHMRC) National Statement on Ethical Conduct in Human Research, 2007. The proposed research study received human research ethics approval from the JCU Human Research Ethics Committee Approval Number #H5115. Refer to Appendix for a copy of the approval letter.

Acknowledgements

I would like to express my sincere gratitude and appreciation to:

- A/Prof Liselotte Sonnesen for her countless assistance, guidance and mentorship. You have truly inspired me.
- Professor Andrew Sandham for his motivational and encouraging words.
- Dr Raahib Dudhia for his assistance with data collection, development of the research protocol and continual guidance.
- Yousef Abdalla for assistance in assessing the validity of the research protocol.
- Professor Eliyathamby A. Selvanathan from Griffith University for his statistical assistance.
- Last but not least, my friends and family for supporting me throughout this journey.

List of figures

List of tables

List of acronyms

C1	First cervical vertebra
C4	Fourth cervical vertebrae
CBCT	Cone beam computed tomography
CG	Crista galli
FH	Frankfurt Horizontal
FMA	Frankfurt mandibular plane angle
Lat ceph	Lateral cephalogram
NS	Not significant
MALT	Mucosa-associated lymphoid tissue
Or	Orbitale
OSA	obstructive sleep apnoea
PA ceph	Postero-anterior cephalogram
SDB	Sleep disordered breathing

Abstract

Introduction:

Pharyngeal airway dimensions are associated with growth, anatomical, postural and mechanical factors, but the interactions of these associations are not yet fully understood. Therefore the aim of the present study was to examine and relate the pharyngeal airway dimensions to dentofacial morphology, upper cervical vertebral column morphology and skeletal maturation in pre-orthodontic children. Furthermore, parameters with the greatest relevance to airway dimensions were analysed.

Subjects and Methods:

Airway volume, minimal cross-sectional area and upper cervical vertebral column morphology were 3-dimensionlly assessed on 105 CBCT scans of healthy pre-orthodontic children (44 boys, 61 girls; mean age, 10.7 ± 2.4 years). Cephalometric features and skeletal maturity were assessed on generated 2-dimensional cephalograms.

Associations were tested by Spearman correlation analyses and analyses of variance (ANOVA). The effect of gender, age and skeletal maturation and the parameters with the greatest relevance to airway dimensions were tested by linear regression analysis.

Results:

The airway volume and minimal cross-sectional area were greater in children of an older age than younger age ($p<0.001$, $p<0.01$ respectively). After adjustment for the effect of age, skeletal maturity and gender, there were moderate positive associations with maxillary and mandibular width and airway volume (r = 0.53**, 0.60*** respectively) and weak positive associations with minimal cross-sectional area (r = 0.35**, r = 0.35*** respectively). Anterior face height (r = 0.51*) and upper anterior face height (r = 0.52*) had moderate positive associations with airway volume whereas sagittal jaw relationship had a weak negative association with minimal cross-sectional area (r= -0.35*). Gender, molar occlusion and upper cervical vertebral column morphology were not significantly associated with airway dimensions. Mandibular width and age were the most relevant factors for airway volume ($r^2 = 0.36$). Mandibular width and sagittal jaw relationship were the most relevant factors for minimal cross-sectional area (r^2 = 0.16).

Conclusion:

The results indicate that airway volume and minimal cross-sectional area have a weak to moderate association with age, skeletal maturation and craniofacial dimensions in pre-orthodontic children.

1.0 Introduction

Increased interest in upper airway dimensions and morphology over the last few decades can be attributed to the appreciation that upper airway configuration is associated with sleep disordered breathing (SDB) as well as its general relationship to craniofacial morphology.[1,2] The upper airway volume and minimal cross-sectional area is significantly smaller in children with SDB and tends to be narrower laterally compared to children without sleep disorders.[3-6] Early diagnosis of SDB, or potential associations of SDB, is essential to encourage normal facial development.[7,8]

Cone beam computed tomography (CBCT) has become an unprecedented diagnostic method to analyse the airway 3–dimensionally[1]. It has broadened the possibilities for quantification of upper airway dimensions. Lateral cephalograms, which are part of standard records for orthodontic treatment planning, are limited to the sagittal and vertical dimensions, therefore restricting accurate assessment of the complexity and size of these structures.

Dimensions of a healthy upper airway are associated with growth,[9-13] anatomical,[14-21] postural,[22-25] and mechanical factors.[26,27] However, the level of these associations is not yet fully understood. Reduced pharyngeal dimensions established early in life could potentially predispose to later development of SDB or even obstructive sleep apnoea (OSA)[28] as soft tissue changes related to ageing, obesity or genetic background further reduce oropharyngeal patency.[29]

2.0 Aims

The aim of this study is to utilise 3-dimensional CBCT technology to assess pharyngeal airway dimensions related to dentofacial morphology, upper cervical vertebral column morphology and skeletal maturation in growing pre-orthodontic children.

3.0 Hypotheses

The following null hypotheses are proposed for this research project:

- Dentofacial dimensions are not associated with pharyngeal airway dimensions
- Upper cervical vertebral column morphological deviations are not associated with pharyngeal airway dimensions
- Skeletal maturity is not associated with pharyngeal airway dimensions

4.0 Literature review

The following literature review will describe the anatomy and function of the pharynx and growth of the upper airways. It will highlight associations between dentofacial morphology and the upper airway as well as between the upper cervical vertebral column and upper airway.

4.1 Anatomy and function of the pharynx

The pharynx extends from the cranial base (sphenoid bone and the basilar part of the occipital bone) to the level of the inferior surface of the sixth vertebra and lower boarder of the cricoid cartilage where it is continuous with the oesophagus.[30] Posteriorly, loose connective tissue separates it from the cervical vertebrae.[30,31] Anteriorly, it opens into the nasal and oral cavities; therefore the anterior wall is incomplete.[30,31] Approximately 12 to 14cm in length, the pharynx is widest superiorly, measuring 3.5cm, and reduces to 1.5cm at its junction with the oesophagus.[31] The pharynx is a flattened tube like structure formed by muscles and membranes.[31] The upper pharynx is developmentally more complicated than the lower pharynx, is differentiated later in foetal development and changes morphologically for a longer period foetally and postnatally.[32]

Anatomically, the pharynx can be divided into 3 parts:[26,30,33-35] nasopharynx, oropharynx and hypopharynx.

4.1.1 Nasopharynx:

The nasopharynx is a cuboid-shaped cavity situated behind the posterior nares of the nasal cavities and above the hard and soft palate.[30,34] It transfers humidified air from the nasal cavity to the oropharynx.[34] Superiorly, it is bounded by the base of the skull that slopes down to form the posterior pharyngeal wall.[11] Except for the soft palate, walls of the nasopharynx are largely fixed and remain motionless during function.[34] The more caudal oropharynx is connected to the nasopharynx via the pharyngeal isthmus which may be sealed via elevation of the soft palate and constriction of the superior pharyngeal constrictor muscle during swallowing.[34] Openings of the bilateral pharyngotympanic (Eustachian) tubes are evident in the lateral walls of the nasopharynx. Mucous glands and lymphoid tissue involved in both immune and non-immune host-defence also exists in the nasopharynx.[34] Mucosa-associated lymphoid tissue (MALT), the adenoidal lymphoid tissue, is located in the roof and posterior wall of the nasopharynx.[30,34]

4.1.2 Oropharynx:

The oropharynx extends from the hard and soft palate superiorly to the vallecula inferiorly (plane of hyoid bone; base of epiglottis).[35,36] It is bordered anteriorly by the circumvallate papillae and the oropharyngeal isthmus. Posteriorly it is bounded by a muscular wall made up of the superior, middle and inferior constrictor muscles that lie in front of the cervical spine.[30] The lateral pharyngeal walls are complicated and consist of muscles, pharyngeal mucosa and lymphoid tissue.[31]

The oropharynx is not only able to transmit food into the esophagus, but also inspired air into the trachea.[34] While in a wake state, the oropharynx is mostly constricted retro-palatally.[4,37] Consequently, this area might be a potential site of collapse during sleep. Additionally, airway closure might occur retro-glossally in the supine position as the tongue approximates the posterior pharyngeal wall due to gravitational force.[38] During sleep, gravity may have a greater influence on upper airway resistance than the relative atonia of muscles of the upper airway.

4.1.3 Hypopharynx:

The hypopharynx extends from the vallecula, where it communicates with the oropharynx, to the inferior border of the cricoid cartilage and encompasses the epiglottis.[30] The infant and adult epiglottis are considerably different in form. The infantile epiglottis is longer, floppier and omega shaped as well as angled 45 degrees from the anterior pharyngeal wall.[39] The adult epiglottis, however, is positioned closer to the tongue base.[40] At birth the hyoid and thyroid structures are closely related, but with growth, the thyroid descends down the neck faster resulting in an angular change of the epiglottis.[34]

4.1.4 Musculature and soft tissues:

Function of the upper airway involves maintenance of patency (during breathing) or airway closure (as in swallowing). More than 20 muscles surround the airway to actively constrict and dilate the upper airway lumen.[41] The muscles can be categorised into 4 groups according to position - regulation of the soft palate (tensor palatini, levator palatine, alai nasi), tongue (styloglossus, hyoglossus, geniohyoid, genioglossus,), hyoid apparatus (geniohyoid, sternohyoid, hyoglossus, genioglossus, digastric) and the posterolateral pharyngeal walls (pharyngeal constrictors, palatoglossus).[26] Airway patency is determined by the complex interaction of these muscle groups.

Walls of the upper airway are constructed of soft tissue structures including the tonsils, soft palate, uvula, tongue and lateral pharyngeal walls.[4] Craniofacial skeletal structures that mainly determine size of the airway are the mandible[42] and the hyoid bone[43] because they act as anchors to which muscles and soft tissue attach. Complex interactions occur where muscle action may instead of moving a structure, cause tension in some of the adjacent soft tissues (e.g. tracheal pull).[26]

In summary, the pharynx is a complicated intricate structure that has various functions. It can be divided into 3 sections; nasopharynx, oropharynx and hypopharynx. Craniofacial osseous structures determine the general size of the upper airways, but the walls, constructed of soft tissue structures, also influence luminal size.

4.2 Growth of the upper airway

According to the functional matrix theory proposed by Moss,[44] nasal breathing allows proper growth and development of the craniofacial complex. The continuous flow of air through the nasal passages induces a constant stimulus for lateral growth of the maxilla and lowering of the palatal vault.[45] Conversely, midfacial hypoplasia can lead to obstruction of the upper airways.[46] In the following section, upper airway dimensions are described in relation to age and skeletal maturation. Most research is based on 2-dimensional cephalometry and predominantly associated with the skeletal structures.

The structural volume of the pharynx increases by about 80% during growth.[10] Transversely, pharyngeal growth (measured as bihamular width) plateaus at the end of the second year of life,[47] but choanal width (maximum distance between medial pterygoid plates) increases moderately by 23% until maturity via relocation at the medial pterygoid laminae.[10] Therefore, although transverse pharyngeal dimensions are established very early in life, the airway is still able to meet increased respiratory demands with growth.

In the antero-posterior dimension, the increase in pharyngeal depth is limited. As measured from posterior nasal spine to Basion (PNS-Ba), it increases by only 9%[10,47] because of the influence of cranial base flexure (angle formed between sella, nasion and basion); with an acute angle leading to a more vertical direction of pharyngeal development.[48]

With age, the angle of the nasopharyngeal roof reduces due to increasingly steeper erection of the vomer's dorsal body, growth changes in the clivus and the geometric effect of PNS and Ba lowering. These changes counteract the growth contribution of the spheno-occitpial synchondrosis and result in a limited increase in nasopharyngeal depth.[11,49]

However, the PNS-Ba measurement does not accurately represent the i*n vivo* antero-posterior dimension of the pharynx. The ventral body of the atlas has a more anterior position than basion and is connected to the pharyngal tubercle on the base of the skull by the anterior ligament of the ventral column. This relationship results in a more anterior position of the pharynx compared to the ventral point of foramen magnum.[11] Regardless of how it is assessed, similar antero-posterior growth changes have been reported. With the atlas considered as the posterior limit, the pharyngeal sagittal depth stabilises during early infancy (the first or second year of life), although individual differences may occur.[9,10,50,51] The sagittal growth effect of the spheno-ocipital synchondrosis is counteracted by forward growth of the cervical vertebrae.[9] Furthermore, when superimposed on the sella-nasion (SN) line, which has inherent issues in growing individuals,[52] the posterior boarder of the palate (PNS) is thought to stabilise antero-posteriorly during the second year of life.[51] After this, it follows a straight downward pathway during growth.[51,53] The maxilla increases in length via transpalatal sutural growth as well as appositional growth at the maxillary tuberosities and the posterior palatine border. However, this posterior growth is compensated by a simultaneous downward and forward displacement of the whole maxilla.

As transverse and antero-posterior change is limited, growth of the pharynx is predominantly vertical in nature, with downward displacement of the palate and mainly vertical growth of the spheno-occipital synchondrosis.[9,10,50] During childhood, these growth changes increase the bony nasopharyngeal height by about 38%,[10] contributing to most of the increase in nasopharyngeal capacity and continues until maturity is reached.[50]

Few studies have assessed pharyngeal changes during adulthood. Johnston and Richardson[54] cephalometrically analysed 16 adults. With a mean age of 20.2 years, a repeat cephalogram was taken 32 years later. Measurements included changes in pharyngeal skeletal structures, pharyngeal soft tissue thickness, pharyngeal airway depth and soft palate dimensions. Although nasopharyngeal skeletal dimensions exhibited no change, antero-posterior depth of the nasopharyngeal lumen increased due to a reduction in thickness of the posterior nasopharyngeal wall and the soft palate became thicker and longer, resulting in a decreased depth of the oropharyngeal airway. It is evident that airway size is dependent on pharyngeal soft tissue growth, which the literature indicates to be variable.

The advent of 3-dimensional airway analysis has allowed a more accurate assessment of airway dimensions, without having to estimate from bony structures. It has been possible to precisely assess cross-sectional and volumetric changes of the airway as opposed to extrapolations from 2-dimensional images. Abramson et al[55] studied changes in the upper airway using medical CT data collected routinely. The airway of interest was delineated from the hard palate to the tip of the epiglottis. In the sample size of 46, 31 were male and the age ranged from 4 months to 46 years. Size and shape of the airway, among other parameters, were compared among 4 different age groups. The authors concluded that adults had a larger airway size, with a more elliptical shape. However the number of patients in each group was unknown and the actual manner of data analysis was unclear.

In 2012, 2 separate studies were published that assessed upper airway volume, length and minimal cross-sectional area in normal pre-orthodontic patients.[12,13] Chiang et al[13] evaluated 387 scans of children who ranged from 8 to 18 years of age (mean age 13.2 ± 2.5 years) , whereas Schendel et al[12] had a much larger sample size of 1300 patients ranging from 6 to 60 years of age. In both studies, the scans were taken with the i-CAT system and loaded into 3dMDVultus software for airway analysis, but how the respiration phase of the subjects was controlled during the scans was not mentioned, especially considering the 40 second acquisition time in the Schendel et al[12] study and unknown parameters in the Chiang et al[13] study. Although the airway was delineated differently in both studies, similar trends were obtained. The following conclusions can be made:

- Airway volume consistently increases until the age of 20, followed by a period of little change and then by a large decrease in all dimensions after 50 years of age. Interestingly, the airway volume at age 45 is only slightly larger than at age 15 years. The studies provide conflicting information as to whether it occurs at a faster rate in males or females. However, generally speaking, males tend to have a larger airway volume compared to females.

- Minimal cross-sectional area also increased until the age of 20, followed by a period of little change but then decreased considerably after 30 years of age.

- Length of the airway increases until about 15 years of age and then begins to plateau. No further changes occur in females, but there is a continued increase in males until about 50 years of age after which it decreases.

- During the ages of active growth (8 to 18 years old), airway volume increases with an increase in length, with an even greater rate of increase when the airway is greater than 60 mm in length.
- Over a greater age period (6 to 60 years old) total airway volume had a high correlation with minimal cross-sectional area, but only mildly with the length. This could indicate that airway length only plays a minor role in the decrease of airway volume with age. Airway area at various segments appears to be more important. This highlights the importance of 3-dimensional imaging for airway analysis as 2-dimensional radiography will not allow analysis in this dimension.

In summary, growth of the upper airway occurs in all 3 dimensions. However, most research is based on 2-dimensional cephalometry. It is evident from the literature that most early changes of the pharynx are due to growth of the bony framework. After maturity is reached, changes are more related to the soft tissues. Research of the relationship between age and airway dimensions is limited. Furthermore, associations between skeletal maturation and the upper airway dimensions in children have not previously been reported in the literature.

4.3 Associations between dentofacial morphology and upper airway dimensions in children

Due to their close relationship, an association between pharyngeal structures and the dentofacial pattern has been proposed. Increasingly, this has been researched in children, which is the focus of the following section.

4.3.1 Upper airway and craniofacial morphology

Using 2-dimensional radiography, various authors have found statistically significant associations between pharyngeal and craniofacial structures.[56-61] Positioning of the jaws has been found to influence upper airway dimensions. Ceylan and Oktay[56] found a negative correlation between oropharyngeal airway size and ANB angle, but no correlation was found between ANB angle and nasopharyngeal airway. A posterior mandibular rotation[57] as well as functional anterior shifting[58] has also been reported to decrease upper airway dimensions. Joseph et al[59] noticed a difference in antero-posterior dimension of the airway according to vertical growth pattern, with smaller dimensions observed in hyper-divergent facial patterns compared to normo-divergent facial patterns. They attributed this difference to skeletal features found in such patients, such as relative bimaxillary skeletal retrusion and vertical maxillary excess. De Freitas et al[60] also noticed considerably smaller upper pharyngeal airways with vertical growth patterns. Similar results were observed by Faruk and Uysal[61] in Class I patients with difference growth patterns. However, singular linear measurements from 2-dimensional images are only weakly correlated to the upper airway cross-sectional area and volume.[62]

As the upper airway is a complicated 3-dimensional structure, van Vlijmen et al[63] concluded in their systematic review that CBCT imaging is much more valuable than conventional plane radiography to assess the upper airway. Most studies that 3-dimensionally analysed the airway assessed correlations to craniofacial measurements from generated lateral cephalograms.[14-19]

Various studies have found weak to moderate associations with the sagittal jaw relationship (ANB; negative),[15,17,19] or mandibular jaw relationship (SNB; positive)[15,18,19] and airway volume. Zheng et al[20] also reported a significant positive correlation between oropharyngeal airway and SNB and negative correlation with ANB, however, the strength of the correlation was not indicated. Furthermore, Alves et al[18] found a moderate positive correlation between SNB and minimal cross-sectional area. Generally, no significant associations were reported between airway dimensions and the maxillary jaw relationship (SNA),[15,18,19] except for Di Carlo[21] who estimated that for every degree increase in SNA, the airway volume would reduce by 149mm^3.

The underlying skeletal pattern has been shown to affect upper airway dimensions. Generally, it was found that Class III patients (assessed by the sagittal jaw relationship; ANB angle) had greater airway volume than Class I which was greater than Class II,[15-20] however this difference was not always statistically significant between the groups[16] or between Class I and Class III.[15] Minimal cross-sectional area was also found to be greater than in Class I subjects than Class II subjects,[18,20] and even greater in Class III subjects.[20] Conversely, Kula et al[64] found no difference between airway volume or minimal cross sectional area between Class I, II or III skeletal patterns. Differences in upper airway morphology have also been described, with individuals of a Class II skeletal pattern exhibiting more of a backward orientation of the airway to the Frankfurt Horizontal (FH) plane, compared to Class III individuals that had a more vertical orientation.[16] Class III skeletal patients were also found to have a more flat shaped airway compared to Class I individuals who had a more square oropharyngeal airway.[14]

Moderate to strong correlations were found between upper airway dimensions and total anterior face height[16,17] and moderate correlation to posterior face height.[17] No studies found a significant correlation between Frankfurt mandibular plane angle (FMA) and upper airway dimensions.[15,17-20]

Di Carlo et al[21] assessed the relationship between the upper airway and craniofacial morphology in CBCT scans of young adults (13 to 34 years of age). Unlike the previously reported studies, the patients were orientated in the supine position. Furthermore, the cephalometric points were assessed 3-dimensionally; not based on 2-dimensional generated radiographs. The authors found no correlations between upper airway dimensions and craniofacial features in either antero-posterior, vertical or transverse dimensions. However, data gathered from patients sitting or standing cannot be adequately compared to those obtained with the individual in the supine position due to the gravitational effects on oropharyngeal structures.[65]

In summary, conflicting results have been reported in the literature between upper airway dimensions and craniofacial morphology. However, a greater antero-posterior discrepancy tends to be associated with reduced airway dimensions, especially due to a retrognathic mandible. The vertical dimension does not seem to influence airway dimensions as much.

4.3.2 Upper airway and malocclusion traits

Research is limited about possible associations between upper airway dimensions and malocclusion traits in children. In a 2-dimensional study, de Freitas et al[60] found that molar relationship did not influence upper airway dimensions. Conversely, Kirjavainen and Kirjavainen[66] found that patients with a Class II Div I malocclusion tended to have narrower oropharyngeal and hypopharyngeal spaces than with a Class I first molar relationship. When 3-dimensionally assessed, no difference in pharyngeal airway volume or minimal cross-sectional area was observed with variation in molar occlusion.[64]

In summary, conflicting results regarding upper airway dimensions and malocclusion traits have been reported. However, most authors agree that molar occlusion does not influence pharyngeal airway dimensions.

4.4 Association between upper cervical vertebral column and upper airway dimensions

Various structures of the neck have been shown to play a role in upper airway patency. However, research is limited into another crucial structure involved with patency of the upper airway; the cervical spine. Positioned posteriorly to the pharynx, the cervical spine comprises of 7 vertebrae and provides motion to the neck via articulations with the occipital bone and between each vertebra.

No studies have previously assessed the association between upper cervical vertebral morphology and upper airway dimensions; however, associations between head posture and upper airway dimensions as well as between head posture and upper cervical vertebral morphology have been described. Associations between upper cervical vertebral morphology and craniofacial morphology have also been observed.

Various studies have shown that pharyngeal airway dimensions are strongly correlated to head posture.[22,23] A change in cranio-cervical angulation of 10 degrees resulted in a 4 mm alteration of the posterior airway space.[22,23] Furthermore, patients with obstructive sleep apnoea tend to have an increased cranio-cervical angle, possibly as a physiological compensatory mechanism to maintain an adequate airway, while the head and visual axis maintain their natural position.[24,25]

Upper cervical vertebral morphology is usually evaluated by either measurements of the first cervical vertebra (C1)[67-69] or visual assessment of the upper 5 cervical vertebrae (C1 to C5).[70-82] Huggare and Kylämarkula[67,68] found correlations between head posture and height of the dorsal arch of the atlas (C1), with a more forward head posture associated with a lower dorsal arch.[68] A significantly reduced height of the dorsal arch of atlas was also observed in children with enlarged adenoids.[67] The associations between nasopharyngeal obstruction and an extended head posture may help explain this phenomenon as children with enlarged adenoids may adopt such a posture.

Huggare[69] then went on to assess associations between anatomy of the atlas, head posture and cervico-vertebral and dentofacial morphology in 78 young adults; 22 women and 17 men in each group of either a high or low dorsal arch. A high dorsal arch was categorised as at least 12mm in women and 13 mm in men. A low dorsal arch was categorised as maximally 6mm in women and 7 mm in men. In the low arch groups, head extension was greater (more so in women), both the dorsal arch and dens of the second vertebra were vertically smaller (more so in men), the clival plane was more parallel to the foraminal plane and the gonial angle more obtuse. Women in the low arch group also had a greater tendency for forward inclination of the cervical spine, showed a steepened mandibular plane, backward rotated condylar head, a decrease in the ratio of posterior to anterior face height, smaller vertical overbite and reduced proclination of the incisors. The prevalence of severe malocclusion was higher than in the corresponding high arch group. Furthermore, vertebral length was reduced more in women.

When visually assessed, deviations in upper cervical vertebral morphology can be divided into 2 main categories: fusion anomalies (i.e. fusion, block fusion and occipitalisation) and posterior arch deficiency (i.e. partial cleft and dehiscence).[70-79] Most research in this area has been conducted by Sonnesen and colleagues. They found that fusion of the cervical vertebral column is associated with occlusion, craniofacial morphology and head posture in patients with obstructive sleep apnoea (OSA) as well as in patients with severe skeletal malocclusions.[71-79,82]

Although also evident in healthy subjects with neutral occlusion (14 to 21%),[71,78] morphological deviations (fusion) of the upper cervical vertebral column occurred more significantly in adult patients with severe skeletal malocclusion traits, such as skeletal deep bite (41%),[76] skeletal openbite (42%),[75] skeletal maxillary overjet (52%)[74] and skeletal mandibular overjet (61%).[73] Fusions were always seen between the second and third cervical vertebrae. Individuals with mandibular overjet also experienced block fusion between the second, third and fourth cervical vertebra. These findings suggest an association between fusion of the cervical vertebral column and severe skeletal malocclusion in adults. In children, it was found that deviations in upper cervical vertebral morphology occurred significantly more often in skeletal maxillary overjet (28%) compared to dentoalveolar overjet (17%),[80] whereas the occurrence was not statistically different between skeletal anterior open bite (23.7%) and dentoalveolar anterior open bite (19.2%).[81] The distribution of upper cervical vertebral column morphological deviations in children varied amongst the groups, but fusion between C2 and C3 was most prevalent, except for the skeletal open bite group where partial cleft of C1 was most common.[80,81]

A series of studies[73-76] revealed an association between fusion of the upper cervical vertebral column and craniofacial morphology in adults. Fusion in adult patients with severe skeletal malocclusions was associated with a large cranial base angle, retrognathia of the jaws and inclination of the jaws. This was also evident in children with a large sagittal jaw relationship.[80] Furthermore, partial cleft of C1 was associated with a large cranial base angle in these children.[80] However, no associations were found in children with anterior open bite.[81]

Fusion of the upper cervical vertebral column is associated with altered posture of the head and neck.[78] Compared to controls, adults with fusions had significantly more curved cervical lordosis and more backward inclination of the upper cervical column. In children with an increased horizontal overjet, occipitilsation was associated with extension of the head compared to the cervical vertebral column. In children with anterior open bite no associations were found between cervical column morphology and craniofacial dimensions, although head posture was associated with craniofacial dimensions, possibly indicating a respiratory component in the aetiology in the sample population malocclusion.[81]

Higher prevalence of fusion anomalies (46%) was also found in adults with OSA which occurred at a lower level in the vertebral column.[79] Fusions occurred between the second and third vertebrae, the third and fourth vertebra, or between the fourth and fifth vertebrae. Fusion anomalies occurred as fusions (26.4%), block fusions (12.1%) and occipitalisation

(14.3%). Similar results were described in a subsequent study by the same principal author.[82] These deviations in cervical column morphology may be involved in the pathogenesis of OSA and therefore contribute to the diagnosis, subdivision and treatment of these individuals.[79,82]

The majority of above mentioned associations were determined from lateral cephalometry which has obvious limitations. Some authors believe that 2-dimensional radiographs present deceptive impressions of pseudo-fusions and that it is difficult to reliably determine cervical vertebral anomalies on one lateral cephalogram.[83-86] Oblique orientation of the cervical facet joints relative to the x-ray beam, flexion or extension of the spine and other morphological variations may cause superimposition of structures and an analogous appearance of fusions.[83,84,86] Using a 2-dimensional radiograph, exclusion of a fusion (clearly visible joint space without overlapping) is quite clear. When a radiographically overlapping joint facet is evident, it is difficult to determine whether it is a true fusion or superimposition.[83]

Patcas et al[86] mentioned that the Gold Standard for detection of fusions is direct observation. He conducted a cadaver study to validate the assessment of the spine on lateral cephalograms, 3-dimensional radiological data and direct observations in the cervical region. They found that lateral cephalograms caused false-positive detection of fusions and that 3-dmensional radiography (MDCT, CBCT) is reliable to exclude fusions. The study had a very small sample size (4) and therefore the results should be interpreted with caution. Furthermore, preparation of the cadaver heads could have interfered with a possible fusion and rotation of the cadaver head could have broken a possible partial fusion.

A recent study of 57 lateral cephalograms and CBCTs demonstrated that visualisation of morphological deviations in the cervical vertebral column showed good agreement between lateral cephalograms and CBCTs with a kappa coefficient (K) of 0.64.[82] The findings indicate that 2-dimensional lateral cephalograms (usually already taken as standard records for orthodontic treatment planning) are sufficient for identifying morphological deviations in the cervical vertebral column. However, for more accurate diagnosis and location of deviations, a CBCT scan is required.[82]

In summary, studies suggest that morphologic deviations of the upper cervical vertebral column are associated with craniofacial morphology, posture of the head and neck, and skeletal malocclusion traits. Furthermore, associations have been shown between upper airway dimensions and head posture as well as craniofacial morphology. These indicate a possible association between upper cervical vertebral morphology and upper airway dimensions. However, no study has yet looked into this. Much focus has been in the adult population with limited research in children. Although spinal morphology can be adequately assessed by an experienced operator with 2-dimensional radiography, it has inherent limitations and raises concerns about pseudo-fusions. 3-dimensional radiography (e.g. CBCT) provides more accurate diagnosis and location of deviations.

4.5 Summary

From this literature review, the following has become evident:

- The pharynx is a complicated intricate structure that has various functions. It can be divided into 3 sections; nasopharynx, oropharynx and hypopharynx. Craniofacial osseous structures determine the general size of the upper airways, but the walls, constructed of soft tissue structures, also influence luminal size.

- Growth of the upper airway occurs in all 3 dimensions. However, most research is based on 2-dimensional cephalometry. It is evident from the literature that most early changes of the pharynx are due to growth of the bony framework. After maturity is reached, changes are more related to the soft tissues. Research of the relationship between age and airway dimensions is limited. Furthermore, associations between skeletal maturation and the upper airway dimensions in children have not previously been reported in the literature.
- In 2-dimensional and 3-dimensional studies, conflicting results have been reported in the literature between upper airway dimensions and craniofacial morphology. However, a greater antero-posterior discrepancy tends to be associated with reduced airway dimensions, especially due to a retrognathic mandible. The vertical dimension does not seem to influence airway dimensions as much.
- Conflicting results regarding upper airway dimensions and malocclusion traits have been reported. However, most authors

agree that molar occlusion does not influence pharyngeal airway dimensions.

- Studies suggest that morphologic deviations of the upper cervical vertebral column are associated with craniofacial morphology, posture of the head and neck, and skeletal malocclusion traits. Furthermore, associations have been shown between upper airway dimensions and head posture as well as craniofacial morphology. These indicate a possible association between upper cervical vertebral morphology and upper airway dimensions. However, no study has yet looked into this.

Therefore, it appears valuable to 3-dimensionally analyse pharyngeal airway dimensions in relation to dentofacial morphology and upper cervical vertebral morphology in children, as well as to age and skeletal maturation. To our knowledge this has not been previously reported in the literature on 3-dimensional CBCTs of growing children.

5.0 Subjects and Methods

5.1 Subjects

All scans that met the inclusion/exclusion criteria were selected from a database containing CBCT scans of healthy children prior to commencement of orthodontic treatment. The database consists of all patients that attended a private practice in Victoria, Australia, for orthodontic treatment between January 2011 and July 2014. Before they were entered into the database all CBCT images were anonymised. Sex, age and malocclusion were also obtained from the database. These were cross-checked with the CBCT scans and clinical reports.

5.1.1 Inclusion Criteria

Inclusion criteria for this study were:

- Healthy children between 8 to 16 years prior to commencement of orthodontic treatment
- Complete imaging of the cranial base, maxilla, mandible, the first 4 cervical vertebrae (C1 to C4) and the associated airway.

5.1.2 Exclusion Criteria

Exclusion criteria for this study were:

- previous orthodontic treatment and/or orthognathic surgery
- previous adeno-tonsillectomy
- known syndromal conditions
- presence of pathology detectable along the upper airway
- History of OSA
- Movement artefact
- Swallowing during scan acquisition

This resulted in the final sample of 105 scans (Figure 1). The sample consisted of 61 girls (58.1%) and 44 boys (41.9%) with a mean age of 10.7 ± 2.4 years (Table 1)

Figure 1: Flow chart of final sample size

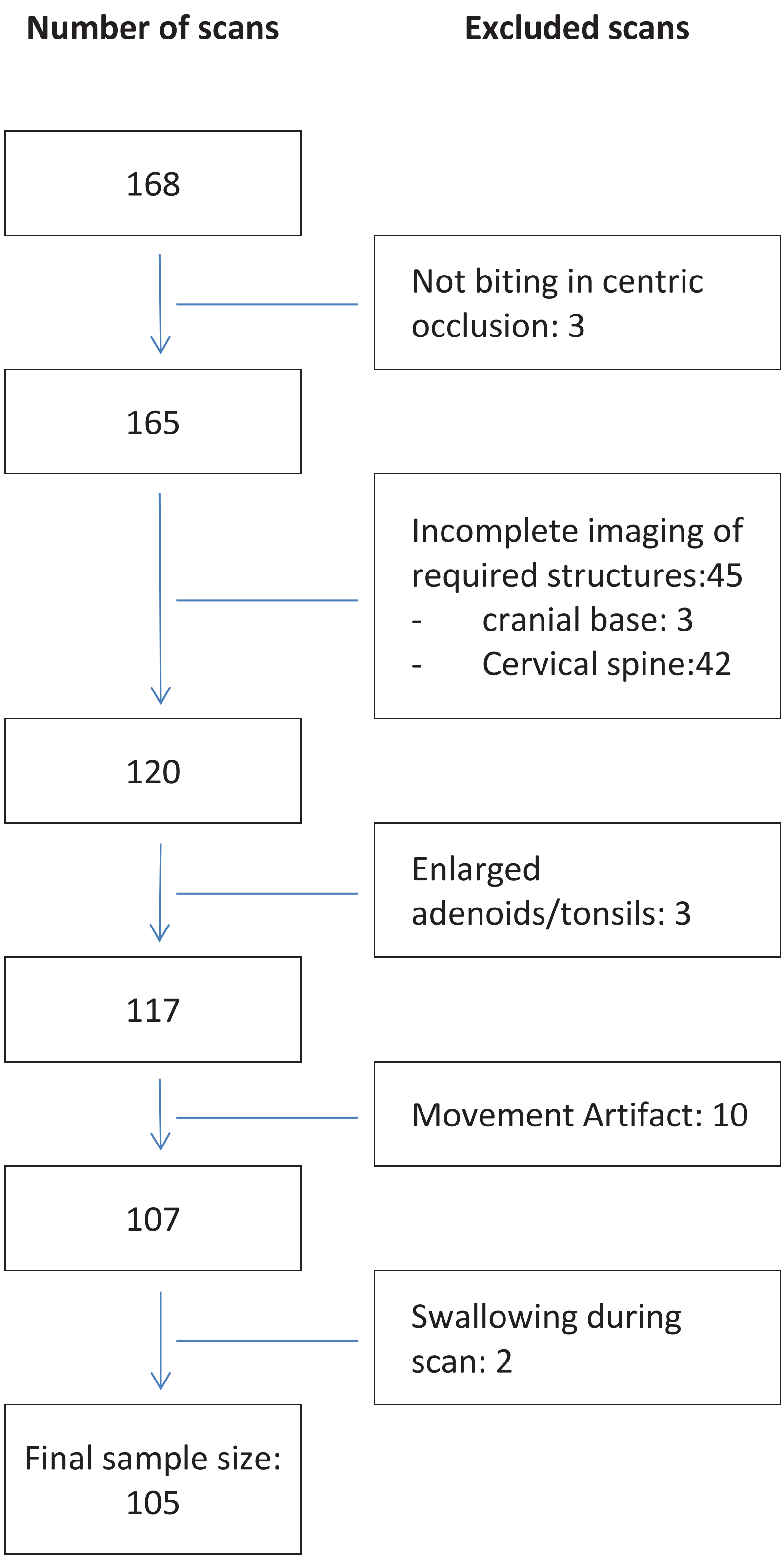


Table 1: Malocclusion, skeletal maturation and upper cervical vertebral morphology in 105 pre-orthodontic children

	Number (n)	Percentage (%)	Gender (p-value)	Age (P-value)	Skeletal maturation (p-value)
Gender				NS	0.017
Girls	61	58.1			
Boys	44	41.9			
Molar occlusion (Angle classification)			NS	NS	NS
1	38	36.2			
2	59	56.2			
3	7	6.7			
Skeletal maturation			0.017	0.000	
Prepubertal	57	54.3			
Pubertal	31	29.5			
Postpubertal	17	16.2			
Upper cervical vertebral morphology			NS	NS	NS
No abnormality	76	72.4			
Occipitalisation	3	2.9			
Partial cleft of C1	26	24.8			

NS, Not significant

5.2 Ethics approval

The experimental protocol used in this study was approved by the James Cook University Human Research Ethics Committee (H5115; Appendix).

5.3 Informed consent

In accordance with the guidelines set out by James Cook University Human Research Ethics Committee, informed consent was obtained by the practice for subjects and their parents whose scans were entered into the database, which included:

- A detailed verbal explanation of the possible use of the scans in the database for further research
- A summarised written form of the explanation
- Each patient and parent filled out the consent form

5.4 Scan Protocol

All patients were imaged in the same i-CAT Next Gen Cone Beam CT machine (Imaging Sciences International, Hatfield, Pa, USA) by the same operator, as part of their dental and orthodontic assessment prior to treatment. All the images were taken in a standardised sitting position: patients were restrained using a headrest and velcro head strap; the chin rest was not used to allow for the patient's head to be positioned so that Frankfurt horizontal was parallel to the floor. Patients were instructed to close into centric occlusion, relax their tongue and lips and to breathe gently and not swallow or move during the acquisition. A standardised protocol was used: 120kV, 5mA, 0.3mm voxel resolution, 8.9 second scan time, 13cm (height) x 16cm (diameter) scan volume. All CBCTs were reviewed by a Dento-maxillofacial Radiologist to ensure no significant pathology was identified and that all inclusion criteria were met.

5.5 Image Preparation

The Digital Imaging and Communications in Medicine (DICOM) data was processed using Dolphin Imaging software (version 11.5; Dolphin Imaging and Management Solutions, Chatsworth, Calif). Images were always manipulated and measured under the same lighting conditions.

5.5.1 Re-orientation

To standardise the measurements and minimise errors, the skull was reorientated in all 3 planes using the following guidelines:

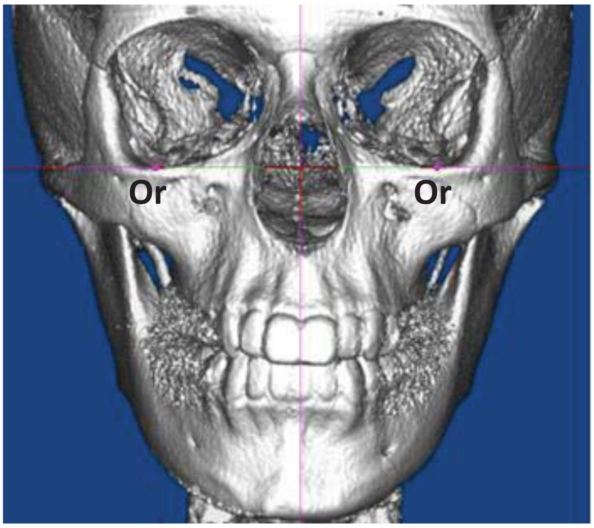
1. Coronal view – So that Orbitale on both sides lie on the same horizontal plane (Figure 2a).
2. Sagittal plane – So that the Frankfort Horizontal was horizontally orientated (Figure 2b).
3. Axial plane – With the patient facing down (endocranial view), so that a line through crista galli and basion was vertical. With the patient facing up (exocranial view), it was ensured that no transversal rotation of the mandible or the zygomatic arches was present (Figure 2c).

5.5.2 Generation of 2-dimensional images

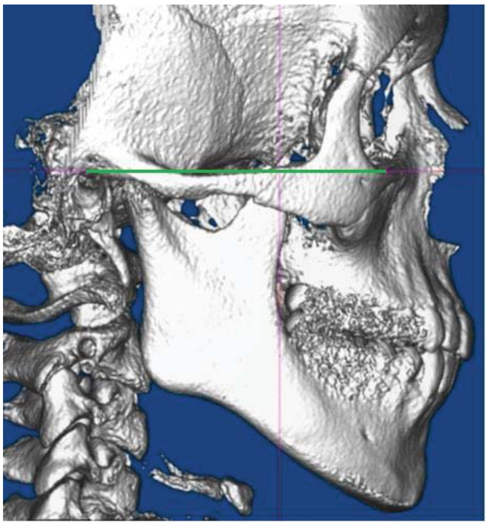
2-dimensional lateral cephalograms were constructed from the CBCT scans with no magnification. A full width lateral cephalogram (lat ceph) was generated to assess sagittal and vertical craniofacial morphology and a partial width (width of the cervical column) to assess skeletal maturity.

Figure 2: Orientation of CBCT scans prior to assessment

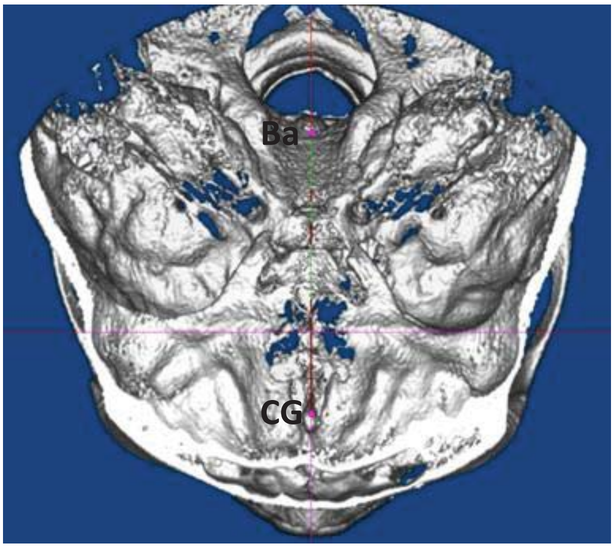
a) Coronal plane; Or = orbitale



b) Sagittal plane; Frankfort plane is indicated by the green line



c) Axial plane; CG = crista galli, Ba = basion



A posteroanterior cephalogram (PA ceph) was generated to assess transverse craniofacial morphology.

5.6 Three-Dimensional Assessment

All assessment and measurements were performed by the same investigator (S.A.) in a blinded fashion. The upper airway volume and minimal cross-sectional area as well as the upper cervical vertebral morphology were assessed 3-dimensionally.

5.6.1 Airway assessment

A new protocol to delineate the upper airway was established according to anatomical margins in children[30,31,36] and previous CBCT studies of children[12,13,15,18,19,87-91] (Table 2, Figure 3a). The following new airway margins were defined:

- Superior: The line passing from the palatal plane (anterior nasal spine; ANS, to posterior nasal spine; PNS) extending to the posterior wall of the pharynx
- Inferior: Line passing from the antero-superior edge of the fourth cervical vertebra (C4) to menton

- Anterior: Line passing from the soft palate to menton
- Posterior: Posterior wall of the pharynx
- Lateral: Respective pharyngeal walls

The margins were outlined on the mid-sagittal plane. The mid-sagittal plane was identified as the sagittal slice that included the anterior nasal spine and incisive canal and confirmed visually using the 3-dimensional volume rendered image. After the mid-sagittal soft palate tip point was identified, it was confirmed on either side (left and right) on sagittal slices where the incisive canal initially reached its minimal width. This was to ensure the anterior boundary was completely in soft issue. If not, the point was modified to ensure it was.

The process of airway segmentation was systemized as follows:

- The 'seed point' was defined as a virtual marker for the region-of-interest demarcation and was placed centrally in the airway region immediately posterior to the soft palate tip (Figure 2a) to facilitate automated segmentation of the airway based on grey-scale values.

- The most appropriate threshold value for each patient was then determined. After the sagittal view was maximized as much as possible while ensuring visualisation of all previously determined margins, the software-determined threshold value was manually adjusted for each dataset (operator-adjusted threshold) until the airway volume (indicated in pink) adequately depicted the airway/ soft tissue interface. Other views were then checked to ensure an adequate threshold was used and there was no ‘bleeding’ (incorrect extension of airway segmentation) into the soft tissues.

The airway volume (mm^3) was then automatically calculated by the software within the defined margins. All measurements were made to the closest one tenth of a cubic millimetre.

For calculation of minimum cross-sectional area, upper and lower limits (red lines, Figure 3b) were then set within the previously defined margins that included both anterior and posterior margins of the airway. This was to ensure that the entire area was calculated and not a partial section created by the difference in airway boundary for volume calculation and the plane of area calculation. Within the defined margins, the software automatically calculated the minimum cross-sectional area (mm^2). All measurements were made to the closest one tenth of a square millimetre.

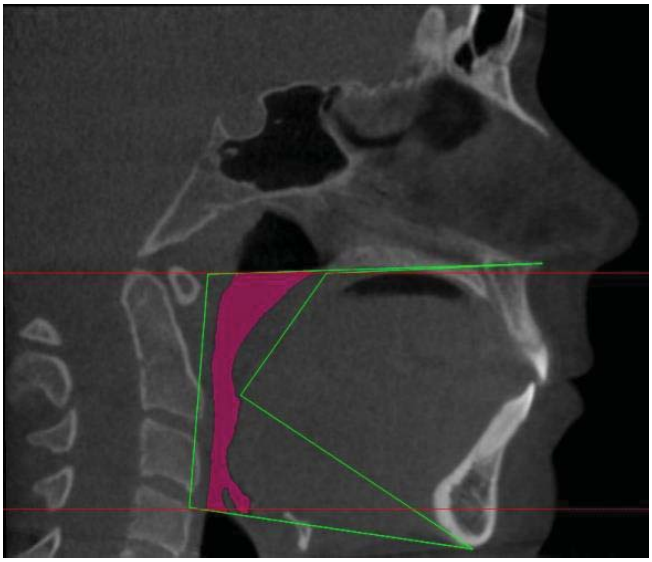
Table 2: Anatomical and technical limits of the upper airway

Limit	Anatomical	Technical
Superior	Hard and soft palate	The line passing from the palatal plane (ANS to PNS) extending to the posterior wall of the pharynx
Inferior	Vallecula (plane of hyoid bone; base of the epiglottis)	Line passing from the antero-superior edge of C4 to menton
Anterior	Circumvallate papillae and the oropharyngeal isthmus	Line passing from the soft palate to menton
Posterior	Respective pharyngeal walls	Posterior wall of the pharynx
Lateral	Respective pharyngeal walls	Respective pharyngeal walls

Figure 3: Upper airway assessment

a) Margins for delineation of the upper airway. Green lines indicate the margins used to delineate the airway according to Table 2.

The yellow point represents the seed point



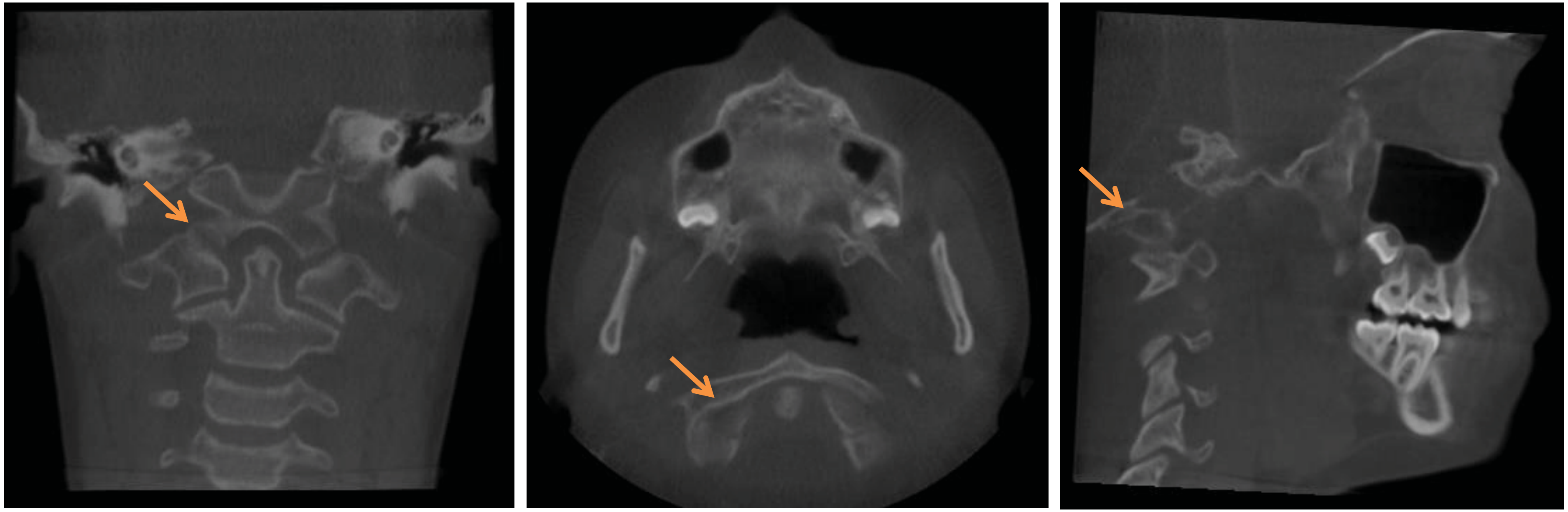
b) Margins for minimal cross-sectional area. The red lines indicate the upper and lower limits used to measure the minimal cross-sectional area.

5.6.2 Assessment of upper cervical vertebral morphology:

The first 4 cervical vertebrae, which are also required for CVM assessment of skeletal maturity, were assessed 3-dimensionally. The multiple planar reconstruction images were simultaneously visualised. Morphology of the upper cervical vertebral column were described according to Sandham[70] and divided into either fusion anomalies or posterior arch deficiency. Fusion anomalies were further divided into fusion, block fusion and occipitilisation. Fusion is defined as the fusion of one cervical vertebrae with another at the articulation facets, neural arch or transverse processes. Occipitilsation is defined as assimilation, either partially or completely, of atlas (C1) with the occipital bone (Figure 4). The definition of block fusion, as modified by Sonnesen and Kjaer[73], is fusion of more than 2 units at the vertebral bodies, articulation facets, neural arch or transverse processes. Posterior arch deficiency included partial cleft and dehiscence. Partial cleft is defined as failure to fuse of the posterior part of the neural arch (Figure 5). Dehiscence is defined as the failure to develop a part of the vertebral unit. If any doubt occurred, the region under consideration was considered to have normal morphology. The principal investigator (S.A.) described all CBCT images in collaboration with the principal supervisor (L.S.)

Figure 4: Occipitalisation seen in the same patient, marked by arrows

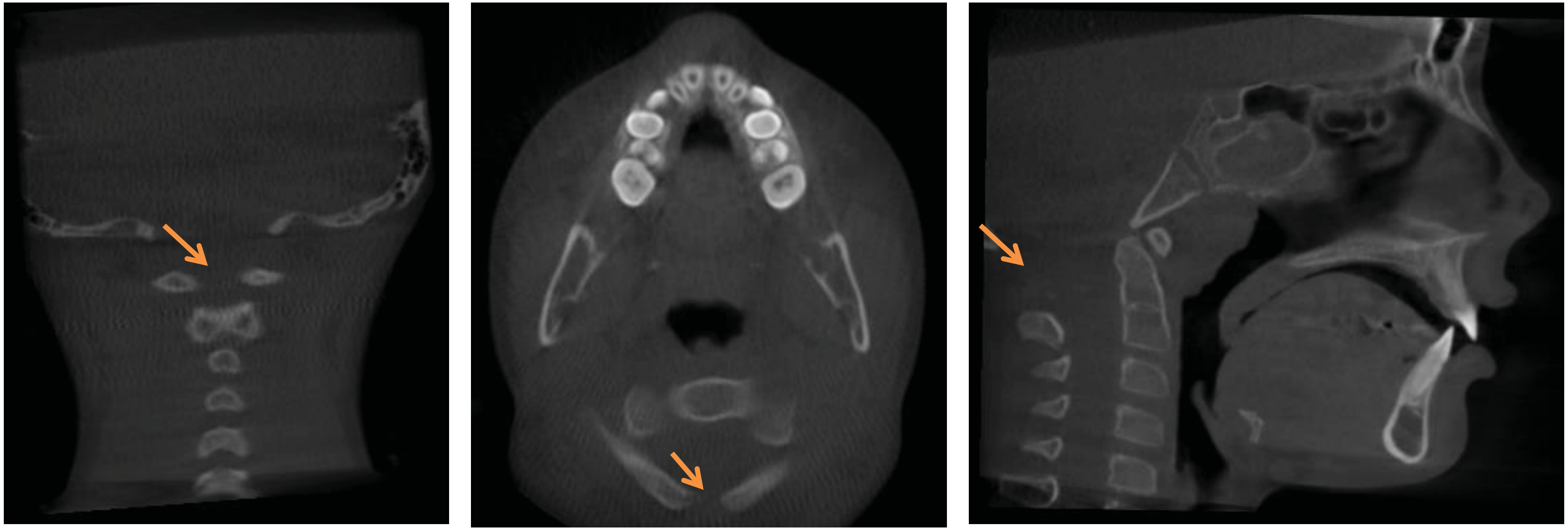
a) Coronal view, b) Axial view, c) Sagittal view



(a) (b) (c)

Figure 5: Partial cleft of C1 seen in the same patient, marked by arrows

a) Coronal view, b) Axial view, c) Sagittal view



(a) (b) (c)

5.7 Two-dimensional Assessment

All landmark identification and measurements were performed by the same investigator (S.A.) in a blinded fashion. Craniofacial morphology and skeletal age were assessed 2-dimensionally.

5.7.1 Assessment of craniofacial morphology

A custom cephalometric analysis was developed in Dolphin version 11.5 and used to make all measurements. Standard craniofacial measurements were made of the cranial base, maxilla and mandible according to Bjørk (1947, 1960)[92,93] and Yoon et al (2004).[94] All measurements were made to the closest one tenth of a degree or millimetre. Descriptions of landmarks, reference lines and angles used in the study are provided in Table 3 and represented visually in Figure 6.

5.7.2 Assessment of skeletal maturation

A partial width (width of the cervical column) lateral cephalogram was used to assess skeletal maturation. This permitted optimal visualisation of cervical vertebra morphology and facilitated cervical staging. Visual inspection via the CVM method according to Baccetti et al,[95] was used to assess skeletal maturation. The skeletal maturation was categorised as pre-pubertal, pubertal and post-pubertal according to Phelan et al.[96]

Table 3: Descriptions of reference points, lines and angles describing craniofacial morphology on lateral and antero-posterior cephalograms

Reference points, lines and angles are according to Solow and Tallgren (1976)[97] and Yoon et al (2004)[94]

Landmark	Abbreviation	Definition
Points		
Sella	S	The centre of sella turcica, the upper limit of which is defined as the line joining the tuberculum and the dorsum sella
Nasion	N	The most anterior point of the fronto-nasal suture
Basion	Ba	The most postero-inferior point on the clivus
A point	A	The most posterior point on the anterior contour of the maxillary alveolar arch
B point	B	The most posterior point on the anterior contour of the mandibular alveolar arch
Pogonion	Pg	The most anterior point on the mid-sagittal mandibular symphysis
Anterior nasal spine	ANS	The apex of the anterior nasal spine

Posterior nasal spine	PNS	The tip of the posterior nasal spine
Menton	Me	The most inferior point on the mid-sagittal mandibular symphysis
Gonion (lat ceph)	Go	The most postero-inferior point on the angle of the mandible, indicated by bisection of the RL to ML
Gonion (PA ceph)	Go and Go’	The most lateral point on the convex margin on the angle of the mandible
Articulare	Ar	The intersection between the external contour of the cranial base and the dorsal contour of the condylar head or neck
Maxillary notch	Mx and Mx’	The intersection of the zygomatic buttress and outline of the tuberosity
Upper 6 occlusal	U6o	The mesio-buccal cusp tip of the maxillary molar
Lower 6 occlusal	L6o	The mesio-buccal cusp tip of the mandibular molar
U1 incisal tip	U1i	The mid-point of the incisal edge of the most prominent upper central incisor
L1 incisal tip	L1i	The mid-point of the incisal edge of the most prominent lower central incisor

Lines

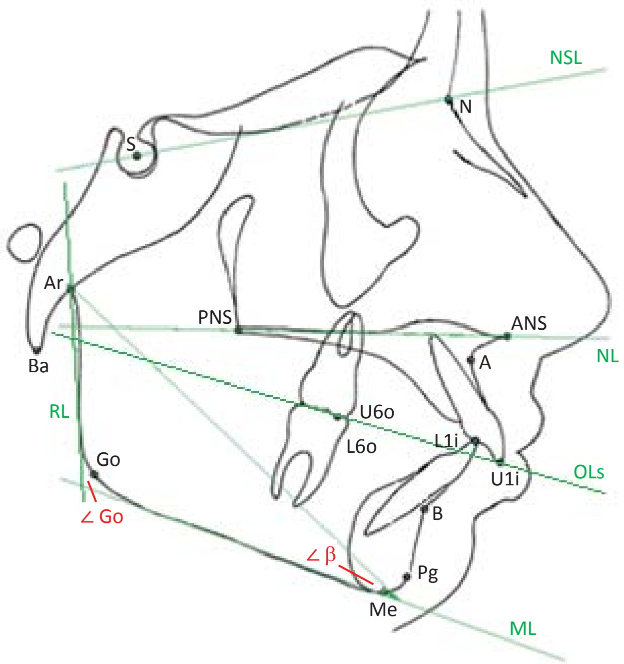
Overjet	OJ	The length difference between U1i and L1i as measured along the Mx occlusal line
overbite	OB	The overlap difference between U1i and L1i as measured perpendicular to

		the Mx occlusal line
Maxillary occlusal line	OLs	The line passing through U6o and U1i
Nasion-sella line	NSL	The line passing through N and S
Nasal line	NL	The line passing through ANS and PNS
Mandibular line	ML	The tangent to the lower boarder of the mandible through Me
Ramal line	RL	The tangent to the posterior boarder of the mandible through Ar
Palatal width	Mx’-Mx	The distance between Mx’ and Mx
Mandibular width	Go’-Go	The distance between Go’ and Go

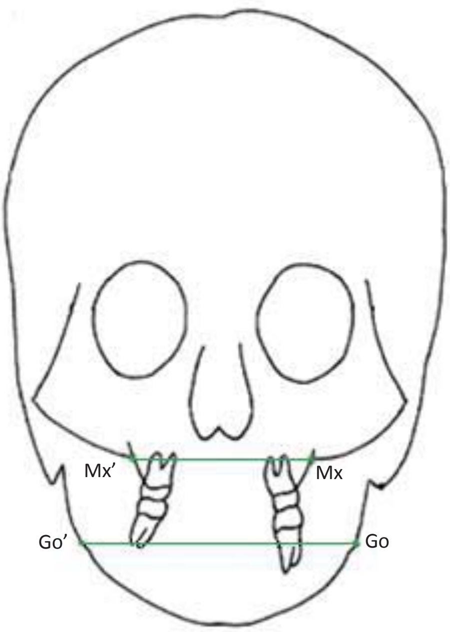
Angles

Gonial angle	∠Go	The angle formed between RL and ML
Beta angle	∠β	The angle formed between a ML and a constructed line from Ar to the intersection between ML and a perpendicular line to it through Pg

Figure 6: Illustrations of reference points, lines and angles describing craniofacial morphology on lateral and antero-posterior cephalograms



a) Lateral Cephalogram. Reference points (black), lines (green) and angles (red) are according to Solow and Tallgren (1976)[97].



b) Antero-posterior Cephalogram. Reference points (black) and lines (green) are according to Yoon et al (2004)[94]

5.8 Method Reliability

In order to test the intra-examiner reliability, 25 scans were randomly selected for each variable and re-measured 2 weeks after the initial measurement. The systematic errors were assessed by calculating the differences between the 2 sets of recordings and tested by paired t-test. The method errors were calculated according to Dahlberg's formula[98] and the Houston[99] reliability coefficient for each of the cephalometric variables and airway dimensions. All numerical data were measured to the closest degree, millimetre, square millimetre or cubic millimetre. Measurement errors were produced to the closest one hundredth of the unit with the percentage error generated to 1 decimal place. The method error of skeletal maturation assessment was assessed with a Cohen's kappa test.[100]

5.8.1 Upper airway dimensions

The validity of the chosen landmarks to delineate the airway and reproducibility of the proposed protocol was assessed prior to adopting it for this study. After training and calibration by the supervisor (LS), the airway was assessed not only by the principal investigator (SA) but also another colleague (YA). The intra-class correlation coefficient (ICC) according to Donner and Koval[101] was calculated to assess intra-observer reliability as well as inter-observer agreement between the measurements of airway volume and minimal cross-sectional area (Table 4). The intra- and inter- observer reliability was high for both the airway volume and minimal cross-sectional area measurements. No systematic error was found between the data ($P > 0.05$) and the method error was 197.5mm^3 (1.9%) for airway volume and 0.6 mm^2 (0.5%) for minimal cross-sectional area. The Houston reliability coefficient and intra-class correlation was 1.0 for each measurement.

5.8.2 Upper cervical vertebral column morphology

Upper cervical vertebral morphology was assessed in collaboration with the supervisor (LS). She has extensive experience in describing the morphology of the cervical vertebral column on cephalograms and CBCT images. The measurement error for the upper cervical vertebral morphology has been previously reported and intra-observer agreement of skeletal maturity was $K = 0.9$.[82]

5.8.3 Craniofacial measurements

For each of the craniofacial measurements (lateral cephalogram and postero-anterior cephalogram), no systematic error was found ($P > 0.05$; Table 5). In the lateral cephalogram, the method error ranged from 0.2 to 0.7 degrees for angular measurements and 0.1 to 0.5 millimetres for linear measurements. The reliability coefficient ranged from 0.9 to 1.0 for angular measurements and was 1.0 for linear measurements (Table 5). In the postero-anterior cephalogram, the measurements were only linear. The measurement error was 0.2 millimetres and the reliability coefficient was 1.0 (Table 5).

5.8.4 Skeletal maturity

Cohen's Kappa test indicated very high intra-observer agreement of skeletal maturity ($K = 0.9$).

5.9 Statistics

The normality of distributions was assessed by parameters of skewness and kurtosis and by Shapiro-Wilks W-test. Airway volume and minimal cross-sectional area differed moderately from the normal distribution. Furthermore, the sample was screened for outliers by box-plots of each variable. No outliers were found.

Associations between airway dimensions and the continuous variables were assessed by the Spearman correlation analysis. Associations between airway dimensions and categorical variables were analysed by analysis of variance (ANOVA). The ANOVAs were followed by post hoc comparisons with the use of Bonferroni tests. Each of the significant associations was then tested for the effect of gender, age and skeletal maturation by linear regression analysis with stepwise backwards elimination.

To assess the most relevant variables for airway dimensions, those that were still statistically significant after correction for age, gender and skeletal maturation were analysed by linear regression analysis with stepwise backwards elimination. The airway dimension (volume and minimal cross-sectional area) was the dependent variable and the statistically significant variables were independent variables. As the airway volume and minimal cross-sectional area were not normally distributed the variables were transformed logarithmically for these analyses. Results from the tests were considered significant at $p < 0.05$. All statistical analyses were performed using SPSS for Windows v. 22.0 (IBM Corp; Armonk, NY).

5.10 Reduction of Bias

In order to reduce potential bias in data collection, a random number generator programme (Research Randomizer Form v4.0 http://www.randomizer.org/form.htm) was used to generate unique codes for the patients for each measurement and recorded on separate spreadsheets. At the end of data collection, the data were collated into the one spreadsheet.

Table 4: Intra- and inter- observer reliability for proposed protocol

Reliability Test	Airway volume (mm^3)		Minimal cross-sectional area (mm^2)	
	Observer 1	**Observer 2**	**Observer 1**	**Observer 2**
Systematic error	None	None	None	None
Method Error	197.5 (1.9 %)	116.5 (1.1 %)	0.6 (0.5 %)	1.2 (0.9 %)
Houston reliability coefficient	1.0	1.0	1.0	1.0
Intra-class Correlation	1.0	1.0	1.0	1.0
	1.0		1.0	

Table 5: Methodology error for craniofacial features

	Systematic error	Method Error	Housten Reliability coefficient
Incisal relationship			
Overjet (mm)	Non	0.2 (5.4%)	1.0
Overbite (mm)	Non	0.2 (8.1%)	1.0
Cranial base angle			
SNBa (degrees)	Non	0.3 (0.2%)	1.0
Sagittal craniofacial dimension			
SNA (degrees)	Non	0.2 (0.3 %)	1.0
SNB (degrees)	Non	0.2 (0.2 %)	1.0
SN-Pg (degrees)	Non	0.2 (0.2%)	1.0
ANB (degrees)	Non	0.2 (5.6%)	1.0
ANPg (degrees)	Non	0.2 (6.8%)	1.0
Vertical craniofacial dimension			
SN-NL (degrees)	Non	0.7 (9.4%)	0.9
SN-MP (degrees)	Non	0.3 (1.0%)	1.0
MMP (degrees)	Non	0.6 (2.5%)	1.0
ANS-Me (mm)	Non	0.2 (0.4%)	1.0
N-ANS (mm)	Non	0.2 (0.4%)	1.0
N-Me (mm)	Non	0.1 (0.1%)	1.0
LAFH (%)	Non	0.2 (0.3%)	1.0
S-Ba (mm)	Non	0.2 (0.5%)	1.0

S-PNS (mm)	Non	0.5 (1.1%)	1.0
S-Go (mm)	Non	0.4 (0.5%)	1.0
Transverse craniofacial dimension			
Mx'-Mx (mm)	Non	0.2 (0.4%)	1.0
Go'-Go (mm)	Non	0.2 (0.2%)	1.0
Mandibular shape			
Gonial angle (degrees)	Non	0.6 (0.5%)	1.0
β-angle (degrees)	Non	0.2 (1.1%)	1.0

mm = millimetres

^{0} = degrees

% = percentage

6.0 Results

Descriptive demographics of the sample are provided in Tables 1 and 6. There were no significant differences in airway dimensions between sexes, so the subjects were combined for subsequent analyses. 54.3% of the population were in the pre-pubertal stage of skeletal maturation, 29.5% in pubertal and 16.2% post-pubertal. The morphological occlusion according to Angle's classification included 36.2 % Class I, 56.2 % Class II, and 6.7 % Class III. 72.4 % of the children had normal upper cervical vertebral morphology and only 2.9 % had occipitalisation (Figure 2) and 24.8 % had a partial cleft (Figure 3).

The mean volume for the entire sample of patients was 10077.3 ± 4251.7 mm^3 with a minimum of 2875.1 mm^3 and maximum of 23519.3 mm^3. The mean minimal cross-sectional was 120.8 ± 61.0 mm^2 with a minimum of 23.5 mm^2 and maximum of 348.5 mm^2. The mean values for the upper airway and craniofacial morphology are presented in Table 6.

Table 6: Upper airway dimensions and dentofacial morphology in 105 children (61 girls and 44 boys)

	Min	Max	Mean	Standard Deviation (SD)
UPPER AIRWAY DIMENSIONS				
Volume (mm^3)	2875.1	23519.3	10077.3	4251.7
Minimal cross-sectional area (mm^2)	23.5	348.5	120.8	61.0
DENTOFACIAL MORPHOLOGY				
Incisal relationships				
Overjet (mm)	-2.5	12.7	4.3	2.8
Overbite (mm)	-4.6	6.3	2.4	1.6
Cranial base angle				
SNBa (degrees)	118.3	145.0	132.7	5.1
Sagittal craniofacial dimension				
SNA (degrees)	74.7	89.1	81.2	2.9
SNB (degrees)	69.3	84.0	77.1	3.1
SN-Pg (degrees)	69.3	84.9	77.2	3.2
ANB (degrees)	-2.1	8.9	4.1	2.6
ANPg (degrees)	-4.4	10.5	4.0	2.9
Vertical craniofacial dimension				
SN-NL (degrees)	.6	15.9	7.7	3.2
SN-MP (degrees)	23.0	48.0	34.3	5.4
MMP (degrees)	14.8	45.6	26.6	5.4

ANS-Me (mm)	48.7	73.2	57.6	5.0
N-ANS (mm)	36.7	54.1	46.6	3.5
N-Me (mm)	89.7	123.5	104.2	7.0
LAFH (%)	50.1	61.4	55.2	2.3
S-Ba (mm)	33.7	49.5	41.2	2.6
S-PNS (mm)	37.1	50.0	42.7	2.5
S-Go (mm)	56.5	79.8	65.7	4.6
Transverse craniofacial dimension				
Mx’-Mx (mm)	46.7	68.9	60.1	3.7
Go’-Go (mm)	71.9	96.8	86.1	5.0
Mandibular shape				
Gonial angle (degrees)	109.2	141.2	124.7	5.9
β-angle (degrees)	13.3	26.0	20.0	2.4

The airway volume and minimal cross-sectional area were greater in children of an older age than younger age (p = 0.000 and 0.003, respectively). Furthermore, the airway volume increased significantly with skeletal maturation from pre-pubertal to pubertal ($p<0.001$) and from pre-pubertal to post-pubertal ($p<0.001$; Figure 7). The upper airway minimal cross-sectional area only increased significantly from pre-pubertal to pubertal ($p<0.01$; Figure 8). Gender, molar occlusion and upper cervical vertebral morphology were not significantly associated with airway volume or minimal cross-sectional area.

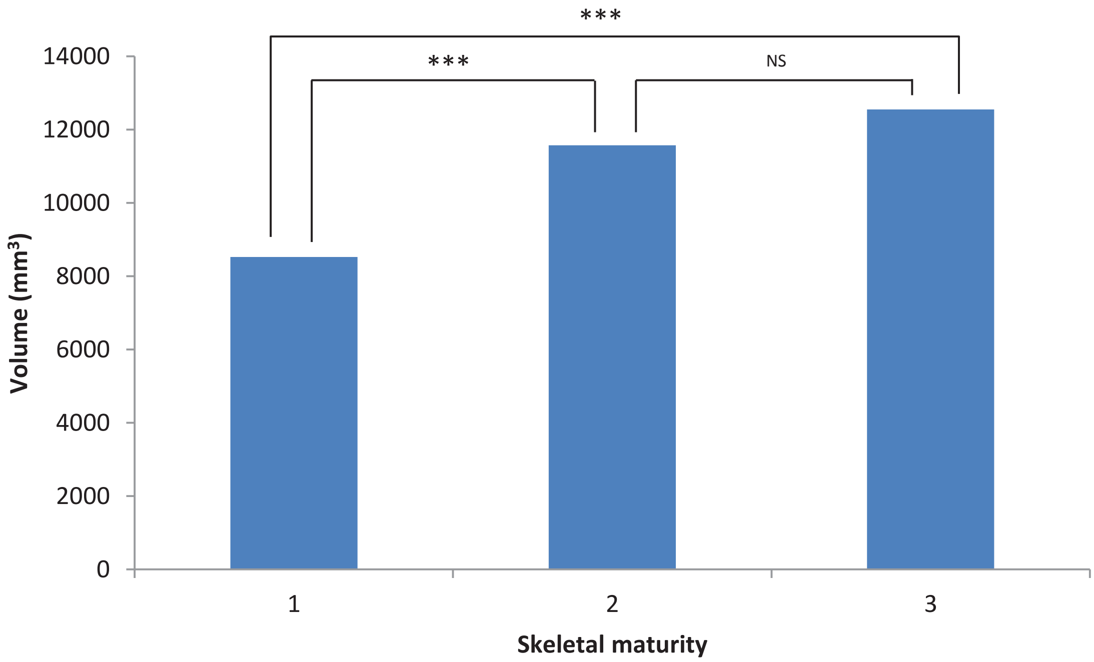
A number of low to moderate associations between upper airway volume and craniofacial morphology were found: anterior facial height (N-Me; r = 0.42***), upper anterior facial height (N-ANS r = 0.47***), lower anterior face height (ANS-Me; r = 0.29**), posterior cranial base length (S-Ba; r = 0.41***), upper posterior face height (S-PNS; r = 0.32***), posterior face height (S-Go; r = 0.45***), maxillary width (Mx'-Mx; r = 0.43***) and mandibular width (Go'-Go; r = 0.59***) were positively correlated and sagittal jaw relationship to pogonion (ANPg; r = -0.23*) negatively correlated (Table 7). However, after adjustment for the effect of age, skeletal maturity and gender, only few associations remained statistically significant, which all had a moderate association: anterior facial height (N-Me; r = 0.51*), upper anterior facial height (N-ANS; r = 0.52*), maxillary width (Mx'-Mx; r = 0.53**) and mandibular width (Go'-Go; r = 0.60***) were positively associated (Table 8, Figure 9).

A number of low associations between craniofacial morphology and upper airway minimal cross-sectional area were also found: anterior facial height (N-Me; r = 0.24*), upper anterior facial height (N-ANS; r = 0.31***), posterior cranial base length (S-Ba; r = 0.26**), upper posterior face height (S-PNS; r = 0.24*), posterior face height (S-Go; r = 0.27**), maxillary width (Mx'-Mx; r = 0.31***) and mandibular width (Go'-Go; r = 0.41***) were positively correlated and sagittal jaw relationship to both B-point and pogonion (ANB; r = -0.23* and ANPg; r = -0.29**) negatively correlated (Table 9). However, after adjustment for the effect of age, skeletal maturity and gender, only few associations remained statistically significant, which all had a low association: maxillary width (Mx'-Mx; r = 0.35**) and mandibular width (Go'-Go; r = 0.35***) were positively associated whereas sagittal jaw relationship to pogonion (ANPg ; r = -0.35*) was negatively associated with airway minimal cross-sectional area (Table 10, Figure 9).

For airway volume the most relevant factors were mandibular width (Go’-Go)*** and age**, (r^2 = 0.36, Table 11, Figure 10). For minimal cross-sectional area the most relevant factors were mandibular width (Go’-Go) *** and the sagittal jaw relationship to pogonion (ANPg) * (r^2 = 0.19, Table 11, Figure 10).

Therefore, hypotheses 1 and 3 are rejected and hypothesis 2 is accepted. Pharyngeal airway dimensions are associated with dentofacial dimensions and skeletal maturity and not associated with upper cervical vertebral column morphological deviations.

Figure 7: Airway volume in relation to skeletal maturity

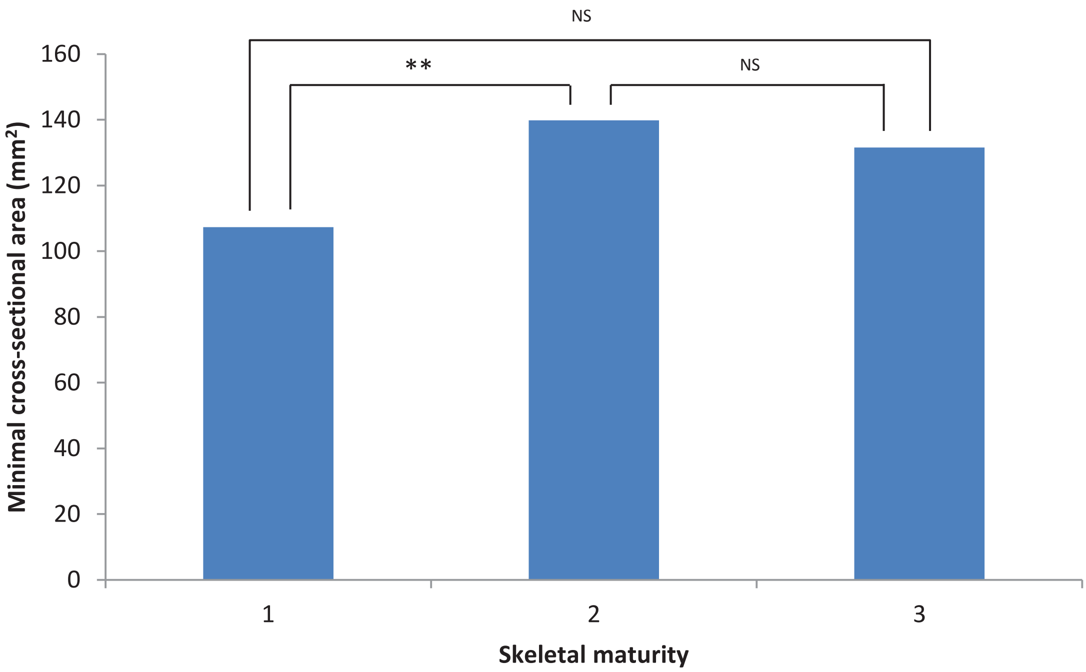


NS, Not significant

* p ≤ 0.05; ** p ≤ 0.01; *** p ≤ 0.001

1 = pre-pubertal, 2 = pubertal, 3 = post-pubertal

Figure 8: Airway minimal cross-sectional area in relation to skeletal maturity



NS, Not significant

* p ≤ 0.05; ** p ≤ 0.01; *** p ≤ 0.001

1 = pre-pubertal, 2 = pubertal, 3 = post-pubertal

Table 7: Significant associations ($p < 0.05$) in 105 children (61 girls and 44 boys) between airway volume and gender, age, skeletal maturity, upper cervical vertebral morphology, craniofacial features and occlusion (prior to adjustment for the effect of gender, age and skeletal maturation)

Variable	Correlation coefficient (r)	Strength of Correlation	p-value
Age	0.48	Moderate	***
Skeletal maturation	0.41	Moderate	***
Sagittal craniofacial dimension			
ANPg	-0.23	Weak	*
Vertical craniofacial dimension			
N-me (mm)	0.42	Moderate	***
ANS-Me (mm)	0.29	Weak	**
N-ANS (mm)	0.47	Moderate	***
S-Ba (mm)	0.41	Moderate	***
S-PNS (mm)	0.32	Weak	***
S-Go (mm)	0.45	Moderate	***
Transverse craniofacial dimension			
Mx'-Mx	0.43	Moderate	***
Go'-Go	0.59	Moderate	***

NS, Not significant; * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$

Table 8: Significant associations (p < 0.05) in 105 children (61 girls and 44 boys) between airway volume and gender, age, skeletal maturity, upper cervical vertebral morphology, craniofacial features and occlusion (after adjustment for the effect of gender, age and skeletal maturation)

Variable	Correlation coefficient (r)	Strength of Correlation	p-value
Vertical craniofacial dimension			
N-Me (mm) ‡	0.51	Moderate	*
N-ANS (mm) ‡	0.52	Moderate	*
Transverse craniofacial dimension			
Mx’-Mx ‡	0.53	Moderate	**
Go’-Go ‡	0.60	Moderate	***

‡ Also significant for the effect of age

NS, Not significant; * p ≤ 0.05; ** p ≤ 0.01; *** p ≤ 0.001

Table 9: Significant associations ($p < 0.05$) in 105 children (61 girls and 44 boys) between airway minimal cross-sectional area and gender, age, skeletal maturity, upper cervical vertebral morphology, craniofacial features and occlusion (prior to adjustment for the effect of gender, age and skeletal maturation)

Variable	Correlation coefficient (r)	Strength of Correlation	p-value
Age	0.31	Weak	***
Skeletal maturation	0.23	Weak	*
Sagittal craniofacial dimension			
ANB	-0.23	Weak	*
ANPg	-0.29	Weak	**
Vertical craniofacial dimension			
N-Me (mm)	0.24	Weak	*
N-ANS (mm)	0.31	Weak	***
S-Ba (mm)	0.26	Weak	**
S-PNS (mm)	0.24	Weak	*
S-Go (mm)	0.27	Weak	**
Transverse craniofacial dimension			
Mx'-Mx	0.31	Weak	***
Go'-Go	0.41	Weak	***

NS, Not significant; * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$

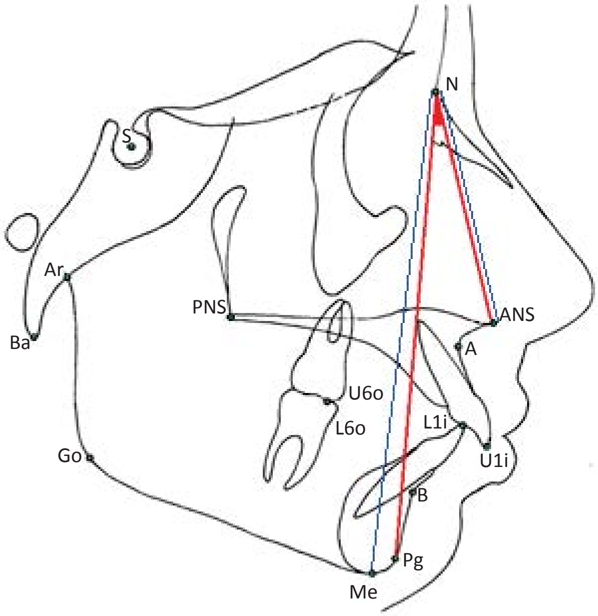
Table 10: Significant associations ($p < 0.05$) in 105 children (61 girls and 44 boys) between airway minimal cross-sectional area and gender, age, skeletal maturity, upper cervical vertebral morphology, craniofacial features and occlusion (after adjustment for the effect of gender, age and skeletal maturation)

Variable	Correlation coefficient (r)	Strength of Correlation	p-value
Sagittal craniofacial dimension			
ANPg ǂ	-0.35	Weak	*
Transverse craniofacial dimension			
Mx'-Mx ǂ	0.35	Weak	**
Go'-Go	0.35	Weak	***

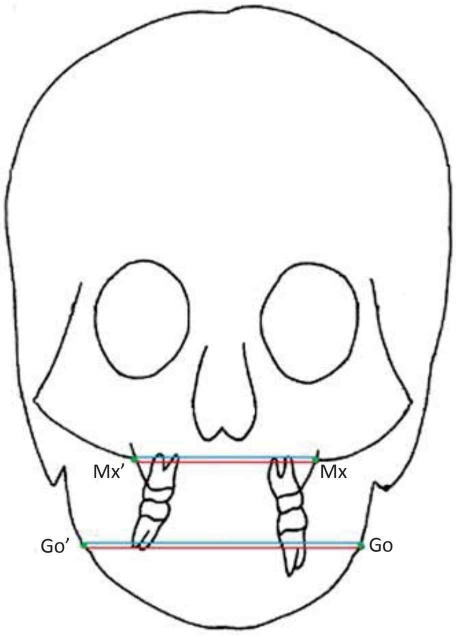
ǂ Also significant for the effect of age

NS, Not significant; * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$

Figure 9: Illustrations of significant cephalometric factors after correction for the effect of age, gender and skeletal maturation



A) Lateral cephalogram



B) Antero-posterior cephalogram

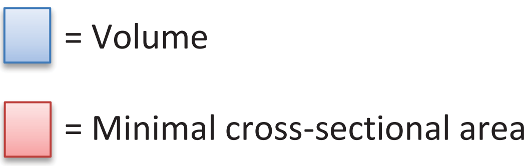
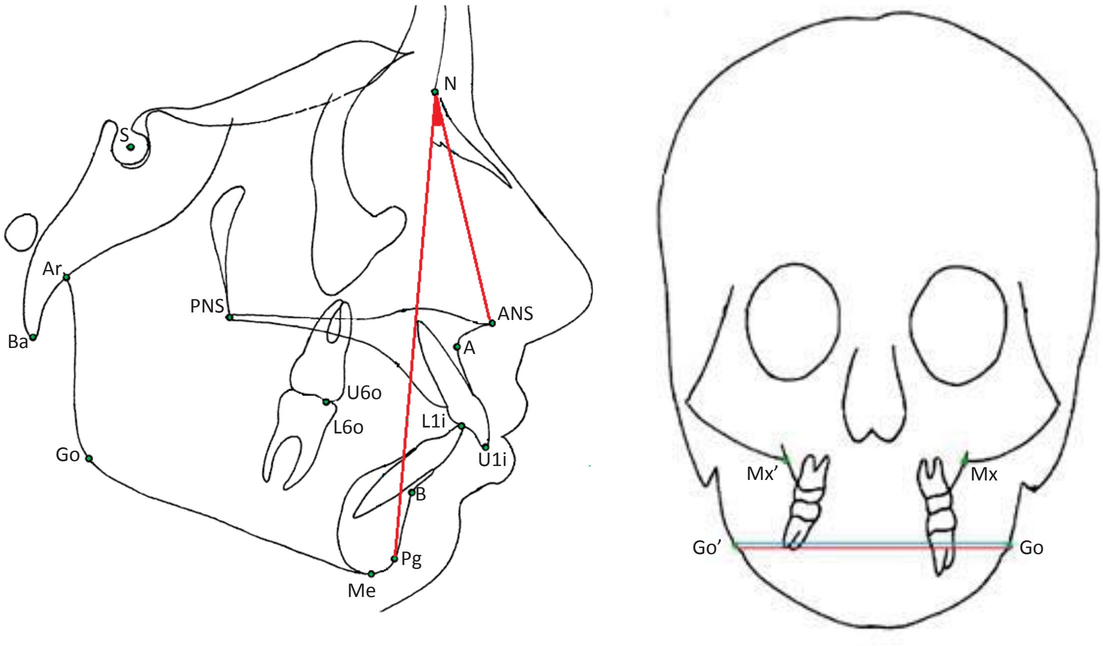


Table 11: Results from the multiple regression analysis

Factor	Correlation coefficient of the model (r)	Coefficient of determination of the model (r^2)	P-value of the significant factors of the models
Volume			
Go'-Go	0.60	0.36	0.000
Age			0.007
Minimal cross-sectional airway			
ANPg	0.43	0.19	0.032
Go'-Go			0.001

Figure 10: Illustrations of the most relevant cephalometric factors for airway dimensions



A) Lateral cephalogram

B) Antero-posterior cephalogram

= Volume

= Minimal cross-sectional area

7.0 Discussion

7.1 Material

This study is of a retrospective cross-sectional design with a convenient sample of pre-orthodontic children and therefore the sample does not represent the population in general. All CBCT scans were collected from a database of previously taken CBCT scans for orthodontic reasons. No patients were contacted or CBCT scans taken for the purpose of this study.[102] No detailed power analysis was conducted as the sample was limited to the available data. Such a study has not been previously reported in the literature. Further research with larger sample sizes representative of the population is required.

The craniofacial morphology in the present study was in general agreement with average norms and standard deviations.[92,93] Furthermore, more than 1/3 of the children had Class 1 molar relationship. This indicated that the deviations in the craniofacial morphology and molar occlusion were not too extreme in the present study of pre-orthodontic children. This could contribute to the lack of associations between some of the assessed variables. Subsequently, it would be of interest to repeat this study with more extreme malocclusions.

The distribution of the craniofacial morphology and the occurrence of malocclusion could explain the relatively low prevalence of upper cervical vertebral column morphological deviations (27.6%) found in the present study. This falls within the range of previously reported upper cervical vertebral column morphological deviations in pre-orthodontic children who were used as a control group to compare cleft lip and palate patients.[70,103-106] In these studies, deviations of the upper cervical vertebral column occurred in 0.8% to 31% of pre-orthodontic children. Previously it has been reported that the prevalence of upper cervical vertebral column morphological deviations in patients with severe skeletal malocclusion occurred in 41% to 61%.[73-76]

7.2 Methodology

CBCT has become an unprecedented diagnostic method to analyse the airway 3-dimensionally[1]. It has broadened the possibilities for quantification of upper airway dimensions. Lateral cephalograms provide

2-dimensional information (height and depth) of a 3-dimensional structure, therefore restricting accurate assessment of the complexity and size of these structures. The axial plane, which is not visualised on a lateral cephalogram, is also a physiologically relevant plane because it is perpendicular to airflow.[107,108] Previous studies that relied on 2-dimensional cephalometry to assess upper airway dimensions were limited to drawing major conclusions from the narrowest antero-posterior sections in the airway. Simply measuring the narrowest constriction in a 2-dimensional image does not adequately represent the spatial relationship of the associated structures in all 3 dimensions.[109]

With CBCT, anatomic landmarks are easily identified without superimposition or distortion.[110] Magnification is negligible with isotropic resolution and a 1:1 ratio in all 3 planes.[111] Several studies have demonstrated its use for evaluation of the upper airway to be accurate and reliable.[1,62,112]

The variables analysed in this study were generally assessed with standard, commonly used methodology.[70,73,92-96] Adequate lateral cephalograms can easily be generated from CBCT data.[113-117] Several studies have assessed their accuracy either using dry skulls[113-115] or *in vivo* comparison.[116,117] All studies indicated that measurements from CBCT-generated and conventional cephalograms were similar, avoiding the need for further imaging when CBCT scans were taken for orthodontic diagnosis. Furthermore, van Vlijmen et al[115] and Chen et al[118] demonstrated that measurements on CBCT-generated cephalograms were more reproducible than those on conventional radiographs.

Among methods for assessment of skeletal maturity, the cervical vertebral maturation (CVM) method has recently gained popularity because of its proposed ease and accuracy.[119-121] Since the vertebrae are already recorded on the lateral cephalogram taken for orthodontic records[95], additional radiographic exposure to the patient is not needed. However, reproducibility of the CVM method has been questioned.[122]

The literature is controversial in regards to use of the CVM method for determining skeletal maturity. Various CVM methods have been proposed. The most frequently used modification of the CVM method was based on the cephalometric analyses of longitudinal records of a small sample size (9 boys and 15 girls) that at best can be considered a convenient sample with unknown representativeness and the sexes were pooled.[123] Several CVM stages were established that were intended to correspond to skeletal maturity. Two systematic reviews[120,121] have been conducted to assess the validity of the CVM method for assessment of skeletal maturity. The first found that although some studies indicated that the CVM method had good correlation with the hand-wrist method and demonstrated considerable levels of reproducibility, methodological flaws were associated with these studies. A meta-analysis could not be conducted due to the variation of CVM and hand-wrist maturation methods. In the more recent systematic review,[121] the authors concluded that the CVM method was reliable and could replace the hand-wrist radiograph to predict the pubertal growth spurt. However, the inclusion/exclusion criteria were not as stringent as the previous review. A meta-analysis was conducted on the Bacetti et al method used in this study either with or without gender distinction and was found to have a moderate to strong correlation ($r = 0.688$ to 0.878). However, even according to the authors' criteria, 50 percent of the studies were not of high quality. The authors recommended caution of the results due to the use of convenient samples in the studies analysed. Both reviews indicated that generally the level of evidence was low and more high quality studies were required. Furthermore, questions such as reproducibility of the methods have not been elucidated. In the present study, the CVM method[95] was used to assess skeletal maturation in this study to avoid the additional radiation exposure of hand/wrist radiographs and the information was easily accessible from the CBCT data.

In a systematic review of CBCT studies in adults and children, Guijarro-Martínez and Swennen[1] demonstrated that anatomical delineation of the upper airway varied amongst studies. Therefore, accurate interpretation of quantitative analyses of the airway and unbiased comparison between studies is difficult. A standardised, consistent, reproducible method for 3-dimensional airway analysis in children is still pending. A summary of the anatomical margins used in previous CBCT studies that included oropharyngeal assessment of healthy children is summarised in Table 12. There was a lack of airway delineation according to anatomical boundaries in children[13,15,19,87,89-91] and/or easily mobile soft tissue landmarks were used.[18,88] Furthermore, anterior or posterior anatomical margins were generally not described (Table 12).

CBCT is a low contrast imaging medium which can only adequately differentiate between considerably different radiographic densities, such as air and soft tissue, soft tissue and bone. However, soft tissue contrast is poor.[62,124-127] Anatomically, the airway is surrounded by soft tissue of varying thickness.[30,31]

Table 12: Anatomical landmarks in previous CBCT studies that included oropharyngeal assessment in healthy children

Article	Anatomical Landmarks			
	Superior	Inferior	Anterior	Posterior
Iwasaki et al (2009)[14]	Hard palate	Base of epiglottis	-	-
Kim et al (2010)[17]	Axial plane parallel to Frankfurt Horizontal passing through PNS	Axial plane parallel to Frankfurt Horizontal passing through superior margin of epiglottis	-	-
El and Palomo (2011[15], 2013[19], 2014[87])	Palatal plane (ANS-PNS) and extending to posterior wall of pharynx	Plane parallel to palatal plane that passes from the most antero-inferior point of the second cervical vertebrae (C2)	-	-
Oh et al (2011)[16]	Plane perpendicular to the sagittal plane through PNS and lower medial boarder of the first cervical vertebra	Plane tangent to the most caudal medial projection of the third cervical vertebrae perpendicular to the sagittal plane	-	-
Alves et al (2011[88], 2012[18])	Edge of hard palate to the posterior of the pharynx (parallel to Frankfurt Horizontal)	Tip of epiglottis on a plane parallel to Frankfurt Horizontal	-	-
Yoshihara et al (2012)[128]	Nasal floor (plane parallel to Frankfurt Horizontal plane that passes through the PNS)	Epiglottic plane (base of epiglottis parallel to Frankfurt Horizontal)	-	-

Schendel et al (2012)[12]	posterior nasal spine (PNS)	Anterior-superior edge of C4, which is generally consistent with the position of the epiglottis	-	-
Chiang et al (2012)[13]	Palatal plane	Lowermost border of C4		
Claudino et al (2013)[90]	Palatal plane extended to the posterior pharyngeal wall	Plane parallel to the palatal lane that intersected the lower and most anterior point of C4	-	-
Diwakar et al (2014)[89]	Line joining the ANS-PNS and extending to the posterior pharyngeal wall	Line parallel to ANS-PNS plane, passing through the antero-inferior border of C2	-	-
Zheng (2014)[20]	Horizontal line through the posterior nasal spine (PNS)	Horizontal line passing from the most antero-inferior point of C2		
Celikoglu et al (2014)[91]	A plane perpendicular to the sagittal plane that includes the posterior nasal spine and the lower medial border of the first cervical vertebrae	Plane tangent to the most caudal medial projection of the third cervical vertebra perpendicular to the sagittal plane	A vertical plane through the point (the intersection of vertical plane from sella to nasion-basion plane) to the sagittal plane at the lowest border of the vomer	Posterior wall of the pharynx

Table 13: Airway volume and minimal cross-sectional area reported in previous studies that included oropharyngeal assessment in healthy children

Article	Age range (years)	Mean age (years)	Skeletal pattern/category	Airway Volume (mm^3)	Minimal cross-sectional area (mm^2)
Iwasaki et al (2009)[14]	NR	8.8 ± 1.0	Class 1	6260.15 ± 3010.03	NR
		8.4 ± 1.0	Class 3	7326.89 ± 2593.40	NR
Kim et al (2010)[17]	9.08-12.92	11.19 ± 1.28	Group 1 (ANB angles ranged from 2^0 to 5^0)	1581.23 ± 509.83 (upper) 3278.00 ± 1101.55 (lower)	NR
			Group 2 (ANB > 5^0)	1402.92 ± 662.49 (upper) 2498.77 ± 1095.03 (lower)	NR
El and Palomo (2011)[15]	14-18	15.6 ± 0.6	Class I (1^0 ≤ ANB ≤ 3^0)	7762.3 6 ± 2783.7	NR
		15.4 ± 0.6	Class II (ANB > 3^0)	6292.8 6 ± 2709.9	NR
		15.4 ± 0.8	Class III (ANB < 1^0)	8042.9 6 ± 2407.7	NR
			SNA ≥ 80^0	7375.3 ± 2759.9	NR
			SNA < 80^0	7192.3 ± 2713.0	NR
			SNB ≥ 78^0	7617.2 ± 2601.5	NR

			SNB < 78^0	6645.5 ± 2956.3	NR
Oh et al (2011)[16]	10-13	11.7 ± 1.11	Class I	4448.44 ± 3019.59	NR
			Class II	4189.29 ± 3072.85	NR
			Class III	4745.63 ± 3995.34	NR
Alves et al (2011)[88]	8-10	9.16 ± 0.64	Nasal breathers	8171.31 ± 1710.28	137.42 ± 44.91
			Mouth Breathers	5594,70 ± 1878.76	86.85 ± 39.97
Alves et al (2012)[18]	8-10	9.16 ± 0.64	Group 1 (ANB angles ranging from 2^0 to 5^0)	7588.82 ± 1892.75	124.16 ± 46.53
			Group 2 (ANB > 5^0)	5561.92 ± 1778.13	92.82 ± 48.15
Yoshihara et al (2012)[128]	9-12	10.9	Juvenile Control	8852.6 ± 2992.8	NR
	13-17	15.4	Adolescent Control	13474.9 ± 4274.9	NR
Schendel et al (2012)[12]	6-8			7.18 ± 3.4 cm^3	77.70 ± 48.78
	9-11			8.39 ± 3.45 cm^3	89.89 ± 47.77
	12-14			11.62 ± 4.79 cm^3	128.64 ± 66.31
	15-17			14.83 ± 6.00 cm^3	169.13 ± 86.19
	18-20			14.9 ± 5.35 cm^3	171.55 ± 113.98
Chiang et al (2012)[13]	8-18	13.2 ± 2.5		11125.4 ± 4402.5	101.9 ± 47.4

Diwakar et al (2014)[89]	12-14	NR	Control	11.38 ± 5.92	NR
El and Palomo (2013)[19]	14-18	15.64 ± 0.50	Class 1 (81 ≥ SNA ≥ 77; 80 ≥ SNB ≥ 76; 3 ≥ ANB ≥ 1)	6956.10 ± 1752.96	NR
			Class II MxP (SNA > 81; 80 ≥ SNB ≥ 76; ANB > 3)	6638.10 ± 3126.54	NR
			Class II MdR (81 ≥ SNA ≥ 77; SNB < 76; ANB > 3)	5837.80 ± 2812.3	NR
			Class III MxR (SNA < 77; 80 ≥ SNB ≥ 76; 3 ≥ ANB < 1)	6978.32 ± 1804.46	NR
			Class III MdP (81 ≥ SNA ≥ 77; SNB > 80; ANB < 1)	9332.60 ± 2468.67	NR
Zheng (2014)[20]	14-18	15.65 ± 1.39	Class I	8673.7 ± 2707.3	235.9 ± 89.8
			Class II	5207.5 ± 1662.1	160.3 ± 46.7
			Class III	12505.6 ± 2403.9	331.5 ± 58.8
Celikoglu et al (2014)[91]	NR	13.4 ± 2.0	Control	17134.5 ± 3972.8	NR
El and Palomo (2014)[87]	NR	14.10± 1.44	Control	8053.5 ± 2658.8	NR
Di Carlo et al (2014)[21]	13-43	NR	Overall	12647.4 ± 3556.9	NR
Feng et al (2015)[129]	9-43	11.81 ± 1.59	≤ 15 years	16334.96 ± 7220.58	NR
		21.09 ± 5.74	>!5 years	21704.02 ± 6810.72	NR

NR = not reported

Radiographically, the lateral and posterior pharyngeal walls are easily identifiable. Therefore, in the present study, these anatomical structures were used to delineate the corresponding margins. This is in agreement with a previous study where the posterior wall of pharynx was used to delineate the posterior airway margin.[91]

Anteriorly, superiorly and inferiorly, identification of the pharyngeal airway margins is much more complicated due to the close association with mobile soft tissues.[30,31,127] However, hard tissue points that can be used to develop margins that approximated the soft tissue boundaries are easily identifiable (Table 2). Furthermore, the hyoid bone and soft tissue of the airway can easily move depending on the respiration state of the patient which can be an issue with children, especially with longer scan acquisition times, sometimes resulting in movement artefact.[130,131] In the present study the superior margin was defined according to a plane through the anterior nasal spine (ANS) and the posterior nasal spine (PNS). This is in agreement with previous studies.[13,15,19,87,89,90]

As patients are in occlusion during scan acquisition, a plane from the antero-superior point of C4 to menton was used in this study to demarcate the inferior margin. The plane represents the anatomical inferior boundary of the oropharyngeal airway[12] as well as being approximately parallel to the palatal plane.

In the present study, the soft palate was used to demarcate the anterior limit of the airway. A soft tissue landmark had to be used for this margin because no hard tissue landmarks could be identified in order to delineate the airway according to anatomical limits. In a previous study that validated delineation of the airway in adults,[132] the anterior limit was the frontal plane perpendicular to Frankfurt Horizontal passing through PNS. However, by that method, parts of the oral cavity were included in some measurements. The landmarks used in the present study have been shown to pass through the structures that anatomically boarder the oropharynx in children.[36]

Airway dimensions are influenced by dynamic variables such as respiration state of the patient,[1,3] head posture[1,22,23] and mobility of the soft tissues.[1,3]

Patient positioning for the scan is very important. The patient can either be scanned in a vertical seated or upright position or supine position, depending on the CBCT apparatus. Data gathered from patients sitting or standing cannot be adequately compared to those obtained with the individual in the supine position due to the gravitational effects on oropharyngeal structures.[65] The upper airway and associated soft tissues morphologically change as a result of gravity and posture.[22,23,133] Because the upright position is closer to the natural head posture and recommended for baseline assessment of upper airway morphology and dimensions,[1] the scans in the present study were obtain from patients scanned in a vertical seated position. The children were seated in a standardised position to maintain consistency amongst the scans. However, this is not a true representation of natural head posture or cranio-cervical angle, which could influence the outcomes of this study.

7.3 Associations between variables assessed

7.3.1 Airway dimensions associated with age, gender and skeletal maturation

During active growth, upper airway dimensions increase.[11-13] This is in agreement with findings in the present study. Furthermore, growth and development of the upper airway is influenced by changes in the bony framework until maturity is reached.[11] However, few studies have described the relationship between age and airway dimensions and no study has previously assessed the associations between skeletal maturity and upper airway dimensions in children.

The dimensional airway changes in relation to skeletal maturation observed in this study could reflect growth-related changes of the bony structures surrounding the pharyngeal airways. Previous studies of upper airway dimensions in children focused more on the patient's age. In this study, similar airway dimensional changes occurred with age as with skeletal maturity. In accordance with other studies,[12,13] airway volume and minimal cross-sectional area were positively correlated with age in the child population. Therefore hypothesis 3 is accepted.

The extent of growth is an important consideration when comparing average airway volumes amongst studies. However, direct comparison is often difficult due to the variation in anatomical landmarks used to identify the upper airway (Table 12). Yoshihara et al[128] assessed the oropharyngeal airway of growing Japanese girls with and without cleft lip and plate. In the control (no cleft) juvenile group (mean age 10.9 years), the average airway volume was 8852.6 ± 2992.8 mm^3, which is much smaller than the results from this study. However, the lower airway margin in the Yoshihara et al[128] study was more superiorly positioned. Schendel et al[12] assessed growth of the upper airway from 6 to 60 years of age with a very large sample size of 1300 patients. The airway was assessed superiorly from the posterior nasal spine to antero-superior edge of C4 inferiorly, but it was not clear in relation to which plane. The average airway volume and minimal cross-sectional area was 8.39 ± 3.45 cm^3 and 89.89 ± 47.77 mm^2 for the 9 to 11 year old group and 11.62 ± 4.79 cm^3 and 128.64 ± 66.31 mm^2 for the 12 to 14 year old group. The airway volume measurements from this study fall within those reported by Schendel et al,[12] but the minimal cross-sectional area measurements are slightly larger. In addition to the variation in delineation of the airway, the difference in CBCT machine, scan protocol, third party software to assess the scans and method of airway volume calculation could contribute to the varying results. [134] A summary of airway volumes and minimal cross-sectional areas from other studies that have assessed oropharyngeal dimensions in healthy children is provided in Table 13.

In the present study, no statistically significant gender differences were found with airway volume or minimal cross-sectional area, which is in agreement with previous findings.[15-17,20,88] However, one study found that boys not only had a longer and larger airway than girls but also experienced a quicker increase in dimensions after 11 years of age.[13]

7.3.2 Airway dimensions associated with craniofacial morphology

In previous studies, craniofacial dimensions were generally assessed on CBCT-generated lateral cephalograms and were also done in this study.[14-19] Various studies found a weak to moderate association with sagittal craniofacial dimensions and upper airway dimensions in regards to volume and minimal cross-sectional area.[15,17-20] In general, airway dimensions were negatively correlated to the sagittal jaw relationship (ANB) and positively correlated to mandibular prognathism (SNB). Therefore, it was found that skeletal Class III patients had greater airway volume than Class I which was greater than skeletal Class II patients.[15-20] However, this difference was not always statistically significant between the groups[16] or between Class I and Class III.[15] Minimal cross-sectional area was also found to be greater in skeletal Class I subjects than skeletal Class II subjects,[18,20] and even greater in skeletal Class III subjects.[20] Conversely, Kula et al[64] found no difference between airway volume or minimal cross sectional area between Class I, II or III skeletal patterns. In the present study, the sagittal jaw relationship (ANPg) had a weak negative association with minimal cross-sectional area after being tested for the effects of age, gender and skeletal maturation.

In the present study, the maxillary jaw relationship (SNA) was not found to significantly affect airway dimensions, which is in accordance with previous studies.[15,18,19] The only association in children was found by Di Carlo[21] who estimated that for every degree increase in SNA, the airway volume would reduce by $149mm^3$. However, the sample also included young adults up to 43 years of age.

In this study, upper anterior face height (N-Me) and total anterior face height (N-ANS) measurements had a moderate positive association with airway volume and weak positive association with minimal cross-sectional area. However, they remained statistically significant only with airway volume after correction for age, gender and skeletal maturation. In previous studies, total anterior face height[16,17] was found to have a moderate to strong positive correlation (even after controlling for the effects of age, sex and size of the face)[16] and posterior face height[17] had a moderate positive correlation with airway dimensions. No studies found a significant correlation between Frankfurt mandibular plane angle (FMA) and upper airway dimensions.[15,17-20] FMA was not assessed in this study, but rather SN to mandibular plane, which also was not significantly correlated to upper airway dimensions.

In the present study associations were found between airway dimensions and the width of the maxilla and mandible. Moderate positive associations were found with airway volume and weak positive associations with minimal cross-sectional area. However, the only other study to assess the transverse dimension in children with CBCT data, although young adults were also included in the study, found no correlations between the upper airway and craniofacial features in this dimension.[21] As associations were found between craniofacial morphology and airway dimensions in this study, hypothesis 1 is rejected.

In all previously mentioned studies, the patients were scanned in an upright position. Alternatively, Di Carlo et al[21] assessed young adults (13 to 34 years of age) in the supine position. They found no correlations between upper airway dimensions and craniofacial features, in all 3 dimensions. The authors also found no significant difference in airway volume between skeletal Class I, II and III patients. Although a slightly older population, this could be due to the lack of extreme malocclusion in the sample. Furthermore the cephalometric points were assessed 3-dimensionally, not based on 2-dimensional generated radiographs, which could more accurately represent facial morphology.

7.3.3 Airway dimensions associated with molar occlusion

In the present study no significant differences in airway volume and minimal cross-sectional area were found between molar class I, II and II. The lack of association between airway dimensions and dental relationships has also been supported by other studies.[56,60] This could be because any malocclusion can exist on any underlying skeletal pattern because of the dentoalveolar compensatory mechanism.[135] It is more the osseous and soft tissue structures that frame the airway that determine its size and morphology.[11,20] Furthermore, molar classification does not always resemble the overall malocclusion and buccal classification of the molar relationship does not always represent the lingual classification.[136]

7.3.4 Airway dimensions associated with upper cervical vertebral column morphological deviations

Surprisingly, upper cervical vertebral column morphological deviations were not significantly associated with upper airway dimensions. Therefore, hypothesis 2 is accepted. Previously, studies found associations between head posture and upper airway dimensions[22,23] as well as between head posture and upper cervical vertebral morphology.[67-69,78,80] Furthermore, a significantly higher prevalence of upper cervical vertebral column morphological deviations (46%) was found in adults with obstructive sleep apnoea where the upper airway is compromised.[79] The lack of associations between upper cervical vertebral column morphological deviations and airway dimensions could be due to the mild to moderate distribution of malocclusion traits and craniofacial morphology in the present study and consequent lack of prevalence or severity of upper cervical morphological deviations. The deviations occurred in approximately 28% of the sample. This falls within the range of previously reported upper cervical vertebral column morphological deviations in pre-orthodontic children who were used as a control group to compare cleft lip and palate patients.[70,103-106] In these studies, deviations of the upper cervical vertebral column occurred in 0.8% to 31% of pre-orthodontic children.

7.3.5 Most relevant factors to airway dimensions

Almost all previous studies that assessed airway dimensions in children did not correct observed associations for the effects of growth or gender. Only one other study[16] controlled for the effects of age, sex and size of the face. Therefore, some of the correlations established in these studies may not be accurate as they are superimposed by the effect of other factors. In this study, various associations with airway dimensions were no longer significant when tested for the effect of age, gender and skeletal maturation.

Dimensions of a healthy upper airway are influenced by growth,[9-13] anatomical,[14-21] postural,[22-25] and mechanical factors.[26,27] Therefore it is important to perform multifactorial analysis of the upper airways. To our knowledge, no previous study has analysed upper airway dimensions in relation to dentofacial and upper cervical vertebral morphology as well as skeletal maturation in a child population, or assessed which factors might have relevance to airway dimensions. Although it can be argued that CBCT analysis does not accurately represent the functional airway,[137] assessment of influencing factors to airway dimensions may provide insight into potential future airway complications. In the present study, mandibular width (Go'-Go) was found to have the most relevance for both airway volume and minimal cross-sectional area, which in combination with age explained 36% of the variation in airway volume, and in combination with sagittal jaw relationship (ANPg) explained 19% of the minimal cross-sectional area.

Age was a most relevant factor for only volume, not minimal cross-sectional area. Skeletal maturity was not for either. This is surprising considering the amount of osseous growth that occurs during the age range of this study. This could possibly be due to the broader categories of skeletal maturity used or the questionable accuracy of the CVM method.[120,122,138] Perhaps the development of more accurate methods might reveal different outcomes.

7.4 Clinical Relevance

Craniofacial features had weak to moderate associations with airway dimensions and this is supported by other studies[14-19,21]. Age and skeletal maturity also had a moderate positive association with airway volume and weak positive association with minimal cross-sectional area. Therefore, the associations were all too weak to have any clinical relevance on group basis or individual basis.

Only 36% of airway volume and 19% of minimal cross-sectional area could be explained by the statistically significant variables and highlights the complexity of the airway. Therefore as many variables as possible should be assessed in the one population as well as the influence of each variable with the other. The results from this study are limited to the variables assessed and the convenient sample. The effect of variables not involved in this study could have altered the outcomes. However, it is extremely difficult to study all potential variables in the one study with a large enough sample size. Perhaps as airway measurements become standardised, meta- analyses will be able to provide much greater insight into what factors affect upper airway dimensions.

7.5 Future Directions

Airway patency is essential for survival. Therefore, the body adapts to a compromised airway which may include extension of the head and neck[139] to encourage adequate airflow. Such adaptive capacity of the body during wakefulness is not as evident during sleep. Consequently, measurement of airway volume itself may not be adequate.[62] Perhaps the morphology and inclination of the airway should also be considered. Furthermore, Grauer et al[140] showed that with different vertical jaw relationships in adults, it is airway shape, not volume that varies. This could help explain the conflicting results evident in the literature in relation to association with upper airway dimensions. Possibly, the upper airway should be expressed as a ratio of volume to shape or inclination. It was not possible in this study due to the patients being seated in a standardised position to maintain consistency amongst the scans, which is not a true representation of natural head posture or cranio-cervical angle.

It may be beneficial to measure the minimum distance in any dimension (i.e. the smallest length along the entire airway) as opposed to minimal cross-sectional area. Area is a combination of antero-posterior and transverse measurements. Reduced tonicity of the soft tissues occurs in all dimensions, so collapsibility can occur in any dimension. It was not possible in this study due to limitations of the software.

Furthermore, upper airway assessment should go beyond simple morphological analyses, especially with more rudimentary methods such as angular and linear cephalometric measurements. Various functions of muscles and ligaments, such as force, direction and duration should also be considered as they greatly influence airway patency.

The major restriction to continual use of CBCT imaging for all orthodontic assessment, especially in children, is radiation dosage to the patient. However, this may soon be a thing of the past. Ludlow and Walker[141] have recently shown an 87% reduction in dose compared to standard exposure protocols for both children and adults with the QuickScan+ protocol (16cm height X 13cm diameter FOV) in the new i-CAT FLX CBCT machine. Furthermore, the QuickScan+ protocols (11.4 µSv in adults and 17.5 µSv in children) have less dose than the combination of 2-dimensional panoramic and lateral cephalometic radiographs (14-24 µSv and 4 µSv respectively).[141-143] However, the dose reduction is associated with significant reductions in image quality.[141] The diagnostic capabilities of these scans have not been fully explored. As CBCT technology and software continues to improve and radiation cost to the patient reduces, more ideal study designs with greater sample sizes will be possible.

8.0 Conclusion

The results indicate that airway volume and minimal cross-sectional area have a weak to moderate association with age, skeletal maturation and craniofacial dimensions in pre-orthodontic children.

9.0 Further study ideas

This study is part of the overall question: "What factors influence airway dimensions?" To better answer the question, I believe that more studies are required, some of which include:

- What is the best method to study the airway, considering radiation exposure, cost, accuracy, etc. For example what relationship do CBCT studies have on the functional airway, including when the patient is asleep (or anaesthetised)?
- What other factors can influence airway dimensions?
- What affects do various orthodontic treatment modalities have on airway dimensions in the long term?
- Longitudinal studies on patients to compare those who did and did not develop SDB

I believe that as we start to answer some of these questions we are better able to provide evidence based high quality treatment that not only focuses on improving the aesthetics and function of the teeth and face, but also airflow to the body.

10.0 Appendix

Ethics Approval

JAMES COOK UNIVERSITY AUSTRALIA

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Human Research Ethics Committee *APPROVAL FOR RESEARCH OR TEACHING INVOLVING HUMAN SUBJECTS*					Application ID **H5115**
PRINCIPAL INVESTIGATOR	Seerone Anandarajah				Student
SCHOOL	Dentistry				
CO-INVESTIGATOR(S)					
SUPERVISOR(S)	Andrew Sandham and Liselotte Sonnesen				
PROJECT TITLE	Investigation of pharyngeal airway dimensions in relation to dentofacial morphology, skeletal maturation and cervical column morphology				
APPROVAL DATE:	**9/07/2013**	**EXPIRY DATE:**	**1/07/2015**	**CATEGORY:**	**1**

This project has been allocated Ethics Approval Number H5115, with the following conditions:

1. All subsequent records and correspondence relating to this project must refer to this number.

2. That there is NO departure from the approved protocols unless prior approval has been sought from the Human Research Ethics Committee.

3. The Principal Investigator must advise the responsible Human Ethics Advisor:
   - periodically of the progress of the project,
   - when the project is completed, suspended or prematurely terminated for any reason,
   - within 48 hours of any adverse effects on participants,
   - of any unforeseen events that might affect continued ethical acceptability of the project.

4. In compliance with the National Health and Medical Research Council (NHMRC) "National Statement on Ethical Conduct in Human Research" (2007), it is MANDATORY that you provide an annual report on the progress and conduct of your project. This report must detail compliance with approvals granted and any unexpected events or serious adverse effects that may have occurred during the study.

Human Ethics Advisor :	Woodward, Lynn
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This project was Approved by Executive on 09 Jul 2013

Dr Anne Swinbourne
Chair, Human Research Ethics Committee

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