Evaluation of the relationship between cervical vertebral maturation variables and fusion of the spheno-occipital synchondrosis

THE UNIVERSITY OF QUEENSLAND

AUSTRALIA

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BDSc(Hons) (Mel) FRACDS(GDP)

A thesis submitted for fulfilment of the requirements for the degree of

Doctor of Clinical Dentistry (Orthodontics)

School of Dentistry
The University of Queensland

Date of Submission: 08/08/2018

Declaration by author

I certify that the work presented in this thesis is to the best of my knowledge and belief, original, except as acknowledged in the text and that the material has not been submitted, either in whole or part, for a degree at this or any other University.

I also certify that to the best of my knowledge any help received in preparing this thesis and all sources used have been acknowledged.

07/08/18

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A thesis submitted for fulfilment of the requirements for the degree of *Doctor of Clinical Dentistry (Orthodontics).* School of Dentistry - The University of Queensland

Statement:

I have read the thesis in final form ☒

I have read the thesis in final draft form but not in final form ☐

I have not read the thesis in either final form or final draft form ☐

I agree that the thesis is in an appropriate form for submission ☒

I do not agree that the thesis is in an appropriate form for submission ☐

Any other comments:

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Professor P. Monsour

Research Supervisor

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A/Professor D.Healey

Research Supervisor

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"You can teach a student a lesson for a day; but if you can teach him to learn by creating curiosity, he will continue the learning process as long as he lives."

Thank you everyone in the department for the ongoing support and assistance during my postgraduate career. In the same line, I would like to also extend a special mention to my research supervisors. To Associate Professor Healey: thank you for providing me with the opportunity and encouragement to always strive to improve. To Professor Monsour: thank you for going out of your way to support my research and for providing me with your invaluable expertise.

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Abstract

Objective: Determination of growth potential is an important part of orthodontic treatment planning. The development of three-dimensional imaging has created the opportunity for alternative measures of growth assessment. With the newfound ability to visualise and digitally measure structures previously concealed in plain film radiographs, there is a need for further research regarding its applicability in the field of orthodontics. The aim of this study was to evaluate the relationship between the cervical vertebral maturation (CVM) method and closure of the spheno-occipital synchondrosis (SOS) in children and young adults using cone-beam computed tomography (CBCT). In addition, quantitative cervical vertebral maturation (QCVM) parameters were assessed to determine their ability to predict skeletal maturation.

Methods: Two hundred and seventy-five extended field CBCT scans of patients aged 6 to 30 years were analysed. The cervical vertebral maturity was assessed using the CVM method. The closure of the spheno-occipital synchondrosis was evaluated using a five-stage scoring system. Correlation and agreement between cervical vertebral maturation and fusion of the spheno-occipital synchondrosis were analysed for statistical significance. Moreover, QCVM parameters were evaluated by performing measurements from the body of the second to the fourth cervical vertebrae. A Receiver Operating Characteristic curve analysis was conducted to determine the optimal parameter that would be predictive of skeletal maturation.

Results: Part one of the study demonstrated a strong significant correlation (r_s = .908; 95% CI: .885, .927) between cervical vertebral maturational status and the closure of the spheno-occipital synchondrosis. Based on the variables assessed, an ordinal regression model was constructed to predict cervical stage, to which age, gender and spheno-occipital synchondrosis closure were statistically significant.

Part two of the study revealed that the parameter AH3/LW3 demonstrated highly significant Area Under the Curve value of .925 (95% CI: .895, .954). The AH3/LW3 ratio of ≥ 0.78 was determined to be associated with optimal sensitivity and specificity.

Conclusion: This pilot investigation demonstrated that the maturation stage of the spheno-occipital synchondrosis and QCVM parameters, specifically AH3/LH3, are potential indicators for skeletal maturity assessment.

List of Submissions and Publications

Publications

- Pending review from the editor(s)

Intended Submissions

- Fu S, Healey D, Sexton C, Monsour P. Relationship between cervical vertebral maturation and spheno-occipital synchondrosis closure
- Fu S, Healey D, Sexton C, Monsour P. Cervical Vertebral Maturational Assessment Through Quantitative Assessment of The Third Cervical Vertebral Body

Oral Presentations

- University of Queensland School of Dentistry Research Day – 2016, 2017
- Australian Society of Orthodontists (Queensland Branch) Regional Meeting – 2016

Poster Presentations

- 26th Congress of the Australian Society of Orthodontists, Sydney, Australia, March 2018

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List of Abbreviations

ANS	Anterior Nasal Spine
ASO	Australian Society of Orthodontists
ASOFRE	Australian Society of Orthodontists Foundation for Research and Education
ASOQ	Australian Society of Orthodontists - Queensland Branch
AUC	Area Under the Curve
C2	Cervical Vertebra 2
C3	Cervical Vertebra 3
C4	Cervical Vertebra 4
CBCT	Cone Beam Computed Tomography
CI	Confidence Interval
CS1	Cervical Stage 1
CS2	Cervical Stage 2
CS3	Cervical Stage 3
CS4	Cervical Stage 4
CS5	Cervical Stage 5
CS6	Cervical Stage 6
CVM	Cervical Vertebral Maturation
CVMI	Cervical Vertebrae Maturation Index
DICOM	Digital Imaging and Communications in Medicine
FOV	Field of View
PNS	Posterior Nasal Spine
QCVM	Quantitative Cervical Vertebral Maturation
ROC	Receiver Operating Characteristic
SOS	Spheno-Occipital Synchondrosis
UQ	University of Queensland

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1. Background

1.1 Introduction

The identification of the optimal timing for orthodontics and dentofacial orthopaedics has been the holy grail of orthodontic research. The current understanding suggests that such timing is linked closely with a patient's growth status. It is essential for clinicians to have the capacity to evaluate a patient's growth status when attempting to diagnose and treatment plan cases involving skeletal discrepancies. Throughout life, bone undergoes 'modelling' and 'remodelling' by the process of apposition and resorption. Frost in 1990 defined bone modelling as an uncoupled process of resorption and formation, resulting in changes in the size and shape of bone.[1] Based on the knowledge of morphological changes in the craniofacial structures, the rate of bone modelling process increases significantly during the pubertal growth spurt. Thus, by understanding its pattern, optimal timing for dentofacial orthopaedics during periods of intense or accelerated growth can be predicted.

There is a general agreement that most effective response to functional orthopaedic intervention occurs during the pubertal growth spurt.[2-5] In fact, it has been proposed that rather than the type of appliance, it is the timing of treatment that would bring about the greatest increase in the growth of mandibular length.[6] In addition, the identification of decreased growth period and skeletal changes is important for the timing of orthognathic surgical intervention. As such, a reliable indicator to detect peak growth velocity becomes a crucial assessment tool in orthodontic treatment planning.

Furthermore, changes in psychosocial status and sexual maturity occurring during circumpubertal age may affect the patient's compliance to treatment. In some cases, there may be refusal to cooperate with treatment due to perceived peer group pressure and social image. As such, clinicians may consider interceptive treatment prior to the growth spurt to gain maximum benefit in certain cases.

2. Research Project

2.1 Research Hypotheses

In this project, we hypothesised that during the stages leading up to, during and after pubertal growth spurt, the height to width ratio of the body of cervical vertebrae, when viewed in the sagittal plane, will change predictably. This in turn reinforces a positive relationship between the QCVM ratio parameters and CVM stages. In a similar fashion, we expected the closure of the spheno-occipital synchondrosis to relate to CVM stages. Thus, the null hypothesis (H_0) was that there is no association between spheno-occipital synchondrosis closure and CVM stages; and that there is no relationship between QCVM parameters and CVM stages.

2.2 Significance of aims

The study aimed to utilise three-dimensional imaging for the assessment of an individual's skeletal maturity. This method will enable clinicians to assess craniofacial and vertebral structures that would otherwise be concealed in a plain film radiograph. The results of this study have the potential to contribute to the development of a skeletal maturation assessment tool that is superior to the current methods available.

As mentioned previously, an individual's growth status is essential in orthodontic treatment planning. Estimation of the growth potential will enable optimal functional orthopaedic intervention, while estimation of the end of growth potential will assist in orthognathic surgical treatment planning. Thus, it is hoped that the present study will contribute to the contemporary orthodontic practice by providing more predictable method to assess the status of growth.

2.3 Aims

The aims of this study were to investigate, using cone-beam computed tomography, the relationship among the following variables: cervical vertebral maturational stages, height-width ratio of the cervical vertebral bodies, and closure of the spheno-occipital synchondrosis. Specifically, the project was designed to determine (1) the relationship between cervical vertebral maturation method and closure of the spheno-occipital synchondrosis and (2) if QCVM parameters can be used to predict the cervical vertebral maturation stage.

2.4 Materials and Methods

2.4.1 Study population

The appropriate size for this cross-sectional study was determined by a power analysis calculation. Using an alpha of .05, a power of .95 and a correlation of .3, the minimum sample size was estimated to be 56. At the time of collection, total of 500 consecutive de-identified CBCT datasets were acquired from The University of Queensland Radiology Clinic and a private radiology practice.

Inclusion criteria were:

- Growing adolescents and young adults (aged between 6 and 30 years)
- Extended field of view (FOV) datasets, with the field of view extending from the anterior cranial base to the lower border of C4

The exclusion criteria were:

- Distortion of the dataset due to patient movement
- Developmental anomalies affecting the craniofacial structures or vertebrae
- Previous history of head and neck surgery

Out of the 500 datasets, 275 CBCT scans fulfilled the inclusion criteria. The majority of the rejections were due to the body of C4 not being included in the scan.

2.4.2 CBCT data

All of the CBCT scans had been previously acquired as a part of orthodontic diagnosis and management requirements. Digital Imaging and Communications in Medicine (DICOM) data of each scan was exported and manipulated with InVivo 5 (Anatomage, San Jose, CA, USA).

2.4.3 Classification Method

CVM stages were defined according to the method described by Bacetti et al.[6] The six stages are depicted in Figure 1 and defined as follows:

- **Cervical stage 1 (CS1):** The lower borders of all the three vertebrae (C2-C4) are flat. The bodies of both C3 and C4 are trapezoid in shape (the superior border of the vertebral body is tapered from posterior to anterior).
- **Cervical stage 2 (CS2):** A concavity is present at the lower border of C2. The bodies of both C3 and C4 are still trapezoid in shape.
- **Cervical stage 3 (CS3):** Concavities at the lower borders of both C2 and C3 are present. The bodies of C3 and C4 may be either trapezoid or rectangular horizontal in shape.
- **Cervical stage 4 (CS4):** Concavities at the lower borders of C2, C3 and C4 are now present. The bodies of both C3 and C4 are rectangular horizontal in shape.
- **Cervical stage 5 (CS5):** The concavities at the lower borders of C2, C3 and C4 are still present. At least one of the bodies of C3 and C4 is squared in shape. If not squared, the body of the other cervical vertebra still is rectangular horizontal.
- **Cervical stage 6 (CS6):** The concavities at the lower borders of C2, C3 and C4 are still evident. At least one of the bodies of C3 and C4 is rectangular vertical in shape. If not rectangular vertical, the body of the other is squared.

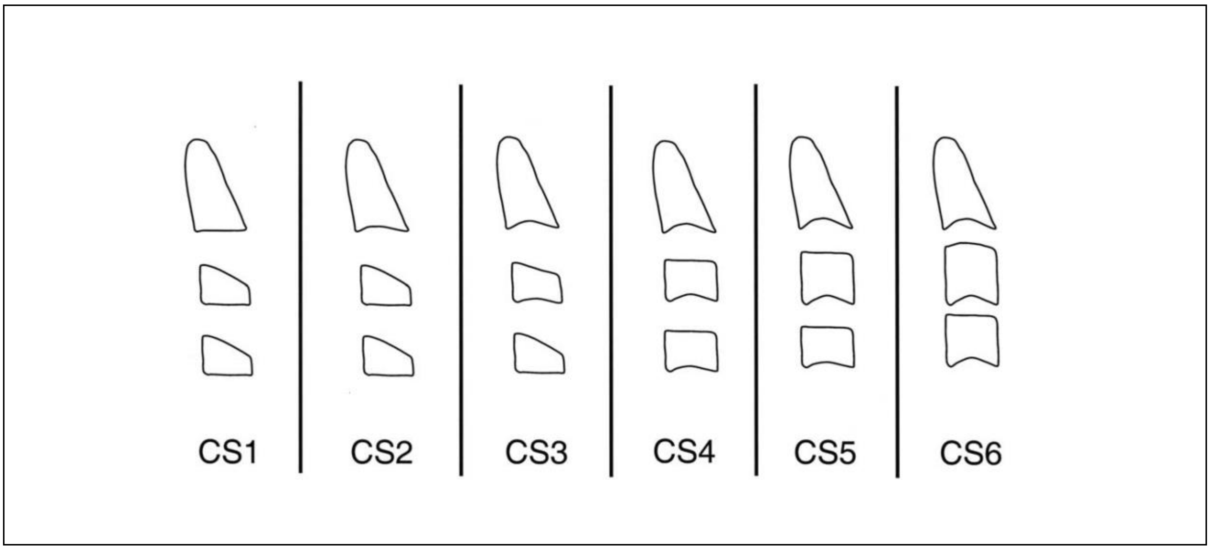

Figure 1. CVM Stages – CS Staging as described by Bacetti et al.[6]

The assessment of the SOS closure was conducted using the five-stage scoring system developed by Bassed et al.[7] The stages are described as follows:

- **Stage 1:** the synchondrosis is completely open/unfused.
- **Stage 2:** the superior border has fused, while the remainder of the fusion site is patent.
- **Stage 3:** half the length of the synchondrosis is closed.
- **Stage 4:** closure is essentially complete, but the site is still visible by way of a fusion scar.
- **Stage 5:** the site has completely obliterated with the appearance of normal bone throughout.

2.4.4 Quantitative measurements of the cervical vertebral body

Prior to the acquisition of the measurements, any head tilt of the patient in the datasets were corrected and standardised with the sagittal plane bisecting the anterior nasal spine and through the intermaxillary suture. Also, the coronal plane was aligned perpendicular to the palatal plane (ANS-PNS).

For this investigation, the QCVM method as described by Chen et al.[8] was adopted. Figure 2 displays the structural points plotted for each dataset. To compensate for scaling and enlargement issue, ratios of the dimensions were used. For every dataset, each parameter was measured and calculations made using the 3D imaging software. The proposed QCVM parameters are listed in Table 1.

It is important to note, these QCVM parameters are assessment of the cervical body when viewed in the sagittal plane. As such, the term "height" correlates to the vertical height of the cervical body, whereas, the term "width" refers depth of cervical body when viewed in the coronal plane. The evaluation of the cervical vertebrae, in particular QCVM measures, in orthodontic literature, have been reported in such a manner as it originates from lateral cephalogram assessment. The acceptance of such descriptors have been adopted as a necessary mean to simplify communication and enable comparison between studies.

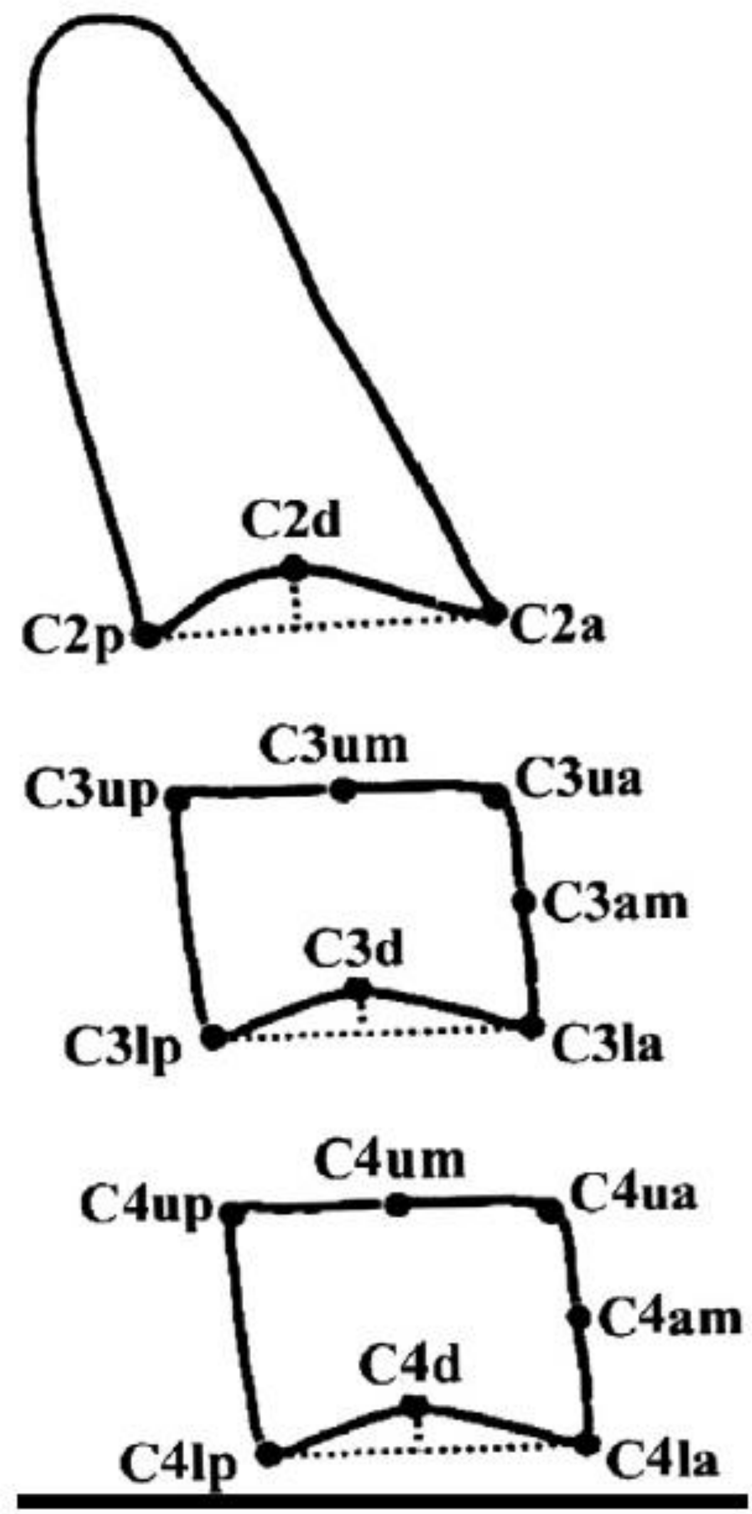

Figure 2. Landmarks as described by Chen et al.[8]

Parameter	Description
C3 Body Variables	
Vertical measurements	
PH3	distance between C3up to C3lp
H3	distance between C3um to C3d
AH3	distance between C3ua to C3la
Horizontal measurements	
UW3	distance between C3ua to C3up
W3	distance between C3am to mid-point between C3up and C3lp
LW3	distance between C3la to C3lp
Vertical Ratio	
AH3/H3	ratio of AH3 to H3
H3/P3	ratio of H3 to PH3
AH3/PH3	ratio of AH3 to PH3
Horizontal ratio	
UW3/LW3	ratio of UW3 to LW3
UW3/W3	ratio of UW3 to W3
LW3/W3	ratio of LW3 to W3
Height/Width Ratio	
AH3/UW3	ratio of AH3 to UW3
AH3/LW3	ratio of AH3 to LW3
H3/UW3	ratio of H3 to UW3
H3/LW3	ratio of H3 to LW3
PH3/UW3	ratio of PH3 to UW3
PH3/LW3	ratio of PH3 to LW3
C4 Body Variables	
Vertical measurements	
PH4	distance between C4up to C4lp
H4	distance between C4um to C4d
AH4	distance between C4ua to C4la
Horizontal measurements	
UW4	distance between C4ua to C4up
W4	distance between C4am to mid-point between C4up and C4lp
LW4	distance between C4la to C4lp
Vertical Ratio	
AH4/H4	ratio of AH4 to H4
H4/P4	ratio of H4 to PH4
AH4/PH4	ratio of AH4 to PH4
Horizontal ratio	
UW4/LW4	ratio of UW4 to LW4

UW4/W4	ratio of UW4 to W4
LW4/W4	ratio of LW4 to W4
Height/Width Ratio	
AH4/UW4	ratio of AH4 to UW4
AH4/LW4	ratio of AH4 to LW4
H4/UW4	ratio of H4 to UW4
H4/LW4	ratio of H4 to LW4
PH4/UW4	ratio of PH4 to UW4
PH4/LW4	ratio of PH4 to LW4

Table 1. Parameters and ratios used in the QCVM analysis

2.4.5 Analysis of results

The data was analysed using statistical software (SPSS version 21.0 for Windows, Chicago, Il, USA). With regard to the level of significance, p-values of less than .05 were considered to be statistically significant. In addition, the confidence interval will be included to support the measure of significance.

In part one of the investigation, the relationship between CVM stage and SOS fusion was analysed with Spearman's Correlation Coefficient (r_s). In part two, Receiver Operator Characteristics (ROC) curve analysis was used to determine vertebrae measurements that were significantly associated with stage of vertebral growth. The confidence intervals for the area under the curve (AUC) that do not contain .5 were considered statistically significant. Optimal post-growth values representing vertebrae measurement that optimised sensitivity and specificity were determined by finding the point closest to the top of the *y*-axis. The AUC value was used to evaluate the strength of the association between the vertebrae measurement variables and stage of growth. The optimal post-growth value was used to convert the continuous variable to a binary form. Binary logistic regression was used to determine the odds ratio for post-vertebral growth based on vertebral stage and AH3/LW3 after adjusting for age and gender.

In this investigation, the complete dataset was analysed by a single scorer (S.F.). To ascertain satisfactory reliability, 25 randomly selected datasets were assessed by another experienced scorer (P.M.). Reassessment was conducted after two weeks to ensure reproducible and consistent measurement. The evaluation of the intra- and inter-rated agreement was conducted using Cohen's Kappa coefficient.

2.5 Timeline for the project tasks

A timeline matrix for the project is listed below in Table 2.

Time Point	Details
Year 1	• Formative direction, scope and planning of research project. • Completion of literature summary/review to assess feasibility of the project. • Acquisition or further development of appropriate research skills - statistics, 3D imaging and radiographic interpretation. • Submission of research protocol/proposal. • Submission of ethics application. • Presentation - UQ Research Day. • Presentation - ASOQ Clinical Meeting. • Presentation - Research Protocol (UQ).
Year 2 Semester 1	• Application of research funding and allowance (UQ Statistics). • Presentation - ASOFRE Meeting. • Commencement of data collection. • Commencement of data analysis.
Year 2 Semester 2	• Mid-Thesis review: discussion and interview with research supervisors. • Refinement and revision of thesis direction, scope and plan. • Commencement of thesis write-up and analysis. • Presentation - ASOQ Clinical Meeting.
Year 3 Semester 1	• Preliminary thesis review. • Submission of thesis. • Submission for journal publication(s).
Year 3 Semester 2	• Thesis feedback and review. • Revision of thesis. • Final submission of thesis. • Presentation - UQ Research Day. • Presentation - ASOQ Clinical Meeting.

Table 2. Timeline matrix

2.6 Budget

A budget matrix for undertaking the study is listed below in Table 3.

Budget Item	Amount	Justification
Expenses		
Statistical support	$1,000.00	This is a study assessing different variables and parameters requiring significant expertise and time for data administration and analysis. The funding for data analysis for this project will go to a statistician to support the project.
Travel	$800.00	Projected travel expenses by the principle investigator to present the results of the research at national professional conferences. The amounts are estimated to include domestic airfare and transportation fee.
Materials and Supplies		
Office supplies	$100.00	Costs associated with this category include duplication of documentation, printing and scanning, along with consumable office supplies and materials.
Storage device	$150.00	DICOM data will be required to be securely stored in a portable media for data backup.
Poster/publication cost	$150.00	Costs associated with the production of poster prints and mounts for presentation.
Total Project Expense	$2,200.00	

Table 3. Budget/Expense matrix

Funding for the project includes the University of Queensland School of Dentistry Statistical Analysis Allowance, as well as Australian Society of Orthodontists Foundation for Research and Education (ASOFRE) Postgraduate Student Research Donation.

2.7 Ethical clearance

Ethics application was submitted and approved by the University of Queensland Dental Sciences Research Ethics Committee (Project Number: 1702).

THE UNIVERSITY OF QUEENSLAND

DENTAL SCIENCES RESEARCH ETHICS COMMITTEE

APPROVAL OF APPLICATION FOR ETHICAL CLEARANCE FOR RESEARCH INVOLVING HUMAN PARTICIPANTS

Chief Investigator:	Chiang Sigid FU 44275352
Project Title:	Evaluation of the relationship between cervical vertebrae maturation variables and fusion of the spheno-occipital synchondrosis
Supervisor:	Prof Paul Monsour & A/Prof David Healey
Co-Investigator(s):	
School(s):	Dentistry
Project Number:	1702
Duration of Approval:	2 years

Comments/Conditions/Restrictions:

Application is approved with **minor revision**. Please note comments from the reviewers of the application.

This project complies with the provisions contained in the *National Statement on Ethical Conduct in Research Involving Humans* and complies with the regulations governing experimentation on humans.

Professor Adam Ye
Director of Research

Signature ______________________

Date: 8 March 2017

2.8 Research environment

The research project was undertaken at the University of Queensland School of Dentistry. The access to the de-identified DICOM dataset was acquired through the UQ Oral Health Centre Radiology Clinic. Manipulation and analysis of the data were conducted through the use of the 3D Medical Imaging software preloaded in the Radiology Clinic Workstation - Anatomage InVivo 5 (Anatomage, San Jose, CA, USA).

Professional development and support for the project were provided by faculty members of the Discipline of Orthodontics and Dento-Maxillofacial Radiology at the University of Queensland. Moreover, the Faculty of Medicine and Biomedical Sciences – School of Public Health (UQ) has been involved for statistical advice and support.

2.9 Role of personnel

A personnel matrix for the project is listed below in Table 4.

	Name
Principal Investigator	Dr. Sigid Fu
Research Supervisors	Professor Paul Monsour
	Associate Professor David Healey
Statistician	Christopher Sexton

Table 4. Personnel matrix

3. Pilot analysis

3.1 Reproducibility

Twenty-five randomly selected datasets were assessed for the inter- and intra-rater agreement coefficients. To optimise the reproducibility and reliability, the assessments were performed over two time points, separated by a two-week interval.

3.11 Intra-rater and inter-rater agreement

The intra-rater agreement at the two time points was .882 (95% CI: .861, .903) for the assessment of the cervical vertebral staging and .933 (95% CI: .921, .952) for the SOS closure. Thus, the strength of intra-rater agreement was excellent. The assessment of the inter-rater agreement was accomplished using the same 25 datasets. The weighted Kappa coefficient agreement was .824 for the vertebrae assessment and .853 for the SOS closure. In all cases, the difference in the assessment for either CVM or SOS staging was no more than one stage. Intra-examiner and inter-examiner reliability of the linear measurements also demonstrated excellent agreement (.982 and .966 respectively).

3.2 Pilot sample

For the preliminary analysis, a total of 100 scans were selected. After careful assessment of the datasets that met both the inclusion and exclusion criteria, 67 datasets were selected and analysed.

3.3 Statistical analysis

The relationship between the cervical vertebral stages was analysed using Spearman's non-parametric Correlation Coefficient (r_s).

3.4 Preliminary result – Correlation of CVM Stage and SOS Stage

Table 5 shows the cross-tabulation matrix of spheno-occipital synchondrosis fusion stage with cervical vertebral staging.

	Vertebrae Stage						
Synchondrosis Stage	*1*	*2*	*3*	*4*	*5*	*6*	*Total*
1	24	3	1	0	0	0	28
2	4	3	1	3	0	0	11
3	0	0	0	2	0	0	2
4	0	0	0	5	2	0	7
5	0	0	0	0	5	14	19
Total	28	6	2	10	7	14	67

Table 5. Frequencies of stages of vertebrae and synchondrosis

The distribution of the scores indicated a positive relationship between cervical vertebrae maturational stages and the closure of the spheno-occipital synchondrosis. Further to this, the correlation coefficient is presented in Table 6.

Variables	**CVM Stage**	**SOS Stage**
CVM Stage	-	.913**
SOS Stage	.913**	-
n	67	67

*p<0.05. **p<0.01. ***p<0.001

Table 6. Spearman's correlation between cervical maturation stages and the spheno-occipital synchondrosis closure

The spheno-occipital synchondrosis stages showed significant positive correlation with cervical vertebral stages (r_s = .913; 95% CI: .894, .932)

3.5 Preliminary result – Quantitative assessment of CVM

The height of C3 body increased over time, as noted through the various cervical maturational stages (Figure 3). The trend appeared to follow that of a positive linear gradient.

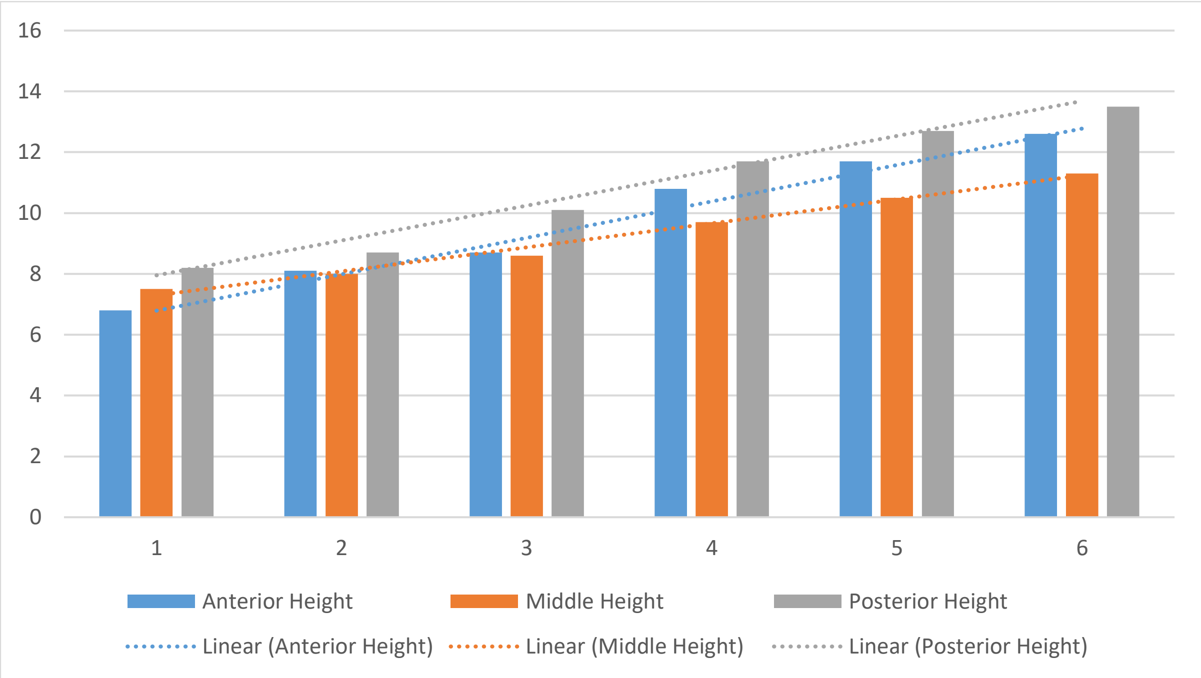

Figure 3. Changes of C3 Height according to CS Stage

Similarly, the width of the C3 body increased over time as it progressed along cervical maturational stages (Figure 4). However, the gradient of the linear relationship appeared to be less than that of the height changes.

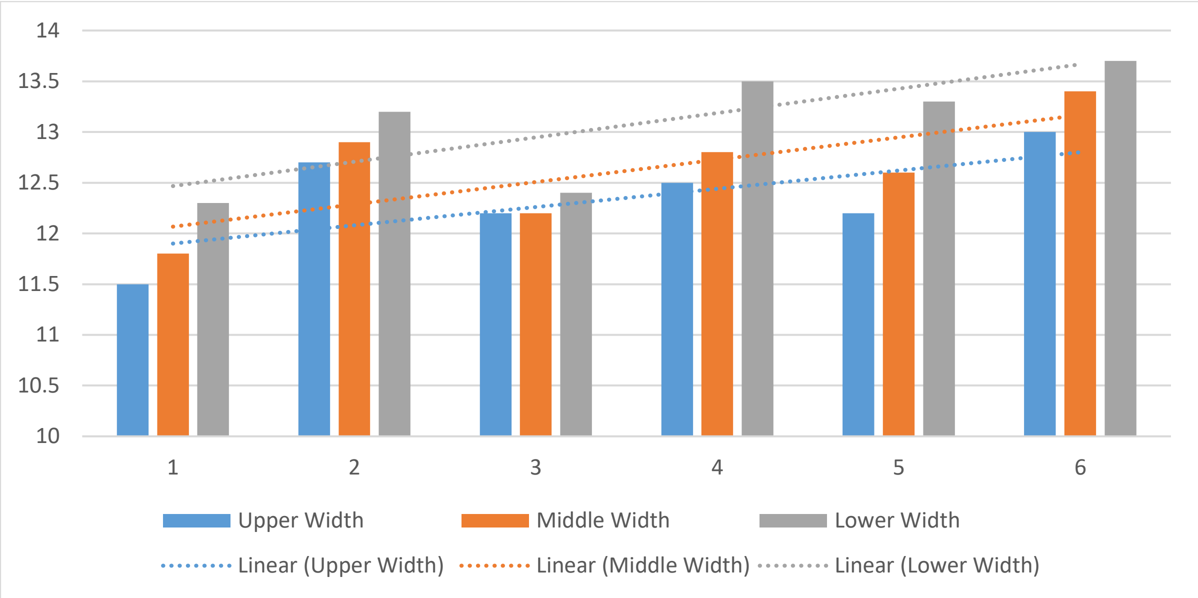

Figure 4. Changes of C3 Width according to CS Stage

The shape of the C3 body, represented by the various height-width ratio, varied with the cervical stages. There was an overall tendency for the ratio to increase over time. As seen in Figure 5, the ratio suggested a tendency for the vertebral body to change from a ‘horizontal’ rectangular shape to a square and then to a ‘vertical’ rectangle.

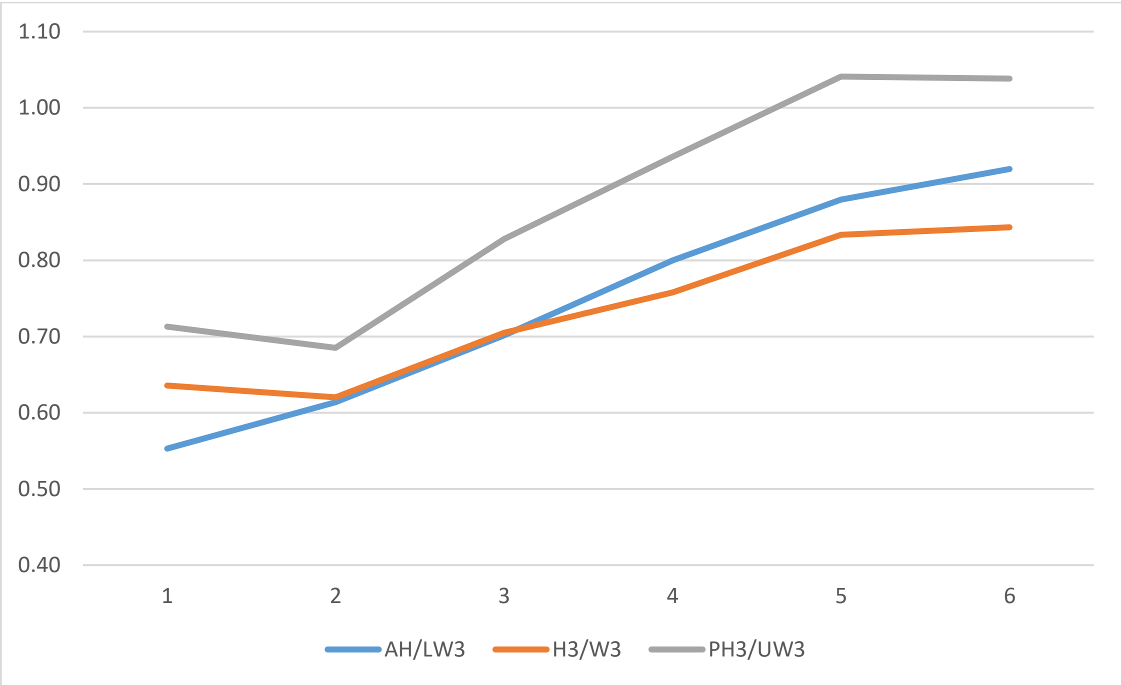

Figure 5. Various Height/Width Ratio of C3 according to CS Stage

3.6 Pilot analysis conclusion

The results from the pilot investigation suggested that the stage of spheno-occipital synchondrosis closure and the cervical vertebral maturation stage are highly correlated. Moreover, there appears to be a predictable change in the height and width of the C3 vertebral body and these changes were accordingly noted through the various height-to-width ratios. With further research and increase in sample size, more meaningful statistical yield can be anticipated.

In summary, results from the preliminary analysis suggested:

- A strong correlation between CVM Stage and SOS Stage
- A predictable change in the height and width of C3 vertebral body
- A predictable change in the various ratios of C3 vertebral body

Upon discussion with the research supervisors, the continuation of the analysis and research direction were deemed appropriate. It was planned that the next phase of the analysis involves completion of the analysis of the remaining data. The key aspects aimed to be studied are as follows:

- The relationship between CVM Stage and SOS Stage.
- The relationship between CVM stage and QCVM variables.
- Based on the understanding of the pattern and relationship of the above variables, assess the possibility of developing a SOS Staging guideline for predicting a patient's growth status and potential.

4. Literature Review (Paper One)

4.1 Growth

There are four main types of tissue systems: neural, general, genital and lymphoid. As reflected in Scammon's curves for growth of the major systems (Figure 6), different tissue will grow at distinct times and rates in various parts of the body.[9] Nonetheless, the most important aspect of growth of a particular tissue is its pattern in relation to growth occurring in other tissue systems. For instance, the maxilla and mandible follow a pattern of growth that is between the neural and somatic growth, with the mandible following the latter more closely.[10]

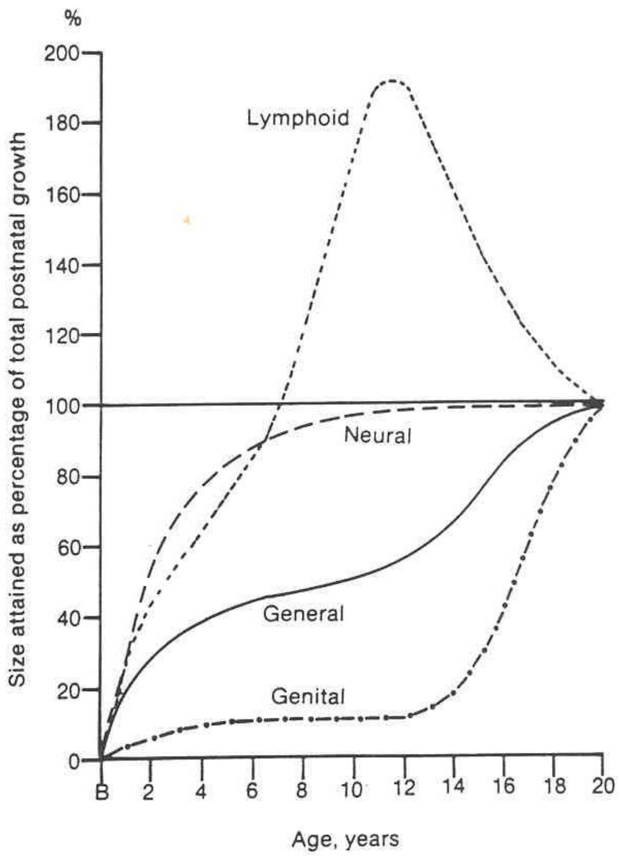

Figure 6. Scammon's Growth Curve[9]

4.2 Assessment of skeletal growth

Several investigators have introduced a variety of biological indicators to assess general body growth. These indicators include: body height, chronological age, dental development, maturation of the hand and wrist, secondary sexual characteristics and cervical vertebral maturation.[11-19] Among these maturation indices, skeletal maturation indicators utilising hand-wrist radiographs are commonly used and considered reliable.[20-22] However, this method requires further radiation exposure and expense to the patient.[22] The various indicators are listed below and discussed:

4.2.1 Chronological age

Attempts have been made in the past to correlate chronological age with the onset of growth spurt. However, there is a large individual discrepancy between age and maturational events.[23] Such individual variation makes chronological age an unreliable maturation indicator on its own.[24,25]

4.2.2 Height and weight

Physical growth status also varies in many children but nonetheless tends to correlate well with skeletal age. Notably, the statural growth spurt precedes the facial growth spurt by about 6 to 12 months.[16,19,26] Accordingly, by comparing the height and weight against population norms and standards, it can assist in identifying peak growth velocity. Unfortunately, such markers are influenced by environmental factors, ethnicity and populations groups and require frequent evaluation and assessment.

4.2.3 Secondary sexual characteristics

Jaw growth correlates with physiological events of puberty in the same way as height. The onset of the pubertal growth spurt coincides with increased jaw growth[10] and peak height velocity.[27] Examples of pubertal characteristics include: body and facial hair development, voice change, body shape change, and specifically to females, menarche. Similar to other maturational indices, there is considerable individual variations, but on average, puberty and the adolescent growth spurt occur two years earlier in girls than in boys.[14] Owing to the sensitive nature of the subject, parents and patients may feel uncomfortable discussing such matters.

4.2.4 Dental development

Dental development correlates poorly with chronological age and physiological development. [12,17] It has been suggested that the age of eruption of dentition is more dependent on environmental factors, such as loss of teeth and crowding than the tooth formation stage.[28] Accordingly, dental development proved to be of little value in assessing puberty or maximum skeletal growth due to significant variations.

4.2.5 Skeletal maturity of the hand-wrist

From a historical perspective, the use of the hand-wrist radiograph has been considered as the gold standard for the evaluation of skeletal maturity.[14,29-34] Assessment method ranges from qualitative to quantitative estimation of the bones and ossification process. Although a view of a single bone is not diagnostic on its own, an assessment of the overall pattern of development of the bones in the wrist, hand and fingers can give an accurate approximation of an individual's skeletal developmental status.[10]

For skeletal maturity assessment, radiographs of the hand and wrist can be compared with the bone age references in Greulich and Pyle[13] 1959 Atlas. Alternatively, based on radiographs of the hand and wrist, ossification stages can be evaluated with Tanner-Whitehouse Method[35] or with the Fishman Method[22] as elaborated below:

The Tanner-Whitehouse Method[35]: In this method, twenty regions of interest in the hand are considered. Assessment of the bones in the hand and wrist and the sum of the scores gives an overall maturity score, which is equivalent to a particular bone age. The original method was based on the evaluation of hand-wrist radiographs of 3000 British boys and girls in the 1950s.

The Fishman Method[22]: In 1982, Fishman used both cross-sectional and longitudinal samples of hand-wrist radiographs to reduce secular error. The cross-sectional sample consisted of 550 males and 550 females, with the additional longitudinal data obtained from 1927 to 1967. From this data, Fishman derived four ossification stages to classify the maturation process of the bones at different anatomic sites. Fishman's method is still a popular method for studying skeletal maturation.

Due to the need for additional radiation exposure, the use of hand-wrist assessment is declining in contemporary clinical practice, while other methods such as cervical spine analysis are becoming increasingly popular.

4.2.6 Cervical Vertebral Maturation

In recent years, to overcome the drawback of hand wrist radiographs, researchers directed their investigation into cervical vertebral maturation as a possible measure. This resulted in the development of the Cervical Vertebral Maturation (CVM) method, which proved to be a useful method due to its simplicity. Unlike hand-wrist radiographs, the major benefit of the CVM method is that it can be applied to lateral cephalogram required as part of the orthodontic diagnostic assessment. Reports in the literature have proven the CVM method to be effective in assessing the adolescent growth spurt for body height and mandibular size.[36-38]

4.3 Growth and development of the cervical spine

Development of the cervical spine commences during intra-uterine life and varies with each individual vertebra. The vertebral column originates from the mesenchymal tissue derived from sclerotome, which is a part of the segmental mesodermal somites. Unlike other vertebrae in the body, the embryological development of the axis and atlas is vastly more intricate. In general, ossification and maturation of the cervical vertebrae begin in the foetal period and continues through to adulthood.[39,40] The features of the development of the cervical vertebrae are discussed below:

Atlas (C1): The Atlas (C1) has a unique ossification pattern. At birth, it is incompletely ossified, and complete ossification does not usually occur until after the first year of life. At this time, the posterior elements begin to ossify, while the anterior portion remains unossified. There are three areas of ossification: two primary areas in the lateral masses and one secondary area in the anterior arch.[40] The posterior lateral segments then combine to form the posterior arch between 3 and 4 years of age.

Axis (C2): As mentioned previously, the development of the Axis (C2) is also intricate. It has 5 primary ossification centres: two in the posterior arch, two in the dens and one in the body.[40] A cartilaginous region called the dentocentral synchondrosis separates the dens ossification centres from the primary ossification centres of the vertebral centrum. This synchondrosis contributes to the heights of the vertebral body and dens. The fusion of the dentocentral junction occurs between 4 and 6 years of age and the junction lines will usually disappear by 9 to 10 years of age.

C3-C7: The remaining cervical vertebrae develop in similar ways. There are three primary ossification centres located in the vertebral body and each lateral mass in the posterior arch. The two secondary ossification centres are located in the spinous process and body of the vertebrae.[42,43]

In addition to these developmental features, the growth of the cervical vertebrae follows a somatic pattern and they reach their final size upon skeletal maturity. The cervical vertebrae (C2, C3, C4) increase in overall height as well as length throughout childhood and with adolescent grow spurt during puberty, therefore coinciding with the general somatic growth spurt. In Hellsing's cross-sectional study, the mean increase in height was 6mm for C2, 7.3mm for C3, and 6mm for C4.[44] A different study by Altan and co-workers agreed with these values but found a larger increase in height of C2 with the value of 8.66mm (Figure 7).[45] With respect to the length, C2 was observed to have the greatest amount of growth of 11mm, with the mean growth for C1, C3 and C4 being approximately 7mm (Figure 8).[45] Interestingly, as the vertebrae increase in size, the inferior surfaces develop concavity in the outline due to increasing depth.

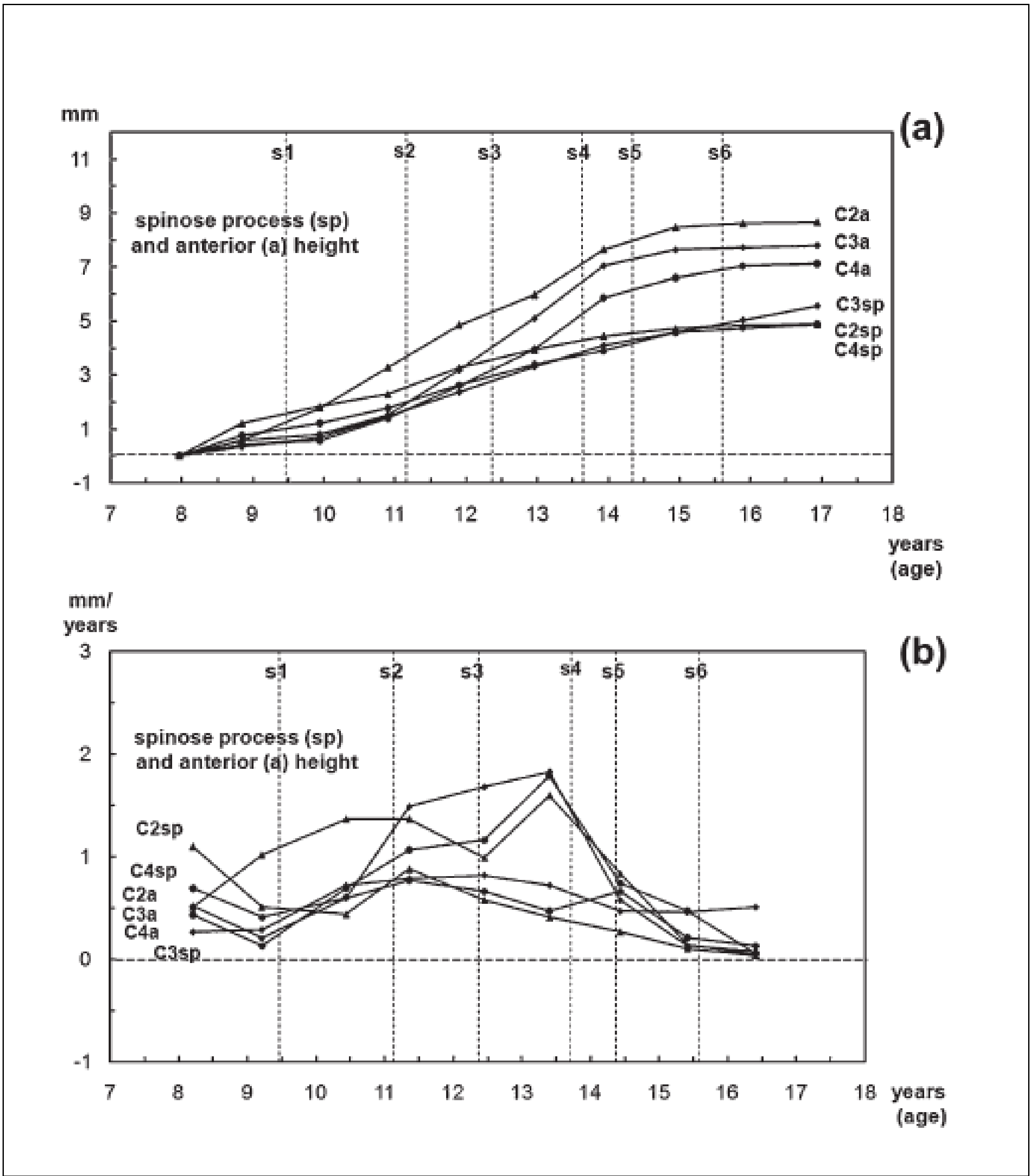

Figure 7. Height changes of C2, C3 and C4[45]

(a) Total height increment curve of C2, C3 and C4

(b) Annual growth rate (height) of C2, C3 and C4

*s1-s6 refers to the cervical vertebral maturational stage based on Hassel and Farman 1995 staging

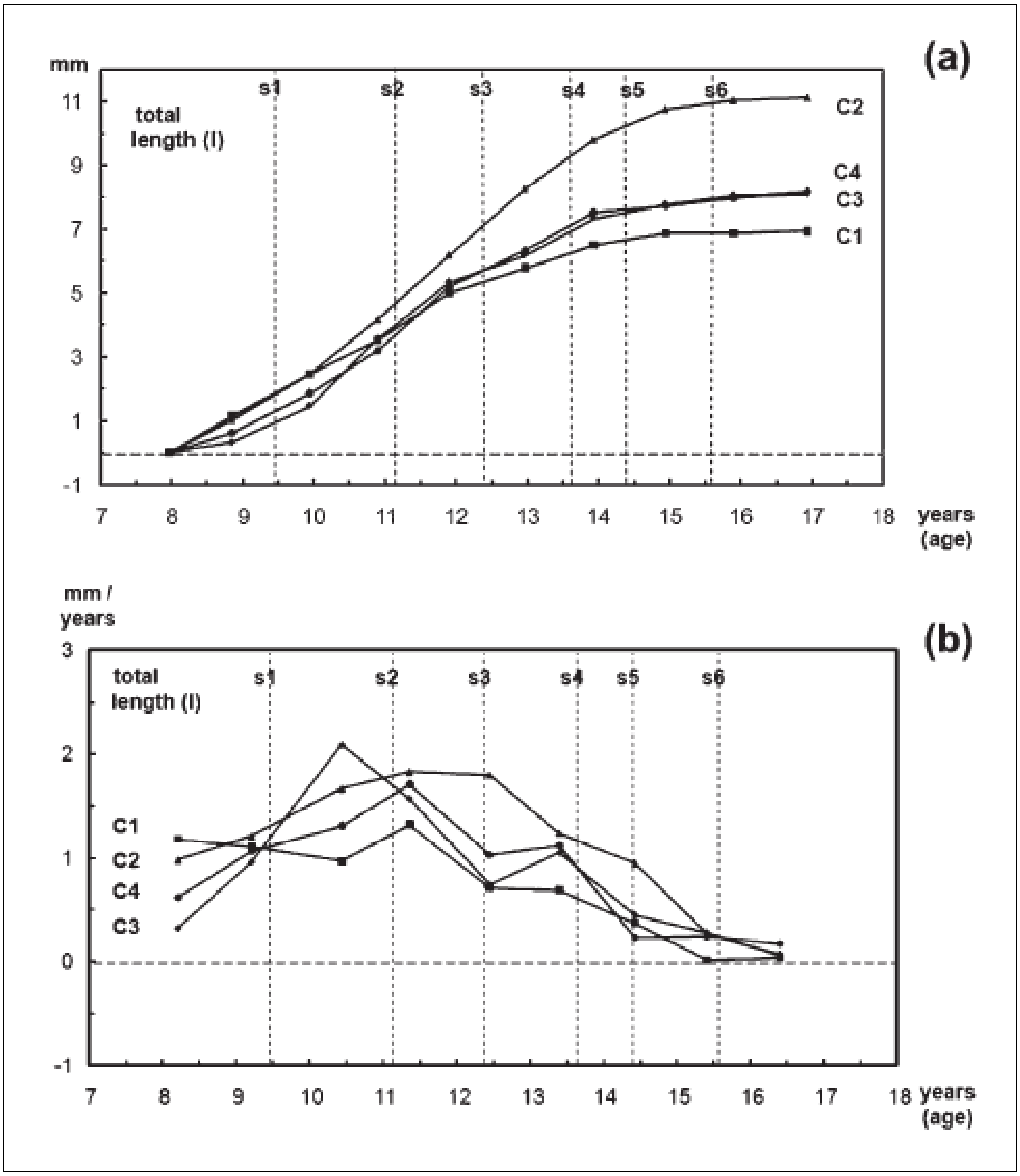

Figure 8. Length changes of C2, C3 and C4[45]
(a) Total length increment curve of C2, C3 and C4
(b) Annual growth rate (length) of C2, C3 and C4
*s1-s6 refers to the cervical vertebral maturational stage based on Hassel and Farman 1995 staging

4.4 Development of the CVM method

Lamparski was the first to publish on the changes in the morphology of the cervical vertebrae.[46] Using a cohort of 72 girls and 69 boys, the shapes of the cervical vertebral bodies were evaluated to assess the correlation with chronological age and skeletal maturity based on hand-wrist radiographs. He developed a six-stage set of standards for evaluating growth based on the two-dimensional morphology of the vertebrae C2, C3 and C4. These stages were further elaborated by Hassel and Farman[19] in 1995, reinforcing the notion that the shapes of the cervical vertebrae change during each stage of skeletal growth (Figure 9).

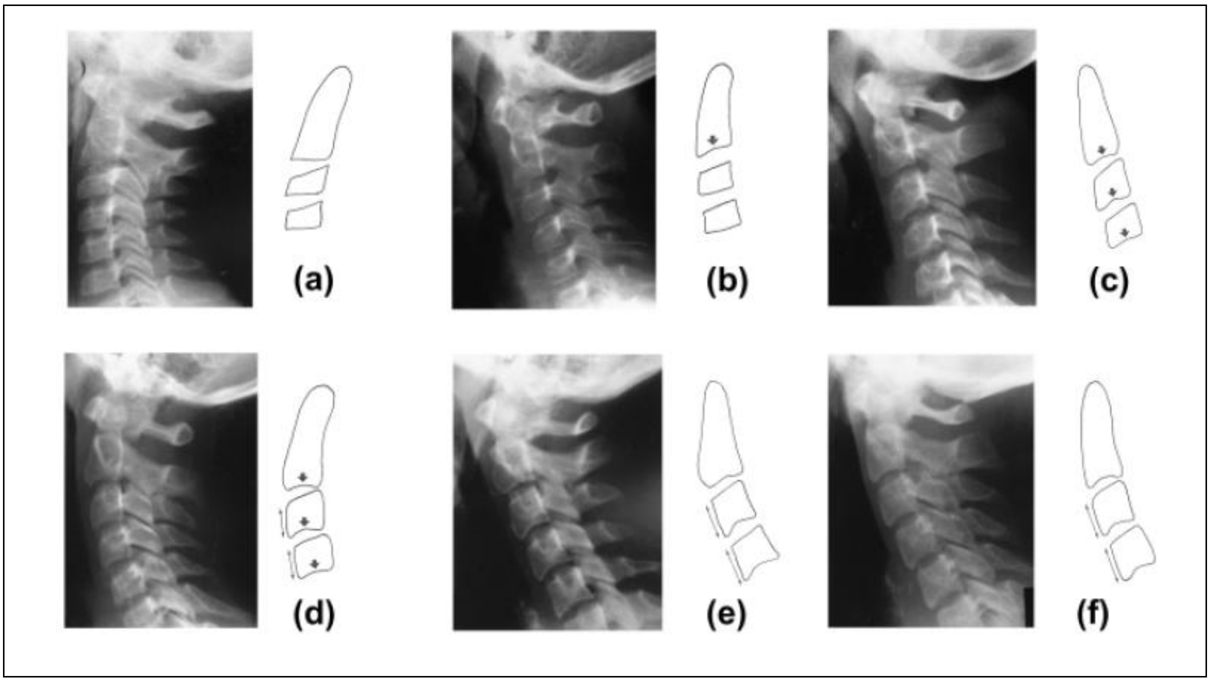

Figure 9. Cervical staging as defined by Lamparski[46] and modified by Hassel and Farman[19]

In orthodontics, the assessment of the amount and timing of remaining jaw growth is critical, as it would ultimately alter the dentofacial orthopaedic management plan. It was not until 1988 that the interest in the assessment of cervical vertebrae as a growth measure resurfaced. Through the assessment of serial lateral cephalometric radiographs of 13 Caucasian girls from 9 to 15 years of age, O'Reilly and Yanniello[18] discovered that there were specific cervical stages when significant increase in mandibular length and corpus and ramus dimension were noted. Thus, they demonstrated a direct relationship between these CVM stages and mandibular growth, rather than simply between CVM and general body growth.[11,47]

In 2000, Franchi and Baccetti[36] evaluated individual patients using Lamparski's original method and found the CVM system to have high validity for determining peak growth rate of the mandible. Following this, Baccetti and Franchi[11] in 2002 published an improved version of the CVM method for the assessment of mandibular growth. They converted the initial six-stage method (CVS 1-6) to a condensed 5-stage method (CVMS I-V), with the peak mandibular growth occurring between CVMS II and III.[11] Advantages of this method included the fact that a single cephalometric film could be used to assess the growth stage, rather than relying on comparisons between consecutive films (Figure 10).

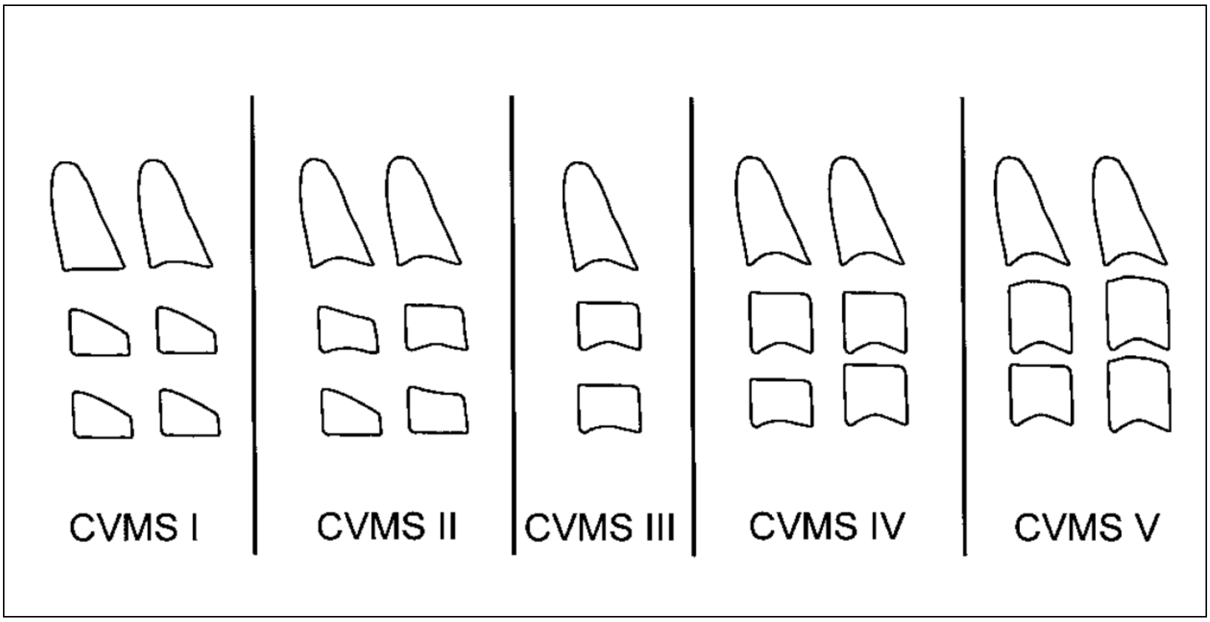

Figure 10. Cervical staging as defined by Baccetti[11] et al. in 2002

In 2005, Baccetti and Franchi[6] made further modification to the CVM assessment, establishing the Cervical Staging (CS 1-6) system. They once again expanded the analysis to include six stages, concluding that at CS 1-2, a patient is pre-pubertal. In this new staging system, the peak mandibular growth occurs between CS3 and CS4, predicted to be around one year after attaining CS2. In addition, 'active' growth is considered to have completed at CS6 (Figure 11).

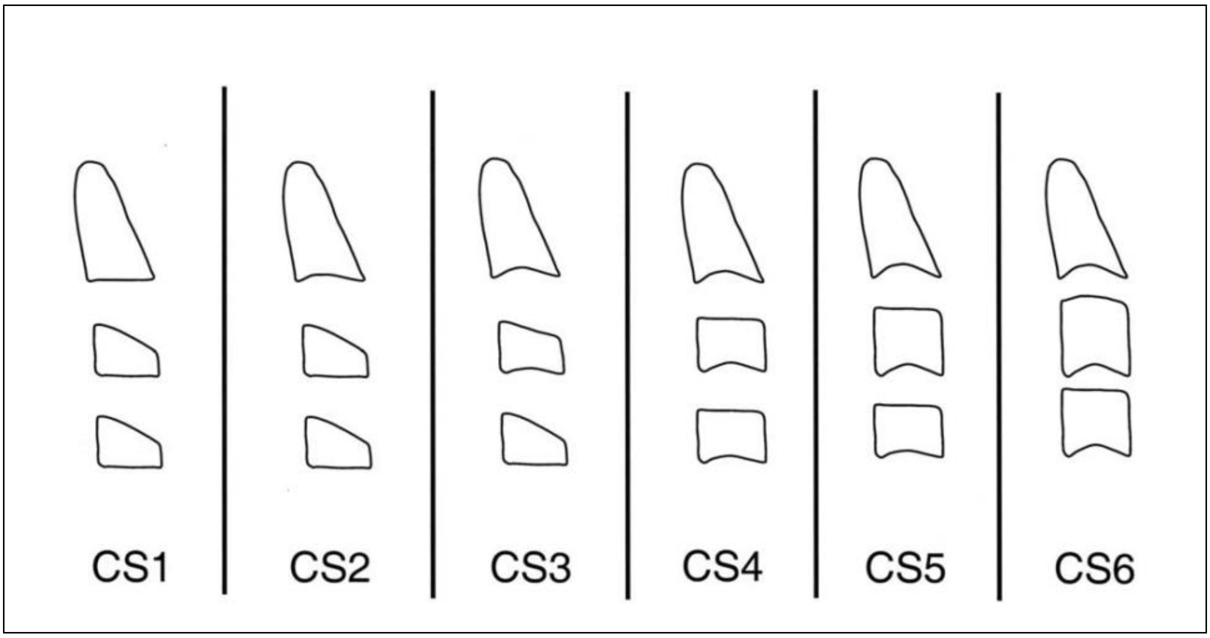

Figure 11. Cervical staging as defined by Baccetti[6] et al. in 2005

4.5 The contemporary CVM Method

The CVM method has gained popularity due to its simplicity without the need for additional radiographs. The main features of the Cervical Vertebral Maturation method as described previously by Franchi and co-workers[36] listed the following:

1. In nearly 95% of North American subjects, a growth interval in CVM coincides with the pubertal peak in both mandibular growth and body height.
2. The appraisal of the shape of the cervical vertebrae is straightforward.
3. The reproducibility of classifying CVM stages is high.
4. The method is useful for the anticipation of the pubertal peak in mandibular growth.
5. Only a limited number of vertebral bodies is used to perform the staging – i.e. C2, C3 and C4.

With the ever-growing interest in the CVM method, studies have attempted to assess the degree of agreement within and between operators as a measure of reliability. Studies have demonstrated high reliability and (greater than 90%) of the CVM method for the assessment of peak growth rate.[37,38,48] However, some authors have raised questions over the methodologies employed in the investigations reporting on high reliability of CVM evaluation. The concern was that the assessment was based on observer tracings rather than the actual lateral cephalograms. It has been suggested that this may introduce bias, thus impacting upon the qualitative assessment of the vertebral morphology.[49,50]

4.6 Limitation of the CVM method

For any accurate diagnostic assessment, the tool should encompass a high degree of sensitivity, specificity, predictability and good reliability. Due to the popularity of the method, the CVM has been extensively studied. In view of assessing the validity of the CVM method, studies have correlated the CVM stages with hand-wrist assessment. [19,51-55] Moreover, other investigations have assessed the CVM stages directly with facial mandibular growth.[6,18,37,52,53,56] Despite the variation in the strength of the association reported in these studies, it has been generally agreed that the CVM method is a practical method in assessing peak growth in patients.

Despite the abundance of literature in support for the CVM method, some studies have reported poor (below 80%) intra- and inter-observer reliability of CVM assessment.[49,50,56] Gabriel and co-workers described poor repeatability in CVM method with 62% intra-observer and 49% inter-observer agreement.[49] Similarly, Nestman et al. in 2011 reported 62% intra-observer and 45% inter-observer agreement.[50] This investigation revealed that the less than optimal reproducibility occurred due to certain vertebrae in certain subjects being more difficult to stage than others. In particular, the evaluation of shape (trapezoidal or square, rectangular, etc.) was found to produce the lowest level of reproducibility, while description of the morphology of the lower border as either flat or curved tended to be high in agreement among the observers. They concluded that the difficulties lie in the shape classification of the bodies, and this issue is amplified in certain cases.

In light of these findings, suggestions of using fewer vertebral bodies and employing more sensitive parameters have been raised.[49] Since the growth and development of cervical vertebrae is a continuous and gradual process, attempting to compartmentalise and stage the process inevitably involves bias and subjective interpretation.[56]

In spite of the reported concerns, recent studies have shown that when standardised training is implemented with the provision of specific guidelines, the CVM assessment may prove to be an “accurate and reproducible” and “satisfactory” method.[38,48] To support this statement, Ballrick and co-workers investigated the accuracy and reproducibility of the CVM method among the orthodontic residents of Ohio State University. The result of the investigation suggested a “very good” reproducibility (kappa value .82) when training was provided to the clinicians.[57] Furthermore, they recommended the use of the CVM assessment as a two phase measure; pre- and post-growth peak, as this would be more clinically applicable and relevant for treatment decision making.

4.7 Quantitative CVM method

Owing to the inherent subjectivity of the cervical staging assessment and potential bias, researchers are now looking into further development of the cervical vertebral assessment based on quantitative rather than qualitative method.[8,58,59] With the move towards Quantitative Cervical Vertebral Maturation (QCVM) method, studies have used the dimensions of second, third and fourth vertebral bodies and the concavity of their lower borders to assess skeletal maturation.[59-61] In 2002, Mito and co-workers[59] devised a regression formula to obtain cervical bone age based on the dimension of the third and fourth vertebral bodies from lateral cephalograms. From this, several researchers were able to derive further formulas to predict mandibular length growth increments using C3 and C4 dimensional ratios as independent variables.[47,60]

More recently, in one investigation, the measurement of C2 vertebral body in three planes, odontoid process and presence of the dentocentral synchondrosis correlated highly with skeletal maturation status.[58] In the study, Byun and co-workers stated that since the growth curve for C2 did not have a distinct peak of growth rate, its growth rate curve was more linear and thus, was considered to be better suited for the multiple linear regression model.

Fundamentally, the changing shape of the cervical vertebral bodies suggest that there is differential growth between its height and width. In the literature, there are very few studies that examine the specifics of the change in cervical vertebral dimensions. Wang and co-workers[62] in their longitudinal assessment identified that the cervical bodies are oval-shaped in early infancy and gradually, the shape changes to a rectangular morphology over time. In the investigation, the average width of the second cervical body changes from 9.13mm to 15.15mm. In comparison, the average height of the second cervical body was 14.51mm and 35.54mm by maturity. Hence, this change in height-to-width ratio of cervical vertebral bodies during growth and development can be utilised to track the stages of skeletal maturity.

4.8 CBCT in Orthodontics

In recent times, utilisation of CBCT of the craniofacial complex has gained immense popularity in many dental settings.[63] Unlike medical Computed Tomography (CT), CBCT is easier to use, cheaper and offers higher resolution for its purposes. Moreover, owing to the compact nature of the CBCT configuration, patients are able to be in the upright or seated position.[64] In regard to orthodontics, the clinical application of CBCT has been limited to locating impacted canines, and to the assessment of root resorptions induced by orthodontic tooth movement.[65]

Without a doubt, CBCT images enable a more accurate and precise assessment of anatomical structures compared to two-dimensional radiographs. Three-dimensional images as obtained from CBCT technology would undoubtedly minimise the inherent limitations such as image superimposition, poor contrast of structures, artefacts, magnification errors and distortions. Ultimately, as summarised by Alqerban[66] "CBCT is a promising radiographic tool that has been proven to provide the clinician with more information than can be obtained from conventional two-dimensional radiographs". In particular, it enables the viewing of the region of interest in a three-dimensional view without overlapping images, thus resulting in increased reliability of diagnosis.[63] Perhaps the use of three-dimensional imaging may even be applied for assessing growth, with its numerous associated advantages.

4.8.1 Comparison between CBCT lateral reconstructed view and lateral cephalograms

With CBCT becoming a popular diagnostic tool for orthodontics particularly in cases involving impacted and ectopic teeth, the suggestion of reconstructed panoramic and lateral view of the dataset has been recommended over taking additional plain-film radiographs. This has the advantage of benefiting the patient from an economical, convenience and radiation hygiene point of view. Subsequently, the comparability of plain film lateral cephalogram and lateral view reconstruction from CBCT dataset has been extensively evaluated. In a study by Joshi and colleagues, a correlation of .975 was reported between CBCT reconstruction and lateral cephalograms for CVM assessment. Similarly, an investigation by Bonfim and co-workers yielded the same conclusion for the use of reconstructed view to assess skeletal maturation based on CVM method.[67]

4.9 Anatomy of the Spheno-Occipital Synchondrosis

The spheno-occipital synchondrosis (SOS) is an essential cartilaginous junction between the occipital and sphenoid bone of the cranium. This anatomical structure is of particular interest, as it plays a prominent role in the development of the craniofacial complex. The flexion and elongation at this junction results in changes in the cranial base angle, which ultimately influences the location of the maxilla and mandible.[68] Due to the noted displacement and changes in the SOS during rapid maxillary expansion, there has been an interest in the assessment of the junction as a marker for the non-surgical expansion intervention.[69] From a growth measure point of view, there is evidence to propose that the fusion of the SOS is linked to the pubertal growth changes[41] and skeletal maturity.[70]

Due to the anatomical location of the spheno-occipital synchondrosis however, two-dimensional radiographic evaluations have been very limited. Much of the literature on the analysis of its closure has relied on macroscopic, histologic and CT investigation. Unfortunately, due to the inconsistent methodologies and variable sensitivity for detection of SOS closure, the reported findings from these investigations were less than meaningful.

Considering the various clinical applications, it is possible that if these limitations can be overcome, the assessment of the spheno-occipital synchondrosis may provide clinicians with more insight and information in making clinical decisions involving growth, maxillary expansion and identification of craniofacial developmental anomalies.

4.9.1 Closure of the Spheno-Occipital Synchondrosis

It has recently been proposed that the skeletal maturity of an individual can be estimated by assessing the closure of the spheno-occipital synchondrosis[71]. This cartilaginous union in the posterior cranial fossa continues to grow throughout childhood and increases the length of the cranial base. With the continued development of the cranial base until adolescence, the closure of the spheno-occipital synchondrosis has been related to the onset of puberty in teenagers. As the structure lies beneath the anterior cranial fossa, growth of the spheno-occipital synchondrosis will affect the position of the mandible, thus influencing the relationship between the maxilla and mandible. However, despite its significance, conventional radiographs have a restricted view in assessing the closure of the synchondrosis due to its location and overlying anatomical structures. Bassed and co-workers[7] investigated the value of using CBCT to overcome this issue, and were able to successfully analyse the fusion of the structure this imaging technique. In the study, they assessed the ossification progress of the SOS using a five-stage system modified from that of Powell and Brodie's classification[72]. They concluded that the "progressive closure of the synchondrosis is correlated with age".

5. Relationship between cervical vertebral maturation and spheno-occipital synchondrosis closure (Paper Two)

5.1 Abstract

Introduction: Increased growth in 3-dimensional imaging has created the opportunity for alternative measures of growth assessment. The aim of this study was to evaluate the relationship between the cervical vertebral maturation (CVM) method and closure of the spheno-occipital synchondrosis (SOS) in children and young adults using cone-beam computed tomography (CBCT).

Methods: Two hundred and seventy-five extended field CBCT scans of patients aged 6 to 30 years were analysed. The cervical vertebral maturity was assessed using the CVM method. The closure of the spheno-occipital synchondrosis was evaluated using a five-stage scoring system. Correlation and agreement between cervical vertebral maturation and fusion of the spheno-occipital synchondrosis were analysed for statistical significance.

Results: A strong significant correlation (r_s = .908; 95% CI: .885, .927) was found between cervical vertebral maturational status and the closure of the spheno-occipital synchondrosis. Based on the variables assessed, an ordinal regression model was constructed to predict cervical stage, to which age, gender and spheno-occipital synchondrosis closure were statistically significant.

Conclusion: This pilot investigation demonstrated that the maturation stage of the spheno-occipital synchondrosis, as determined using CBCT, is a potential indicator for skeletal maturity.

5.2 Introduction

The identification of the optimal timing for orthodontics and dentofacial orthopaedics has been a topic of great interest in orthodontic research. The current understanding suggests that such timing is linked closely with a patient's growth status. There is a general agreement that the most effective response to functional orthopaedic intervention occurs during the pubertal growth spurt.[2-5] In fact, it has been proposed that rather than the type of appliance, it is the timing of treatment that would bring about the greatest increase in the quantity of mandibular growth.[6] In addition, the identification of the decreased growth period and skeletal changes is important for the timing of orthognathic surgical intervention. As such, a reliable indicator to detect peak growth velocity becomes a crucial assessment tool in orthodontic treatment planning.

A variety of biological indicators have been employed to assess general body growth. These indicators include: body height, chronological age, dental development, maturation of the hand and wrist, secondary sexual characteristics and cervical vertebral maturation (CVM).[11-19] With the advent of three-dimensional imaging technology, clinicians are now provided with more details and landmarks previously inaccessible with two-dimensional imaging modalities. One such structure able to be much better visualised with three-dimensional imaging such as cone-beam computed tomography (CBCT) is the spheno-occipital synchondrosis (SOS), an essential cartilaginous junction between the occipital and sphenoid bones of the cranium.

This anatomical structure is of particular interest, as it plays a prominent role in the development of the craniofacial complex. The flexion and elongation at this junction results in changes in the cranial base angle, which ultimately influences the location of the maxilla and mandible.[68] Due to the noted displacement and changes in the SOS during rapid maxillary expansion, there has been an interest in the assessment of the junction as a marker for the non-surgical expansion intervention.[69] From a growth measure point of view, there is evidence to propose that the fusion of the SOS is linked to the pubertal growth changes and skeletal maturity.[41,70]

Considering the various clinical applications, it is possible that the assessment of the spheno-occipital synchondrosis may provide clinicians with more insight and information in making clinical decisions involving growth, maxillary expansion and identification of craniofacial developmental anomalies.

In this study, the aim was to assess the relationship between the CVM stage and SOS closure in children and young adults using CBCT. This will serve as a pilot investigation into the use of SOS closure as a potential indicator of growth maturation.

5.3 Materials and Methods

The appropriate size for this cross-sectional study was determined by using a power analysis calculation. Using an alpha of .05, a power of .95 and a correlation of .3, the minimum sample size was estimated to be 56. At the time of collection, total of 500 consecutive de-identified CBCT datasets were acquired from The University of Queensland Radiology Clinic and a private radiology practice. Ethical approval was obtained from the University of Queensland (Project Number: 1702). All of the CBCT scans had been previously acquired as a part of orthodontic diagnosis and management requirements. DICOM data of each scan was exported and manipulated with Anatomage InVivo 5 (Anatomage, San Jose, CA, USA).

Datasets chosen to be analysed were extended field-of-view scans of subjects aged 6 to 30 years. It was a requirement that the field of view extends from the anterior cranial base to the lower border of C4. Participants were excluded if any of the following were noted: distortion of the dataset due to patient movement; developmental anomalies affecting the craniofacial structures or vertebrae; or previous history of head and neck surgery.

Out of the 500 datasets, 275 CBCT scans fulfilled the inclusion criteria. The majority of the rejections were due to the body of C4 not being included in the scan.

Qualitative assessment of the CVM stages was based on the six-stage system described by Bacetti et al.[6] The assessment of the SOS closure was conducted using the five-stage scoring system developed by Bassed et al[7].

Statistical analysis

The data was analysed using statistical software (SPSS version 21.0 for Windows, Chicago, Il, USA). With regard to levels of significance, p-values of less than .05 were considered to be statistically significant. Furthermore, the relationship between CVM stage and SOS fusion was analysed with Spearman's Correlation Coefficient (r_s).

In this investigation, the complete dataset was analysed by a single scorer (S.F.). To ascertain a satisfactory reliability, 25 randomly selected datasets were assessed by another experienced scorer (P.M.). Reassessment was conducted after two weeks to ensure a reproducible and consistent measurement. The evaluation of the intra- and inter-rater agreements was conducted using Cohen's Kappa coefficient.

5.4 Results

The intra-rater agreement at the two time points was .88 (95% CI: .86, .90) for the assessment of the cervical vertebral staging and .93 (95% CI: .92, .95) for the SOS closure. Thus, the strength of intra-rater agreement was excellent. The assessment of the inter-rater agreement was accomplished using the same 25 datasets. The weighted Kappa coefficient agreement was .82 for the vertebrae assessment and .85 for the SOS closure. In all cases, the difference in the assessment for either CVM or SOS staging was no more than one stage.

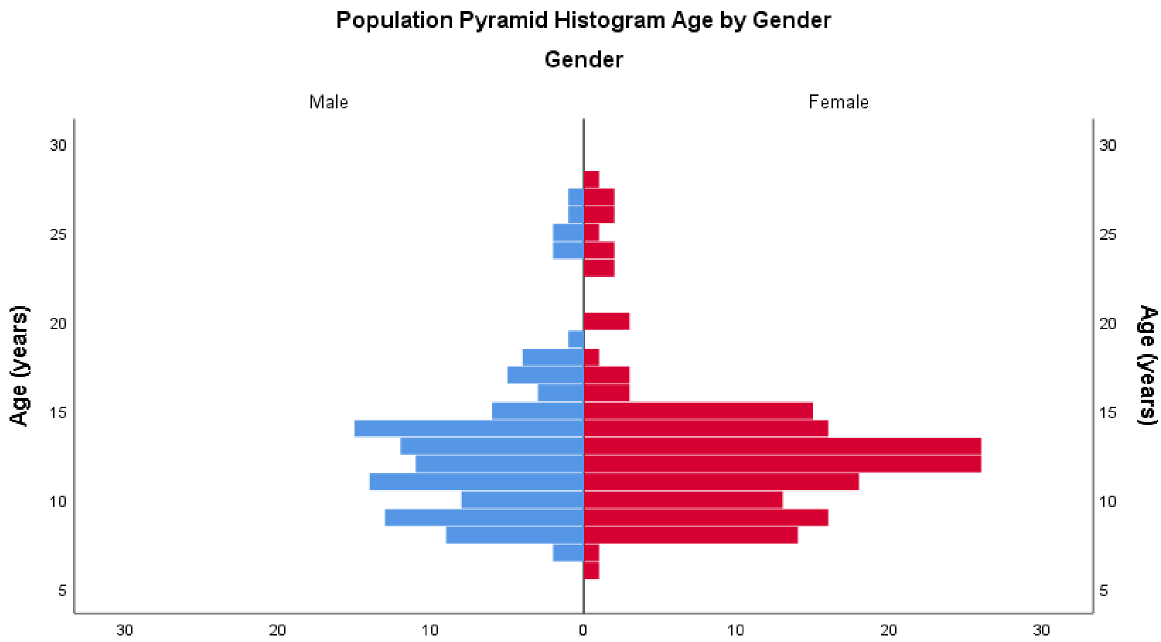

Figure 12. Demographic characteristics of the sample

The demographic distribution by gender of the sample is shown in Figure 12. Most participants were within the age range of 10 to 15 years, with more females (166; 60%) than males (109; 40%).

Synchondrosis Stage	Vertebrae Stage 1	2	3	4	5	6	Total
1	52	39	8	0	0	0	99
2	5	13	36	5	0	0	59
3	0	1	6	15	1	0	23
4	0	0	3	22	20	1	46
5	0	0	0	3	15	30	48
Total	57	53	53	45	36	31	**275**

Table 7. Distribution of synchondrosis stage by vertebrae stage

The distribution of the maturational stages of the synchondrosis by cervical vertebrae is shown in Table 7. The pattern indicated the positive relationship between CVM stages and the closure of the SOS. In addition, correlation coefficient between the cervical vertebral stage and spheno-occipital closure was found to be r_s = .908 (95% CI: .885, .927). The correlation between SOS stage and age was r_s = .857 (95% CI: .822, .885).

Characteristics	CS Stage Pre-growth n (%)	 Post-growth n (%)
Gender		
Female	84 (50.6)	82 (49.4)
Male	79 (72.5)	30 (27.5)
Synchondrosis stage		
1	99 (100)	0 (0)
2	54 (91.5)	5 (8.5)
3	7 (30.4)	16 (69.6)
4	3 (6.5)	43 (93.5)
5	0 (0)	48 (100)

Pre-growth ≤ 3 on CS stage; Post-growth ≥ 4 on CS stage.

Table 8. Characteristic variables and the percentage of participants at pre- or post-growth based on CS stage

The percentage breakdown of SOS stage by pre- or post-peak growth peak, based on CS maturation, is shown in Table 8.

CS Stage	Odds Ratio	95% Confidence Interval		P-Value
		Lower Bound	Upper Bound	
Age (years)	1.84	1.53	2.20	< 0.001
Gender				
Female *(reference)*				
Male	0.29	0.16	0.51	< 0.001
SOS Stage				
1 (*reference)*				
2	6.7	2.8	15.7	< 0.001
3	88.2	21.6	360.0	< 0.001
4	495.8	98.3	2499.7	< 0.001
5	5803.5	825.8	40784.0	< 0.001

Table 9. Results of the ordinal logistic regression model with the cervical vertebral maturation as the outcome variable and age, gender and SOS closure as predictors

The result of ordinal regression is shown in Table 9. The findings indicated that an increase in SOS stage was associated with an increase in CS stage, though the rate of increase was not linear. Moreover, significant association among the variables of age, gender and SOS closure stages were noted. The model shows that all variables were independently associated with cervical vertebral maturation stages.

5.5 Discussion

Treatment timing is an essential consideration in orthodontic management, particularly when dentofacial orthopaedics is involved. It has been suggested that the use of a functional appliance during the peak growth period produces more favourable skeletal change. [2-5,73] At present, despite a multitude of methods suggested, there is no single optimum method for the determination of the period of accelerated growth. Therefore, clinicians resort to using a combination of the currently available methods.

The CVM method has been studied extensively in recent times and has been suggested as an acceptable way of assessing skeletal growth in orthodontic patients.[37] Owing to the subjective nature of the CVM method, many studies examining the inter-rater reliability have shown concerns over its consistency in identifying distinct stages of the gradual, non-linear process that is growth. However, from a clinical perspective, such concern proved to be minimal, as it is the identification of the pre- and post-peak growth that is essential. For the purposes of distinguishing pre- and post-mandibular growth peak, Ballrick and colleagues have recommended using the CVM stage as a 2-phase measure (pre- and post-peak growth), rather than differentiating it into 5 or 6 detailed stages.[74] The result of their study showed the CVM method to be not only a valid tool, but one that is reliable and clinically useful. Furthermore, the delineation between pre- and post-peak growth have commonly been established between CS3 and CS4, as suggested by Bacetti and co-workers in their seminal paper in 2005.[6]

It has recently been proposed that the skeletal maturity of an individual can be estimated by assessing the closure of the spheno-occipital synchondrosis.[71] This cartilaginous union in the posterior cranial fossa continues to grow throughout childhood and increases the length of the cranial base. With the continual development of the cranial base until adolescence, the closure of the spheno-occipital synchondrosis has been related to the onset of puberty in teenagers. Much of the previous literature on the analysis of spheno-occipital synchondrosis closure has largely relied on macroscopic, histologic, and CT investigations. Unfortunately, due to the inconsistent methodologies and variable sensitivity for detection of SOS closure, the reported findings from these investigations were less than meaningful. Overcoming the limitation of conventional radiographs with restricted view of the synchondrosis closure, Bassed and co-workers were able to successfully analyse the fusion of the structure using

CBCT.[7] In their study, they evaluated the closure of the SOS by modifying the classification system suggested by Powell and Brodie[72]. They concluded that the ossification of the SOS is correlated with chronological age.

The present study assessed the relationship between CVM maturational stage and the closure of the SOS within a dataset of 275 CBCT scans. The results showed statistically significant and strong positive association (r_s = .908), which is similar to that of a recent study done by Fernández-Pérez et al[71] Moreover, it was found that age has a strong positive association with SOS closure (r_s = .857), establishing that the ossification is likely related to skeletal maturity.

The findings of this study established a promising potential for using CBCT to evaluate SOS stages and accordingly skeletal maturity. Interestingly, upon reaching SOS stage 3, the fusion of the superior half of the synchondrosis, there is a high likelihood that the patient has passed their peak growth (69.6%). Beyond this, in SOS stages 4 and 5, this percentage increases to 93.5% and 100% respectively.

From a clinical perspective, while a routine CBCT scan is not recommended for every patient undergoing orthodontic management, should a CBCT dataset be available, the staging of the SOS may assist in determining the growth status of the patient. Moreover, with the continued refinement of three-dimensional imaging technology, it may just be a matter of time before CBCT supersedes conventional radiographs and provide a more accurate view of the anatomical structures with lower radiation doses. Considering this, further diagnostic markers will undoubtedly be identified to capture additional information useful for planning orthodontic interventions such as functional appliances or maxillary expanders.

This study has demonstrated a promising potential of SOS closure assessment to determine growth status. However, there are limitations to this study that need to be mentioned. The assessment of the CVM staging was conducted by two operators who underwent a calibration process and followed the guidelines as suggested by Bacetti et al.[6] in their six-stage assessment of the cervical vertebrae. Many studies have shown that the agreement among a small number of raters proved to be excellent.[37,49,55] However, when more than three operators were introduced, the reliability reduced.[75] To overcome such issue, as suggested by Ballrick and colleagues, the use of the CVM assessment was based upon two-phase measure: pre- and post-growth peak.[74] Nonetheless, our assessment with either the six-stage or 2-phase assessment of the cervical vertebrae showed a strong and significant relationship between the CVM stage and SOS closure.

A limitation of this investigation, although a commonly encountered problem, is the absence of uniformity in the demographic distribution of the cohort. All of the dataset was anonymised before the collection of the data and thus, the only accessible information available was the gender and age. Consequently, it was not possible to sort the sample into their cultural or ethnic backgrounds. Conversely, it can be interpreted that such diverse sample is representative of a snapshot of the Australian population that may undergo orthodontic treatment.

Based on the literature regarding SOS closure assessment, there is currently no singular diagnostic assessment standard. This is due to the SOS being difficult to assess using plain film imaging modalities. Traditionally, the assessment has been based on anthropological/forensic evaluation involving macroscopic and/or histological studies. It is only in recent times that three-dimensional modalities have been utilised to assess the structure. As such, this is a relatively recent method that has yet to be comprehensively investigated.

5.6 Conclusion

The results from this pilot investigation indicated that the stage of spheno-occipital synchondrosis closure and the cervical vertebral maturation stage as analysed from CBCT images are highly and significantly correlated with each other. With further research, it should be possible to develop a system for using the SOS stages evaluated using CBCT, to assess growth maturation.

5.7 Acknowledgements

The authors would like to thank the Australian Society of Orthodontists (ASO) and the Australian Society of Orthodontists Foundation for Research and Education (ASOFRE) for the continual support and assistance.

6. Cervical Vertebral Maturational Assessmeent Through Quantitative Assessment of The Third Cervical Vertebral Body (Paper Three)

6.1 Abstract

Introduction: With the demand for a more objective skeletal maturational assessment, the notion of a quantitative cervical vertebral maturation method (QCVM) has been suggested to supersede its subjective counterpart. The aim of this investigation was to evaluate and determine which QCVM parameters based on the third cervical vertebral body would be predictive of skeletal maturation in children and young adults using cone-beam computed tomography (CBCT).

Methods: Two hundred and seventy-five extended field CBCT scans of patients aged 6 to 30 years were analysed. The cervical vertebral maturity was assessed using the CVM method. The QCVM parameters were evaluated by using measurements from the body of the third vertebra. A Receiver Operating Characteristic (ROC) curve analysis was conducted to determine the optimal parameter that would be predictive of skeletal maturation.

Results: The parameter AH3/LW3 demonstrated a statistically significant Area Under the Curve value of .925 (95% CI: .895, .954). The AH3/LW3 ratio of ≥ 0.78 was determined to be the threshold of optimal sensitivity and specificity.

Conclusion: The pilot investigation demonstrated that QCVM parameters, specifically AH3/LH3 ratio, is a potential indicator for skeletal maturity.

6.2 Introduction

Accurate determination of the optimal timing for orthodontics and dentofacial orthopaedics has been investigated continuously and extensively in the literature. The current understanding suggests that such timing is linked closely with a patient's growth status. There is a general agreement that the most effective response to functional orthopaedic intervention occurs during the pubertal growth spurt.[2-5] In fact, it has been proposed that rather than the type of appliance, it is the timing of treatment that would bring about the greatest increase in the quantity of mandibular growth.[6] In addition, the identification of the decreased growth period and skeletal changes is important for the timing of orthognathic surgical intervention. As such, a reliable indicator to detect peak growth velocity becomes critical to orthodontic treatment planning.

Several biological markers have been employed to assess general body growth. These indicators include: body height, chronological age, dental development, maturation of the hand and wrist, secondary sexual characteristics and cervical vertebral maturation (CVM).[11-19] The CVM method has gained popularity owing to the ease of assessment and the lack of need for additional radiographs. Despite the abundance of literature in support for the CVM method however, some studies have suggested poor (below 80%) intra- and inter-observer reliability of CVM assessment.[49,50,56] Gabriel and co-workers reported poor reproducibility of the CVM method with 62% intra-observer and 49% inter-observer agreement.[49] Nestman et al. in 2011 reported similar results with 62% intra-observer and 45% inter-observer agreement.[50]

In light of these findings, suggestion of using fewer vertebral bodies and employing more sensitive parameters has been raised.[49] Since the growth and development of cervical vertebrae is a continuous and non-linear process, attempting to compartmentalise and 'stage' the process inevitably involves bias and subjective interpretation.[56] Nestman and co-workers have shown that some vertebrae in some subjects were easier to assess. Additionally, certain analysis parameters were more clearly defined than others.[50] For instance, description of the morphology of the lower border as either flat or curved tended to be high in agreement among the observers. On the other hand, the evaluation of shape (trapezoidal or square, rectangular, etc.) was found to produce the lowest level of reproducibility.

Owing to the inherent subjectivity of the cervical staging and potential bias, researchers are now looking into further development of the cervical vertebral assessment based on quantitative rather than qualitative method.[8,58,59] With the move towards Quantitative Cervical Vertebral Maturation (QCVM) method, studies have used the dimensions of second, third and fourth vertebral bodies and the concavity of their lower borders to assess skeletal maturation.[8,58-61] In 2002, Mito and co-workers devised a regression formula to obtain cervical bone age based on the dimension of the third and fourth vertebral bodies from lateral cephalograms.[59] From this progress, several researchers were able to derive further formulas to predict mandibular length growth increments using C3 and C4 dimensional ratios as independent variables.[47,60]

The findings from these investigations have put forward novel approaches for the assessment of growth. Nonetheless, studies on QCVM to date have only utilised regression analysis to map and predict growth as a linear concept. As somatic growth does not follow a linear pattern, such method of analysis would fall short with multicollinearity problems. Byun and co-workers were able to overcome such a problem by using C2 parameters that showed more linear growth pattern.[58]

It is thought that the future direction of research for QCVM would be the development of a parameter that is simple to use and sensitive enough to determine a window bordered by pre- and post-mandibular growth spurt. Accordingly, the aim of this study was to assess the relationship between the CVM stage and various QCVM parameters of the third cervical body in children and young adults using CBCT. This will serve as a pilot investigation into the assessment of QCVM parameter(s) that may be useful as potential indicators of growth maturation.

6.3 Materials and Methods

The appropriate size for this cross-sectional study was determined by a power analysis calculation. Using an alpha of .05, a power of .95 and a correlation of .3, the minimum sample size was estimated to be 56. At the time of collection, a total of 500 consecutive de-identified CBCT datasets were acquired from The University of Queensland Radiology Clinic and a private radiology practice. Ethical approval was obtained from the University of Queensland (Project Number 1702). All of the CBCT scans had been previously acquired as a part of orthodontic diagnosis and management requirements. DICOM data of each scan was exported and manipulated with Anatomage InVivo 5 (Anatomage, San Jose, CA, USA).

Datasets chosen to be analysed were extended field-of-view scans of subjects aged 6 to 30 years. It was a requirement that the field of view extends from anterior cranial base to the lower border of C4. Participants were excluded if any of the following were noted: distortion of the dataset due to patient movement; developmental anomalies affecting the craniofacial structures or vertebrae; or previous history of head and neck surgery.

Out of the 500 datasets, 275 CBCT scans fulfilled the inclusion criteria. The majority of the rejections were due to the body of C4 not being included in the scan.

Qualitative assessment of the CVM stages was based on the six-stage system described by Bacetti et al.[6] Quantitative measurements were completed using the QCVM method as described by Chen et al.[8] Figure 13 displays the structural points that were plotted for each dataset. The measured parameters are listed in Table 10. In the investigation, to accommodate for magnification, ratios of the linear measurements were utilised.

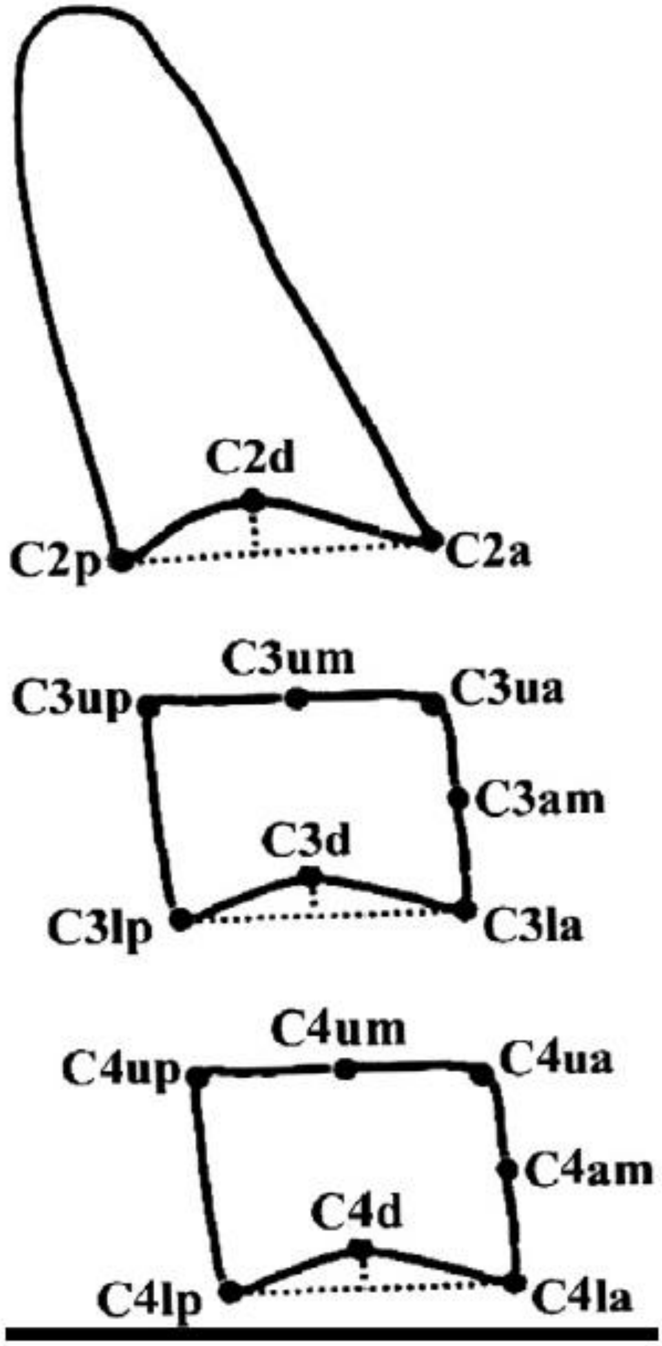

Figure 13. Cervical Vertebral Structural points plotted for each dataset

Parameter	**Description**
C3 Body Variables	
Vertical measurements	
PH3	distance between C3up to C3lp
H3	distance between C3um to C3d
AH3	distance between C3ua to C3la
Horizontal measurements	
UW3	distance between C3ua to C3up
W3	distance between C3am to mid-point between C3up and C3lp
LW3	distance between C3la to C3lp
Vertical Ratio	
AH3/H3	ratio of AH3 to H3
H3/P3	ratio of H3 to PH3
AH3/PH3	ratio of AH3 to PH3
Horizontal ratio	
UW3/LW3	ratio of UW3 to LW3
UW3/W3	ratio of UW3 to W3
LW3/W3	ratio of LW3 to W3
Height/Width Ratio	
AH3/UW3	ratio of AH3 to UW3
AH3/LW3	ratio of AH3 to LW3
H3/UW3	ratio of H3 to UW3
H3/LW3	ratio of H3 to LW3
PH3/UW3	ratio of PH3 to UW3
PH3/LW3	ratio of PH3 to LW3

Table 10. Parameters and ratios used in the QCVM analysis

Statistical analysis

The data was analysed using statistical software (SPSS version 21.0 for Windows, Chicago, Il, USA). With regard to levels of significance, p-values of less than .05 were considered to be statistically significant. In this investigation, the complete dataset was analysed by a single scorer (S.F.). To ascertain a satisfactory reliability, 25 randomly selected datasets were assessed by another experienced scorer (P.M.). Reassessment was conducted after two weeks to ensure a reproducible and consistent measurement. The evaluation of the intra- and inter-rated agreement was conducted using Cohen's Kappa coefficient.

Receiver Operator Characteristics (ROC) curve analysis was used to determine vertebrae measurements that were significantly associated with vertebrae stage of growth. The confidence intervals for the area under the curve (AUC) that do not contain .5 were considered statistically significant. Optimal post-growth values were determined as the vertebrae measurement that optimised sensitivity and specificity by finding the point closest to the top of the *y*-axis. The AUC value was used to measure the strength of the association between the vertebrae measurement variables and stage of growth. The optimal post-growth value was used to convert the continuous variable to a binary form. Binary logistic regression was used to determine the odds ratio for post-vertebral growth based on vertebrae stage and AH3/LW3 after adjusting for age and gender.

6.4 Results

The intra-rater agreement at the two time points was .88 (95% CI: .86, .90) for the assessment of the cervical vertebral staging and .94 for the linear measurements (95% CI: .93, .95). Thus, the strength of intra-rater agreement was excellent. The assessment of the inter-rater agreement was accomplished using the same 25 datasets. The weighted Kappa coefficient agreement was .82 for the vertebral assessment and .96 for the linear measurements. In all cases, the difference in the assessment was no more than one stage.

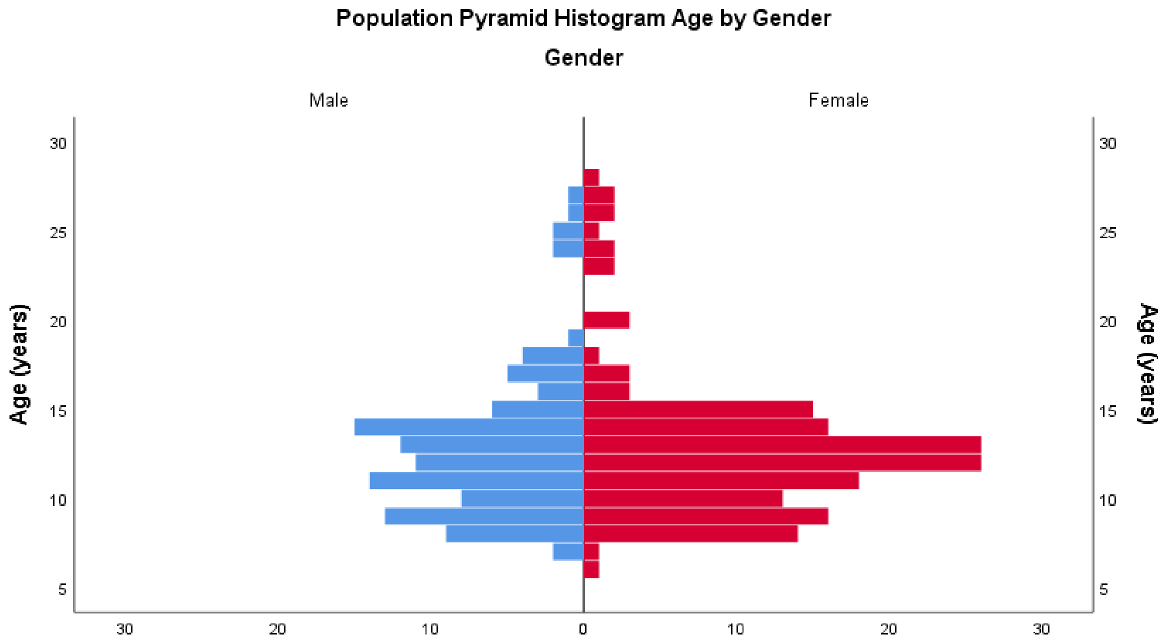

Figure 14. Demographic characteristics of the sample

The demographic distribution by gender of the sample is shown in Figure 14. Most participants were within the age range of 10 to 15 years, with more females (166; 60%) than males (109; 40%).

Characteristics	CS Stage Pre-growth n (%)	 Post-Growth n (%)
Gender		
Female	84 (50.6)	82 (49.4)
Male	79 (72.5)	30 (27.5)

Table 11. Characteristic variables and the percentage of participants at pre- or post-growth based on CS stage

The frequency distribution of gender and CS maturation stage is shown in Table 11.

Variable	AUC†	95% CI	Optimal post-growth value‡	Sensitivity (%)	Specificity (%)
AH3/LW3	0.925	(0.895, 0.954) *	≥ 0.78	88.4	84.7
PH3/UW3	0.890	(0.853, 0.927) *	≥ 0.90	84.0	79.8
AH3/H3	0.835	(0.788, 0.883) *	≥ 1.08	75.0	78.0
H3/W3	0.810	(0.760, 0.860) *	≥ 0.78	66.1	81.0
AH3/PH3	0.738	(0.678, 0.796) *	≥ 0.91	75.0	63.8
H3/PH3	0.719	(0.659, 0.778) *	≤ 0.87	73.2	66.3
UW3/W3	0.602	(0.534, 0.670) *	≤ 0.97	59.8	55.8
LW3/W3	0.602	(0.534, 0.670) *	≤ 0.97	59.8	55.8
UW3/LW3	0.530	(0.460, 0.600)	≤ 0.92	52.7	57.1

†Area under the curve.
‡Optimal post-growth value is the value that optimises sensitivity with specificity for predicting post growth stage.
*Significant at P < 0.05

Table 12. Receiver Operating Characteristic (ROC) curve analysis for spinal measurements predicting post-growth stage of vertebral development

The ROC curve is shown in Figure 15 and the result of the ROC curve analysis in Table 12. The findings indicated that the variable AH3/LW3 with the ratio ≥ .78 provided the highest area under the curve value of .925. Moreover, the ratio demonstrated significant association to predict post peak growth with the highest sensitivity and specificity. The model showed that all cervical variables were independently associated with cervical vertebral maturation stages.

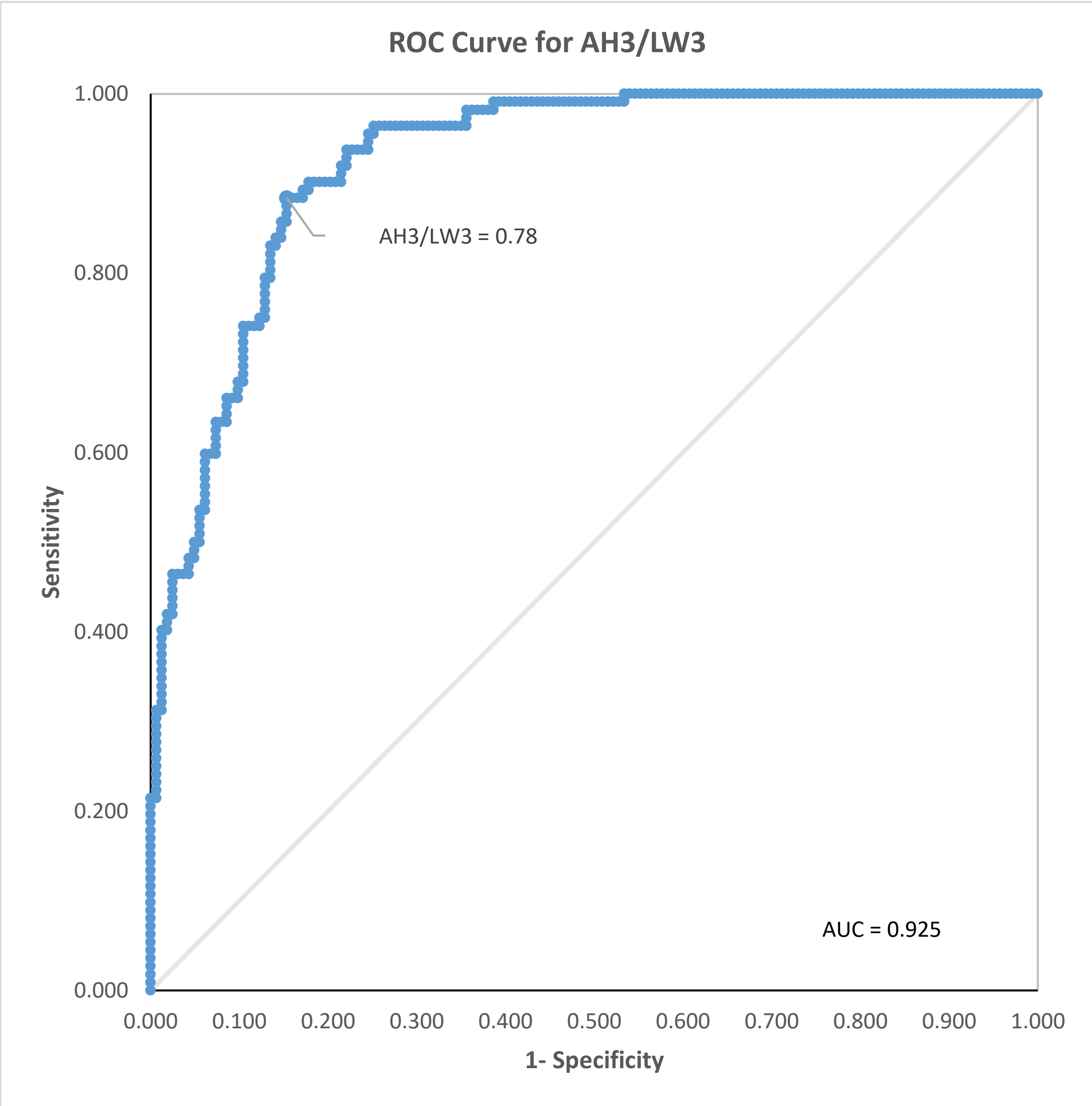

Figure 15. ROC curve for AH3/LW3

6.5 Discussion

Treatment timing is an essential consideration in orthodontic management, particularly when dentofacial orthopaedics is involved. It has been suggested that the use of a functional appliance during the peak growth period would produce more favourable skeletal change. [2-5,73] At present, despite a multitude of techniques suggested, there is no single optimum methodology for the determination of the period of accelerated growth. Therefore, clinicians resort to using a combination of the currently available methods.

The CVM method has been studied extensively in recent times and has been suggested as an acceptable way of assessing skeletal growth in orthodontic patients.[37] Owing to the subjective nature of the CVM method, many studies examining the inter-rater reliability have shown concerns over its consistency in identifying distinct stages of the gradual, non-linear process that is growth. However, from a clinical perspective, such concerns proved to be minimal, as it is the identification of the pre- and post-peak growth that is essential. For the purposes of distinguishing pre- and post-mandibular growth peak, Ballrick and colleagues have recommended using the CVM stage as a 2-phase measure (pre- and post-peak growth), rather than differentiating it into 5 or 6 detailed stages.[74] The result of their study showed the CVM method to be not only a valid tool, but one that is reliable and clinically useful. Thus, the present study utilised the CVM stages as a 2-phase measure to determine the individual's growth status. Furthermore, the delineation between pre- and post-peak growth have commonly been established between CS3 and CS4, as suggested by Bacetti and co-workers in their seminal paper in 2005.[6]

Moreover, in recent times, utilisation of CBCT of the craniofacial complex has gained immense popularity in many dental settings.[63] In the field of orthodontics, the use of CBCT scans is often limited to locating ectopic teeth and assessing dental morphology and root resorptions.[65] Without a doubt, CBCT images enable a more accurate and precise assessment of anatomical structures compared to two-dimensional radiographs. Three-dimensional data obtained from that of CBCT imaging would minimise the inherent limitations of two-dimensional images such as image superimpositions, poor contrast of structures, artefacts, magnification errors and distortions due to positioning inaccuracies.[63]

With the availability of three-dimensional data and ease of manipulation offered by radiographic software, researchers are exploring ways to transition from qualitative to quantitative methods of assessing cervical vertebral maturation.[8,58,59] Early investigation of the quantitative analysis utilised the third and fourth cervical vertebral measurements to assess skeletal maturation.[8,58-60] More recently however, one investigation revealed that the measurement of C2 vertebral body in three planes, odontoid process and presence of the dentocentral synchondrosis correlated highly with skeletal maturation status.[58] In the study, Byun and co-workers stated that since the growth curve for C2 did not show a distinct peak of growth rate and exhibited a more linear growth curve, parameters relating to C2 may be better suited for the multiple linear regression model.[58]

The conventional qualitative CVM method has been based upon analysing the changing shape of the cervical vertebral bodies. This suggests that there is a differential growth between its height and width dimensions. In the literature, there are very few studies that investigated the growth and development of the cervical spine. Wang and co-workers in their longitudinal assessment identified that the cervical bodies are oval-shaped in early infancy and gradually, the shape changes to a rectangular morphology over time.[62] In the study, the average width of the second cervical body changes from 9.13mm to 15.15mm. In comparison, the average height of the second cervical body was 14.51mm and 35.54mm by maturity. Hence, during growth and development, the height-to-width ratio of the vertebral body markedly changes. Results from our study certainly follows this trend, with the growth in width completing earlier than the height parameters.

In our earlier investigation, the second to the fourth cervical vertebrae were plotted, analysed and measured for QCVM parameters. It was found that C2 showed little morphological changes and due to its location, was comparatively more difficult to measure. On the other hand, C3 and C4 were easily isolated and assessed. The decision to select and use C3 parameters was based upon the idea that in some CBCT capture, depending on the field of view and the use of lead collar or apron, there may be limited view of the C4 body. Considering the importance of accurate measurement and practicality, our investigation solely focused on C3 body parameters.

With regard to the use of lateral view reconstruction of CBCT image, study by Joshi and colleagues reported a correlation of .975 was reported for CVMI assessment made using either CBCT reconstruction or lateral cephalograms.[76] Similarly, investigation by Bonfim and co-workers reached the same conclusion for the use of reconstructed view to assess skeletal maturation based on CVM method.[67] Accordingly, we anticipate the results from our investigation to be applicable to plain-film lateral cephalograms.

The present study assessed various ratios and parameters associated with the third cervical vertebrae and has indicated that the parameter AH3/LW3 may be a useful indicator to assess a patient's stage of skeletal maturity. In particular, the value of AH3/LW3 of ≥ 0.78 provided the highest sensitivity and specificity. Currently, there are limited reports in the literature on the analysis of the QCVM parameters, with studies primarily focusing on developing a regression method. Whilst formulae and regression calculations may be useful from a research point of view, it is difficult to be applied in day to day clinical practice. Moreover, it is essential to appreciate that growth does not follow a linear trend and that clinically, the most essential information operators need is whether or not a patient is at pre- or post-peak growth stage of maturation. Perhaps a single parametric ratio of a cervical body would be an attractive tool for clinicians to determine skeletal maturity in a clinical setting.

A limitation of this investigation, although a commonly encountered problem, is the absence of uniformity in the demographic distribution of the cohort. All of the dataset was anonymised before the collection of the data and thus, the only accessible information available was the gender and age. Consequently, it was not possible to sort the sample into their cultural or ethnic backgrounds. Conversely, it can be interpreted that such diverse sample is representative of a snapshot of the Australian population that may undergo orthodontic treatment.

Based on the literature regarding QCVM assessment, there is currently no singular diagnostic assessment standard. As such, this is a relatively new field that has yet to be comprehensively investigated. Perhaps the future direction of research should consider its validity and reproducibility.

6.6 Conclusion

The results from this pilot investigation indicated that the QCVM parameter AH3/LW3 is predictive of the cervical vertebral maturation stages analysed with CBCT dataset. With further research, it should be possible to develop a system for using the QCVM system to assess growth maturation from CBCT dataset.

6.7 Acknowledgements

The authors would like to thank the Australian Society of Orthodontists (ASO) and the Australian Society of Orthodontists Foundation for Research and Education (ASOFRE) for the continual support and assistance.

7. Research Report Summary and Conclusion

7.1 Research report commentary

The present study investigated potential methodologies for growth assessment using CBCT data. Due to the time constraint, budget and availability of data, the classification of an individual's growth status was based upon the currently accepted CVM stages. This provided an efficient method to assess a large amount of data and test the research hypothesis.

Should the opportunity for further research arise in the future, the direction should be towards testing the validity of using SOS stages and QCVM parameters in clinical practice. To provide a benchmark evaluation, these assessment methods should be directly compared with mandibular length changes, to determine an individual's peak mandibular growth window.

7.2 Conclusion

Clinical decision-making in orthodontics heavily relies on the assessment of a patient's likely growth potential. Various treatments such as dentofacial orthopaedics and orthognathic surgery require accurate determination of interventional timings to correct dental and skeletal discrepancies.

Through the increased implementation of three-dimensional imaging in clinical practice, clinicians are now provided with visual access to structures that were not visible on plain film radiographs, as well as digital software that enables ease of viewing and manipulation. As a result, there is a need for further research in the utilisation of these newfound opportunities.

This study aimed to evaluate the relationship between the cervical vertebral maturation (CVM) method and closure of the spheno-occipital synchondrosis (SOS) in children and young adults using cone-beam computed tomography (CBCT). In addition, quantitative cervical vertebral maturation (QCVM) parameters were assessed to determine its ability to predict skeletal maturation.

Given the results, the investigation revealed a strong significant correlation between cervical vertebral maturation status and the closure of the spheno-occipital synchondrosis.

Furthermore, the QCVM parameters, specifically AH3/LW3, was also revealed to be closely associated with maturation of the cervical vertebrae. From such findings, it can be inferred that these measures can be used as potential indicators for skeletal maturity assessment.

Whilst this study only provided an initial insight, the findings of this study set forth a promising prospect of using CBCT to assess skeletal maturity. It is anticipated that the results will enable further investigation into its clinical validity. The future direction will hopefully capture larger sample sizes and a direct comparison with mandibular length changes.

8. References

1. Frost H. Skeletal structural adaptations to mechanical usage: 1. Redefining Wolff's law: the bone modeling problem. The Anatomical Record 1990;226:403-413.

2. Hägg U, Pancherz H. Dentofacial orthopaedics in relation to chronological age, growth period and skeletal development. An analysis of 72 male patients with Class II division 1 malocclusion treated with the Herbst appliance. The European Journal of Orthodontics 1988;10:169-176.

3. Malmgren O, Ömblus J, Hägg U, Pancherz H. Treatment with an orthopedic appliance system in relation to treatment intensity and growth periods A study of initial effects. American Journal of Orthodontics and Dentofacial Orthopedics 1987;91:143-151.

4. McNamara JA, Bookstein FL, Shaughnessy TG. Skeletal and dental changes following functional regulator therapy on Class II patients. American Journal of Orthodontics 1985;88:91-110.

5. Petrovic A, Stutzmann J, Lavergne J. Mechanism of craniofacial growth and approach to orthodontic decision making. Craniofacial growth and orthodontic treatment 1990;23:13-74.

6. Bacetti T, Franchi L, McNamra J. The cervical vertebral maturation (CVM) method for the assessment of optimal treatment timing in dentofacial orthopaedics. Semin Orthod 2005;11:119-129.

7. Bassed RB, Briggs C, Drummer OH. Analysis of time of closure of the spheno-occipital synchondrosis using computed tomography. Forensic science international 2010;200:161-164.

8. Chen L-L, Xu T-M, Jiang J-H, Zhang X-Z, Lin J-X. Quantitative cervical vertebral maturation assessment in adolescents with normal occlusion: a mixed longitudinal study. American Journal of Orthodontics and Dentofacial Orthopedics 2008;134:720-727.

9. Scammon RE. The measurement of the body in children. The Measurement of Man 1930.

10. Proffit W. Fields HW, Sarver DM. Contemporary Orthodontics. 4th ed. St Louis: Mosby Year Book 2007;194.

11. Baccetti T, Franchi L, McNamara Jr JA. An improved version of the cervical vertebral maturation (CVM) method for the assessment of mandibular growth. The Angle Orthodontist 2002;72:316-323.

12. Björk A, Helm S. Prediction of the age of maximum puberal growth in body height. The Angle Orthodontist 1967;37:134-143.
13. Greulich WW, Pyle SI. Radiographic atlas of skeletal development of the hand and wrist. The American Journal of the Medical Sciences 1959;238:393.
14. Hägg U, Taranger J. Menarche and voice change as indicators of the pubertal growth spurt. Acta Odontologica Scandinavica 1980;38:179-186.
15. Hägg U, Taranger J. Maturation indicators and the pubertal growth spurt. American Journal of Orthodontics 1982;82:299-309.
16. Hunter CJ. The Correlation Of Facial Growth With Body Height And Skeletal Maturation At Adolescence. The Angle Orthodontist 1966;36:44-54.
17. Lewis AB, Garn SM. The relationship between tooth formation and other maturational factors. The Angle Orthodontist 1960;30:70-77.
18. O'Reilly MT, Yanniello GJ. Mandibular Growth Changes and Maturation of Cervical Vertebrae: -A Longitudinal Cephalometric Study. The Angle Orthodontist 1988;58:179-184.
19. Hassel B, Farman AG. Skeletal maturation evaluation using cervical vertebrae. American Journal of Orthodontics and Dentofacial Orthopedics 1995;107:58-66.
20. Houston W, Miller J, Tanner J. Prediction of the timing of the adolescent growth spurt from ossification events in hand-wrist films. British Journal of Orthodontics 1979;6:145-152.
21. Bowden B. Sesamoid bone appearance as an indicator of adolescence. Australian Orthodontic Journal 1971;2:242-248.
22. Fishman LS. Radiographic evaluation of skeletal maturation: a clinically oriented method based on hand-wrist films. The Angle Orthodontist 1982;52:88-112.
23. Sierra AM. Assessment of dental and skeletal maturity: a new approach. The Angle Orthodontist 1987;57:194-208.
24. Fishman LS. Chronological versus skeletal age, an evaluation of craniofacial growth. The Angle Orthodontist 1979;49:181-189.
25. Moore RN, Moyer BA, DuBois LM. Skeletal maturation and craniofacial growth. American Journal of Orthodontics and Dentofacial Orthopedics 1990;98:33-40.
26. Bambha JK. Longitudinal cephalometric roentgenographic study of face and cranium in relation to body height. The Journal of the American Dental Association 1961;63:776-799.
27. Sullivan P. Prediction of the pubertal growth spurt by measurement of standing height. The European Journal of Orthodontics 1983;5:189-197.

28. Grøn A-M. Prediction of tooth emergence. J Dent Res 1962;41:573-585.
29. Chapman SM. Ossification of the adductor sesamoid and the adolescent growth spurt. The Angle Orthodontist 1972;42:236-244.
30. Demirjian A, Buschang PH, Tanguay R, Patterson DK. Interrelationships among measures of somatic, skeletal, dental, and sexual maturity. American Journal of Orthodontics 1985;88:433-438.
31. Grave K. Timing of facial growth: a study of relations with stature and ossification in the hand around puberty. Australian Orthodontic Journal 1973;3:117.
32. Helm S, Siersbaek-Nielsen S, Skieller V, Björk A. Skeletal maturation of the hand in relation to maximum puberal growth in body height. Tandlaegebladet 1971;75:1223.
33. Pileski RC, Woodside DG, James GA. Relationship of the ulnar sesamoid bone and maximum mandibular growth velocity. The Angle Orthodontist 1973;43:162-170.
34. Singer J. Physiologic timing of orthodontic treatment. The Angle Orthodontist 1980;50:322-333.
35. Tanner JM, Whitehouse R, Marshall W, Healty M, Goldstein H. Assessment of Skeleton Maturity and Maturity and Prediction of Adult Height (TW2 Method) 1975.
36. Franchi L, Baccetti T, McNamara JA. Mandibular growth as related to cervical vertebral maturation and body height. American Journal of Orthodontics and Dentofacial Orthopedics 2000;118:335-340.
37. Soegiharto BM, Moles DR, Cunningham SJ. Discriminatory ability of the skeletal maturation index and the cervical vertebrae maturation index in detecting peak pubertal growth in Indonesian and white subjects with receiver operating characteristics analysis. American journal of orthodontics and dentofacial orthopedics 2008;134:227-237.
38. Perinetti G, Caprioglio A, Contardo L. Visual assessment of the cervical vertebral maturation stages: A study of diagnostic accuracy and repeatability. The Angle Orthodontist 2014;84:951-956.
39. Bailey DK. The Normal Cervical Spine in Infants and Children 1. Radiology 1952;59:712-719.
40. Bick EM, Copel JW. Longitudinal growth of the human vertebra. J Bone Joint Surg Am 1950;32:803-814.
41. Scheuer L, Black S, Cunningham C. Developmental Juvenile Osteology. Academic Press; 2000.

42. Chandraraj S, Briggs CA. Multiple growth cartilages in the neural arch. The Anatomical Record 1991;230:114-120.
43. Ford D, McFadden K, Bagnall K. Sequence of ossification in human vertebral neural arch centers. The Anatomical Record 1982;203:175-178.
44. Hellsing E. Cervical vertebral dimensions in 8, 11, and 15-year-old children. Acta odontologica Scandinavica 1991;49:207-213.
45. Altan M, Dalci ON, Iseri H. Growth of the cervical vertebrae in girls from 8 to 17 years. A longitudinal study. The European Journal of Orthodontics 2012;34:327-334.
46. Lamparski DG. Skeletal age assessment utilizing cervical vertebrae. American Journal of Orthodontics 1975;67:458-459.
47. Mito T, Sato K, Mitani H. Predicting mandibular growth potential with cervical vertebral bone age. American journal of orthodontics and dentofacial orthopedics 2003;124:173-177.
48. Rainey B-J, Burnside G, Harrison JE. Reliability of cervical vertebral maturation staging. American Journal of Orthodontics and Dentofacial Orthopedics 2016;150:98-104.
49. Gabriel DB, Southard KA, Qian F, Marshall SD, Franciscus RG, Southard TE. Cervical vertebrae maturation method: poor reproducibility. American Journal of Orthodontics and Dentofacial Orthopedics 2009;136:471-478.
50. Nestman TS, Marshall SD, Qian F, Holton N, Franciscus RG, Southard TE. Cervical vertebrae maturation method morphologic criteria: poor reproducibility. American Journal of Orthodontics and Dentofacial Orthopedics 2011;140:182-188.
51. Alkhal HA, Wong RW, Rabie ABM. Correlation between chronological age, cervical vertebral maturation and Fishman's skeletal maturity indicators in southern Chinese. The Angle Orthodontist 2008;78:591-596.
52. Gandini P, Mancini M, Andreani F. A comparison of hand-wrist bone and cervical vertebral analyses in measuring skeletal maturation. The Angle Orthodontist 2006;76:984-989.
53. Grave K, Townsend G. Hand-wrist and cervical vertebral maturation indicators: how can these events be used to time Class II treatments? Australian orthodontic journal 2003;19:33.
54. Kucukkeles N, Acar A, Biren S, Arun T. Comparisons between cervical vertebrae and hand-wrist maturation for the assessment of skeletal maturity. The Journal of clinical pediatric dentistry 1999;24:47-52.

55. Lai EH-H, Liu J-P, Chang JZ-C, Tsai S-J, Yao C-CJ, Chen M-H et al. Radiographic assessment of skeletal maturation stages for orthodontic patients: hand-wrist bones or cervical vertebrae? Journal of the Formosan Medical Association 2008;107:316-325.
56. Zhao X-G, Lin J, Jiang J-H, Wang Q, Ng SH. Validity and reliability of a method for assessment of cervical vertebral maturation. The Angle Orthodontist 2011;82:229-234.
57. Ballrick J, Fields H, Vig K, Beck F, Germack J, Baccetti T. Reliability and validity of cervical vertebral maturation and hand-wrist radiographs. Proceedings of 83rd General Session of the IADR/AADR/CADR 2005:9-12.
58. Byun B-R, Kim Y-I, Yamaguchi T, Maki K, Son W-S. Quantitative Assessment of Cervical Vertebral Maturation Using Cone Beam Computed Tomography in Korean Girls. Computational and mathematical methods in medicine 2015;2015.
59. Mito T, Sato K, Mitani H. Cervical vertebral bone age in girls. American journal of orthodontics and dentofacial orthopedics 2002;122:380-385.
60. Chen F, Terada K, Hanada K. A new method of predicting mandibular length increment on the basis of cervical vertebrae. The Angle Orthodontist 2004;74:630-634.
61. San Román P, Palma JC, Oteo MD, Nevado E. Skeletal maturation determined by cervical vertebrae development. The European Journal of Orthodontics 2002;24:303-311.
62. Wang JC, Nuccion SL, Feighan JE, Cohen B, Dorey FJ, Scoles PV. Growth and development of the pediatric cervical spine documented radiographically. The Journal of Bone & Joint Surgery 2001;83:1212-1218.
63. Scarfe WC, Farman AG, Sukovic P. Clinical applications of cone-beam computed tomography in dental practice. Journal-Canadian Dental Association 2006;72:75.
64. Quereshy FA, Savell TA, Palomo JM. Applications of cone beam computed tomography in the practice of oral and maxillofacial surgery. Journal of Oral and Maxillofacial Surgery 2008;66:791-796.
65. Walker L, Enciso R, Mah J. Three-dimensional localization of maxillary canines with cone-beam computed tomography. American journal of orthodontics and dentofacial orthopedics 2005;128:418-423.
66. Alqerban A, Jacobs R, Fieuws S, Willems G. Comparison of two cone beam computed tomographic systems versus panoramic imaging for localization of impacted maxillary canines and detection of root resorption. The European Journal of Orthodontics 2011;33:93-102.

67. Bonfim MA, Costa AL, Fuziy A, Ximenez ME, Cotrim-Ferreira FA, Ferreira-Santos RI. Cervical vertebrae maturation index estimates on cone beam CT: 3D reconstructions vs sagittal sections. Dentomaxillofacial Radiology 2015;45:20150162.
68. Enlow DH. Facial growth. WB Saunders Company; 1990.
69. Leonardi R, Cutrera A, Barbato E. Rapid maxillary expansion affects the spheno-occipital synchondrosis in youngsters: a study with low-dose computed tomography. The Angle Orthodontist 2010;80:106-110.
70. Lottering N, MacGregor DM, Alston CL, Gregory LS. Ontogeny of the spheno-occipital synchondrosis in a modern Queensland, Australian population using computed tomography. American journal of physical anthropology 2015;157:42-57.
71. Fernández-Pérez MJ, Alarcón JA, McNamara Jr JA, Velasco-Torres M, Benavides E, Galindo-Moreno P et al. Spheno-Occipital Synchondrosis Fusion Correlates with Cervical Vertebrae Maturation. PloS one 2016;11:e0161104.
72. Powell TV, Brodie AG. Closure of the spheno-occipital synchondrosis. The Anatomical Record 1963;147:15-23.
73. Baccetti T, Franchi L, Toth LR, McNamara JA. Treatment timing for Twin-block therapy. American Journal of Orthodontics and Dentofacial Orthopedics 2000;118:159-170.
74. Ballrick JW, Fields HW, Beck FM, Sun Z, Germak J. The cervical vertebrae staging method's reliability in detecting pre and post mandibular growth. Orthodontic Waves 2013;72:105-111.
75. Uysal T, Ramoglu SI, Basciftci FA, Sari Z. Chronologic age and skeletal maturation of the cervical vertebrae and hand-wrist: is there a relationship? American Journal of Orthodontics and Dentofacial Orthopedics 2006;130:622-628.
76. Joshi V, Yamaguchi T, Matsuda Y, Kaneko N, Maki K, Okano T. Skeletal maturity assessment with the use of cone-beam computerized tomography. Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology 2012;113:841-849.