UMEÅ UNIVERSITY

DENTOALVEOLAR AND CRANIOFACIAL CHANGES FROM EARLY ADOLESCENCE TO LATE ADULTHOOD

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To my family and friends

I am grateful to the 53 adults at the age of 60 years who accepted to participate in this project and it was my privilege to meet these adults, all of whom were kind during our meetings. It was pleasing to show them their photographs and dental models taken when they were 12 and 30 years old. Those individuals who had undergone extraction of four premolars, to treat dental crowding, were happy because they avoided having to wear dental braces.

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Abstract

Objectives: Study I: To evaluate the reliability and validity of different superimposition methods and to increase the precision with which craniofacial growth and treatment can be quantified. **Study II**: To explore the craniofacial changes that occur from early adolescence to late adulthood. **Study III**: To assess the impact of premolar extractions on dentoskeletal and facial morphologies up to late adulthood. **Study IV**: In a 50-year follow-up, to study how early extraction of four premolars affects the development of age-related lower incisor crowding.

Materials and Methods: Study I: Forty pairs of cephalograms were analysed at mean ages of 9.9 (T1) and 15.0 (T2) years. Three superimposition methods were assessed: the Sella-Nasion (SN); the Tuberculum Sella-Wing (TW); and Björk's structural. Björk's structural method was performed using three techniques: direct, tracing template, and subtraction. **Study II:** Thirty subjects with a Class I normal occlusion and harmonious facial profile were investigated. Study data were obtained from cephalograms performed at 12 (T1), 15 (T2), 30 (T3), and 62 (T4) years of age. The craniofacial changes were assessed using superimposition-based and conventional cephalometric methods. **Study III**: Two groups were included. The Extraction group (N=30 with Class I crowding malocclusion) had their first premolars extracted at a mean age of 11.5 years, without subsequent orthodontic treatment. The Control group included 30 untreated subjects with Class I normal occlusion. Study data were obtained from cephalograms performed at 12 (T1), 15 (T2), 30 (T3) and 62 (T4) years of age. The dentoskeletal and soft tissue changes were assessed using superimposition-based and conventional cephalometric methods. **Study IV**: Two groups were included. The Extraction group (N=24 with Class I crowding malocclusion) that had their first premolars extracted at mean age of 11.5 years, without subsequent orthodontic treatment. The Control group included 21 untreated subjects with Class I normal occlusion. Study data were obtained from dental casts and cephalograms performed at mean ages of 11.4 and 13.0 years, for the two groups, respectively (T1), and at mean ages of 30.9 years (T2) and 61.7 years (T3).

Results: Study I: The numerical data from the superimposition-based cephalometrics reflected a graphical illustration of superimposition and differed significantly from the data acquired using conventional cephalometrics. While there were no significant differences between the TW method and Björk's three techniques, significant differences were found between the SN method and the other methods. **Study II:** The maxilla and mandible showed significant anterior growth from T1 to T2, and significant retrognathism from T3 to T4. The anterior facial height and jaw dimensions increased significantly until T3. From T3 to T4, significant posterior rotation of the mandible and opening of the vertical jaw relation were observed, in addition to significant retroclination of the upper incisors, decrease in lip prominence, and straightening of the facial profile. **Study III**: There were no significant differences between the Extraction and Control groups in terms of the skeletal sagittal relation, incisor inclination and protrusion (or for most of the soft tissue parameters) during the observation period. **Study IV**: The Extraction group showed significant improvement in the space deficiency of the lower teeth and no changes in the irregularity of the lower incisors up to late adulthood. In contrast, both the space deficiency of the lower teeth and irregularity of the lower incisors were significantly exacerbated in the Control group, up to late adulthood.

Conclusions: The superimposition-based cephalometric method accurately generates numerical data for the craniofacial changes. Superimposition using the TW method is valid, reliable, and feasible, and is recommended to be used for superimposition-based cephalometrics. Moreover, craniofacial changes and development of lower incisor irregularity and crowding continue up to late adulthood in untreated subjects who were originally classified as having normal occlusion. For successful long-term outcomes, clinicians should therefore consider age-related changes in patients when planning for orthodontic, orthognathic, and prosthodontic treatments. Treatment with the extraction of four premolars alone in patients with Class I malocclusion with severe crowding does not impact the long-term dentoskeletal and soft tissue profile, and results in unchanged lower incisor alignment.

Abbreviations

3D – Three-Dimensional

2D – Two-Dimensional

μSv – Microsieverts

ANOVA – Analysis of Variance

BD –Björk's structural – Direct

BS –Björk's structural – Subtraction

BT –Björk's structural – Tracing template

CBCT – *Cone Beam Computed Tomography*

GW – Gestation week

N – Nasion landmark

N-sample – Normal sample

PX-sample – Premolar extraction sample

RF-sample – Rune Filipsson-sample

S – Sella landmark

SN – Sella-Nasion plane

T – Tuberculum Sella landmark

TSALD – Tooth Size –Arch Length Discrepancy

TSALDtot – TSALD of dental arch mesial to the first molars

TSALDant – TSALD of six anterior teeth

TW – Tuberculum Sella – Wing plane

W – Wing landmark

Enkel sammanfattning på svenska

Bakgrund: God kunskap om skallbasens samt ansiktets hård- och mjukvävnaders växt över tid är viktig för de olika professionerna inom odontologi. Kunskapen behövs för såväl optimerad diagnostik som behandlingsplanering-, prediktion, utfall och prognos.

Mål: Målen med studierna var att studera; **Studie I**: olika analysmetoders tillförlitlighet och precision avseende växt i skallbas och ansikte i profilröntgenbilder tagna över tid. **Studie II**: växt i skallbas och ansikte från tidiga tonår till sen vuxen ålder hos obehandlade personer med normalt bett. **Studie III**: effekten av tidig extraktion av fyra kindtänder på käkarnas relationer samt ansiktsprofilen från tidiga tonåren till sen vuxen ålder. **Studie IV**: effekten av tidig extraktion av fyra kindtänder på bettets relationer samt på trångställning av underkäkens framtänder, från tidiga tonår till sen vuxen ålder.

Material och metoder
Studie I: Tre superponeringsmetoder utvärderades; Sella-Nasion (SN); Tuberculum Sella-Wing (TW); och Björk's strukturella metod. Björk's strukturella metod utfördes med tre olika tekniker; s.k. "direkt", "tracing" och "subtraktionsteknik". Fyrtio par profilröntgenbilder analyserades vid 9,9 år (T1) och 15,0 år (T2). **Studie II**: Patienter (n=30) med normalt bett och harmonisk profil analyserades vid 12 (T1), 15 (T2), 30 (T3) och 62 (T4) års ålder. Förändringar i skallbasens och ansiktets växt över tid analyserades med konventionella- och superponeringsbaserade metoder. **Studie III**: Växt hos en extraktionsgrupp (n=30) med klass I bett, grav trångställning, extraktion av fyra kindtänder vid i snitt 11,5 års ålder utan efterföljande tandreglering, analyserades och jämfördes med en kontrollgrupp. Kontrollgruppen (n=30) bestod av obehandlade personer med normala bettförhållanden som undersöktes vid åldrarna 12 (T1), 15 (T2), 30 (T3) och 62 år (T4). Förändringar i käkar och ansiktsprofil avseende växt jämfördes med hjälp av konventionell och superponeringsbaserad analys av profilröntgen. **Studie IV**: Tändernas och käkarnas relationer analyserades och jämförelser gjordes mellan en extraktionsgrupp och en kontrollgrupp. Extraktionsgruppen (n= 24) hade klass I trångställning och hade fått sina fyra kindtänder extraherade vid i snitt 11,5 års ålder, utan efterföljande tandreglering. Kontrollgruppen (n=21) bestod av obehandlade personer med normalt bett. Analys av studiemodeller och profilröntgen utfördes vid 11,4 respektive 13,0 års ålder (T1), 31 års ålder (T2) samt 62 års ålder (T3).

Resultat

Studie I: De superponeringsbaserade analyserna gav mer tillförlitliga resultat avseende förändringar i skallbasens och ansiktets växt över tid jämfört med konventionell profilröntgenanalys. Inga signifikanta skillnader i precision fanns mellan TW- metoden och Björk's tre tekniker, däremot var skillnaderna signifikanta mellan SN- metoden och övriga metoder. **Studie II**: Överkäken och underkäken växte framåt mellan T1 och T2 och bakåt mellan T3 och T4. Käkarnas dimensioner och den främre ansiktshöjden ökade markant fram till T3. Mellan T3 och T4 roterade underkäken bakåt vilket resulterade i en vertikal öppning mellan käkarna. Dessutom noterades en rakare ansiktsprofil, minskning av läpparnas prominens samt ökad inåt-lutning av framtänderna i överkäken. **Studie III**: Inga signifikanta skillnaderna fanns mellan extraktions- och kontrollgruppen, varken avseende de skelettala relationerna mellan käkarna, framtandslutningen, eller ansiktets mjukvävnadsprofil. Mellan T2 och T3 visade extraktionsgruppen dock större minskning av vissa vinklar (ML/NSL, ML/NL och Gonial) samt större ökning i ansiktshöjd. **Studie IV**: Extraktionsgruppen visade en signifikant minskning av utrymmesbristen i underkäken och inga förändringar i ojämnhet av framtänderna i underkäken mellan tidiga tonår och sen vuxen ålder, medan både utrymmesbristen i tandbågen och ojämnheten bland framtänderna i underkäken ökade i kontrollgruppen mellan tonåren och sen vuxen ålder.

Slutsatser

Superponeringsbaserad profilröntgenanalys ger mer tillförlitliga numeriska data än konventionell analys av profilröntgen (kefalometri) vid studier av förändringar i skallbasens- och ansiktets växt över tid. Superponering med TW-metoden visar god precision, därför rekommenderas metoden vid superponeringsbaserad analys. Skallbas och ansikte fortsätter att förändras fram till sen vuxen ålder. Käkar- och ansiktsprofil påverkas marginellt över tid om man behandlar patienter med svår trångställning genom enbart extraktion av fyra kindtänder. Trångställning i underkäksfronten ökar inte på samma sätt hos patienter som behandlats med extraktion jämfört med patienter som inte fått extraktionsterapi. Graden av trångställning är alltså mer avgörande för beslut om extraktionsterapi vid trångställning av klass I bett, än förväntade framtida förändringar i tänder och käkar.

List of publications

This thesis is based on the following original publications, which will be referred to in the text by their Roman numerals:

I. Al-Taai N, Levring Jäghagen E, Persson M, Ransjö M, Westerlund A. A Superimposition-Based Cephalometric Method to Quantitate Craniofacial Changes. Int J Environ Res Public Health. 2021 May 14;18(10):5260. doi: 10.3390/ijerph18105260. PMID: 34069290; PMCID: PMC8156959.

II. Al-Taai N, Persson M, Ransjö M, Levring Jäghagen E, Fors R, Westerlund A. Craniofacial changes from 13 to 62 years of age. Eur J Orthod. 2022 Mar 28:cjac011. doi: 10.1093/ejo/cjac011. Epub ahead of print. PMID: 35348638.

III. Al-Taai N, Persson M, Ransjö M, Levring Jäghagen E, Westerlund A. Dentoskeletal and soft tissue changes after treatment of crowding with premolar extractions: a 50-year follow-up. Eur J Orthod. 2022 Jul 6:cjac035. doi: 10.1093/ejo/cjac035. Epub ahead of print. PMID: 35791441.

IV. Persson M, Al-Taai N, Pihlgren K, Westerlund A. Early extractions of premolars reduce age-related crowding of lower incisors: 50 years of follow-up. Clin Oral Investig. 2022 Jun;26(6):4525-4535. doi: 10.1007/s00784-022-04416-x. Epub 2022 Feb 24. PMID: 35201405; PMCID: PMC9203403.

Introduction

Good knowledge of craniofacial growth is essential for specialists in orthodontics, prosthodontics and orthognathic surgery, to detect deviations from normal craniofacial growth and development in children and adults. This knowledge will support diagnosis and treatment planning, as well as the timing of treatment and prediction of post-treatment outcomes.[1-4]

Craniofacial growth has traditionally been regarded as being completed once body-length growth decreases.[5] As a consequence, both surgical correction of jaw abnormalities and the installation of dental implants are usually postponed until longitudinal growth ceases, so as to ensure the stability of the treatment outcome. However, few studies have explored the craniofacial changes that occur up to late adulthood.[6,7] Age-related craniofacial changes in adulthood, even if they are minor compared to those that occur in adolescence, could constitute a risk factor for the stability of orthodontic, orthognathic and prosthodontic treatments. In addition, dentofacial aesthetics can be influenced by ongoing age-related dentoalveolar changes (e.g., lower incisor crowding) in the adult.[1,8,9]

The demands for dentofacial aesthetic and functional alterations have increased over time, particularly in the adult population. The frequency of cosmetic treatments to counteract age-related facial changes (e.g., filler injections) has increased in recent years. Orthodontic treatment of adults has increased to about 30% of the orthodontic patient population.[10] Therefore, it is important to understand the magnitude and direction of the normal changes in the dentoalveolar and craniofacial structures that occur throughout life, so as to be aware of these changes and provide patients with an insight into the limitation of stability.

There have been very few studies on craniofacial growth-related changes that have been followed-up for decades in untreated patients and no corresponding studies on patients who have undergone serial dental extractions. This has been the case because of the obvious problems linked to longitudinal studies, as well as for ethical reasons. The present studies give valuable new information on craniofacial growth-related changes in the adult population.

Background

Growth is an anatomical phenomenon that refers to an increase in the size of any tissue, whereas development refers to the formation or differentiation of tissues.[11,12] Both processes are controlled by both genetic and environmental factors.[13]

Growth is usually described in terms of its magnitude (amount of growth in vertical, sagittal and transverse dimensions), direction (net direction of growth), and velocity (rate of growth per unit).[12] Prenatally, the growth rate is very high, and it decreases during infancy. Whereas the growth rate slows during childhood, it accelerates markedly in early adolescence through the maximum growth spurt. Thereafter, the growth rate decreases once again and effectively ceases completely in adulthood.[14] The growth of the craniofacial complex is related to the somatic growth.[11] For both somatic growth and craniofacial growth, two episodes of maximum growth (spurts) have been documented. The smaller of these, the juvenile growth spurt, occurs in about 50% of children from 6.5 to 8.5 years of age. The more-pronounced adolescent growth spurt starts with the beginning of puberty, at about 9 to 10 years of age in girls and at 11 to 12 years of age in boys.[15]

In the study of human growth, it is important to consider the concepts of: pattern, variability, and timing.

Growth pattern refers to the change that occurs in the proportional relationships of the human body over time. The head represents about a quarter of the total body length at birth, whereas it represents about one-eighth of the total body length in adults. Maximal head growth occurs in the height and depth and the least growth is in the width.[16,17] Another way of viewing growth pattern is that all the body tissue systems do not grow at the same time or at a similar rate; for example, the mandible grows more and for a longer time compared to the maxilla.[18] These changes represent a part of the normal growth pattern.

Growth variability refers to the fact that humans do not grow in a similar manner. It is clinically important to determine if the craniofacial growth of an individual is simply within the range of the normal variation or is outside the normal range, in order to decide on the best therapy. There is large individual variation of jaw growth, which is attributed to simultaneous changes in other parts of the craniofacial complex, together with the effects of environmental and functional factors.[19-21] Moreover, there are ethnic differences in facial morphologies, which have been shown by many studies of different ethnic groups.[3,22]

Growth timing refers to the same event occurring at different times in different individuals. The growth spurt, for example, happens at different times in different individuals. Thus, the use of chronological age is inadequate for making clinical decisions. To reduce the effects of variability of growth timing, it is more appropriate to use developmental age as an expression of an individual's growth maturation.[23,24]

Craniofacial growth and development

The growth of the craniofacial skeleton includes changes to the size, shape and position of the skeletal parts (facial bones, cranial base and cranium), so as to preserve appropriate bone function and proportionate growth. The growth and development of each structure in the craniofacial skeleton are dependent upon other structures and are under genetic control and can be affected by epigenetic factors.[25,26]

Bone formation occurs developmentally through the following two processes:
Endochondral bone formation: A temporary cartilage template is formed initially and is gradually replaced by bone, as is the case for the long bones, ribs, vertebrae, and the cranial base.
Intra-membranous bone formation: Mesenchymal stem cells condense and differentiate into osteoblasts, which deposit an osteoid matrix that mineralises to bone, as happens in the facial skeleton and vault of the cranium.[13]

Bone growth occurs through two physiological mechanisms: modelling and remodelling.[13]
Bone modelling is a process in which bone resorption occurs without subsequent bone formation, or where bone formation takes place without any preceding bone resorption. Modelling is manifested mainly during growth (on periosteal and endosteal surfaces), driving the development, growth and shaping of the bones; bone modelling is considered to be the main process of facial growth.[27] After maturation, bone modelling decreases, although it can be re-activated during bone fracture healing and during pathological processes in the skeleton. Furthermore, bone modelling is controlled by genetic factors and environmental factors (physical strain), as well as by systemic hormones, locally produced cytokines and growth factors.[28]
Bone remodelling is defined as a coupled and sequential process of bone resorption (by osteoclasts) followed by bone formation (by osteoblasts), which normally operates in a balanced manner to ensure bone turnover

while maintaining bone mass.[29] The bone remodelling process replaces old and damaged bone with new bone, thereby supporting a healthy and functional skeleton. The current consensus is that the various growth factors released from the bone tissue during the resorption process mediate the coupling activity and induce bone formation.[30] Throughout life, the adult skeleton is renewed by bone remodelling every 10 years.[28]

Prenatal development

The prenatal period consists of the ovum stage (gestation week, GW, 1), embryonic stage (GW 2–7), and foetal stage (GW 8–40).

The head of the foetus grows rapidly, such that at the end of the embryonic stage, it exhibits the outer features of a human being. The head makes up nearly 50% of the total body length after about 4 weeks into the foetal stage. At this stage, the cranium is large in relation to the face, while the limbs are still developmentally primitive.[31]

The bones of the cranial vaults appear during the first 4 weeks of the foetal stage as mesenchymal condensations, which thereafter start to mineralise and expand (intra-membranous bone formation). By the second 4 weeks of the foetal stage, the bones of the cranial vault are close to each other, such that the sutures are initiated.[32]

The cranial base is first seen at the beginning of the foetal stage (GW 8), where discrete cartilage components start forming the chondrocranium, which extends from the foramen magnum anterior to the nasal cavity. Thereafter, multiple ossification centres develop in the chondrocranium, which in turn changes to an ossified cranial base throughout the foetal stage (GW 9–36). The growth and displacement of the cranial base is possibly due to the synchondroses. These are chondrocranium residuals that function as areas of growth between the ossified bones.[32]

The bones of the maxillary complex, as well as those in most of the tissues in the face and neck, emerge from the cranial neural crest cells.[33] At the end of the embryonic stage, the palatal shelves, which are mesenchymal extensions of the maxillary processes of the first branchial arches, are formed, then fuse and give rise to the hard and soft palates.[34]

During the embryonic stage, mandibular processes develop bilaterally in the first branchial arch. Each mandibular process contains a cartilaginous core (Meckel's cartilage), which provides early structural stability. At the end of the embryonic stage, centres of ossification arise lateral to the Meckel's cartilage.[35] At about the fourth month of the foetal stage, the Meckel's cartilage disappears, and the remnants form the malleus and incus (ear ossicles).[36]

At the beginning of the foetal stage, the condylar process arises as a discrete carrot-formed blastema of cartilage extending from the ramus. By the end of the first month of the foetal stage, the temporomandibular joint (TMJ) is formed between the condylar process and the squamous part of the temporal bone. Since the cartilage in the mandibular condyle appears "secondarily" in a skeletal part, derived from the periosteum, and away from the primary embryonic cartilage, it is called 'secondary cartilage'.[26,37,38] Secondary cartilage appears in regions of early stresses and strains in the intra-membranous bones and in regions with rapid growth and development of bone.[39]

The coronoid and the angular processes of the mandible may also display the features of secondary cartilage, as these are regions of very rapid bone growth related to the functions of the muscles of mastication.[27]

Postnatal growth

At birth, the craniofacial skeleton has reached about half of its eventual size and the head makes up about one-quarter of the body height. In comparison, in adulthood, the head makes up about one-eighth of the body height.

The postnatal period is usually divided into the following stages: the infantile stage (1–12 months of age); juvenile stage (6–8 years of age); early adolescence stage; and late adolescence stage. During early adolescence (puberty), a growth spurt occurs with a peak height of velocity (PHV) at about 12.5 years of age in girls and about 14 years of age in boys. During late adolescence, growth gradually declines and is essentially completed by the age of 20 years, when adulthood is reached.[40]

Postnatally, the size of the cerebral cranium increases by about 50%, whereas the facial skeleton more than doubles in size. This difference in proportions is related to the early development of the brain, the growth of which is basically finished at 4 years of age.[31] In addition, the facial skeleton increases in all dimensions postnatally: the vertical dimension (height) increases about 200%, the sagittal dimension (depth) increases about 150%, and the transversal dimension (width) increases about 75%.[13] The facial width is the first dimension to attain the mature size.

Several studies of cephalometric norms for subjects from different ethnic groups and of different ages have reported ethnic differences in relation to facial features.[3,41] These include dentofacial pattern changes during the period of active growth, and growth acceleration between the ages of 13 and 16 years.[3] Changes are also observed between 5 and 7 years and between 16 and 31 years of age.[3] Furthermore, changes have been reported up to mid- and late adulthood.[6,7,42] Therefore, comprehensive knowledge of craniofacial growth (cranial base, maxillary complex, and mandible) in normal subjects can provide the basis for a detailed diagnosis (differential diagnosis) and for treatment planning in patients with any type of malocclusion.[6,7,42-44] However, only a few studies have investigated craniofacial changes up to late adulthood.[6,7] In addition, it is necessary to quantify these changes with high precision, so as to be able to predict long-term treatment outcomes.

Cranial vault

Postnatally, growth of the cranial vault is seen largely at the sutures through expansion of the brain.[45] Apposition of bone along the border of the bones of the cranial vault takes place rapidly, so as to eliminate the open spaces (fontanelles). In addition, bone remodelling (bone resorption on the inside of the cranial vault and simultaneous bone formation on the outside) produces changes in the contour of the cranial vault during growth.[31]

The cranial vault reach 95% of its adult size at about 10 years of age. The bones of the cranial vault persist, being separated by a narrow, periosteum-lined suture for several years, and they fuse during adulthood. By the third decade of life, the cranial vault sutures cease to grow. However, a certain level of expansion of the cranial vault occurs throughout life due to the periosteal apposition to specific areas of the cranial vault, such as the glabellar and nuchal regions, appearing as a secondary gender characteristic in men.[27]

Cranial base

The growth of the cranial base is essential for craniofacial growth, since the maxillary complex is in close relation to the anterior cranial base and the mandible articulate with posterior cranial base via the temporomandibular joint. In addition, the cranial base is of particular interest to orthodontists and orthognathic surgeons, as it is often used as a reference structure in cephalometric superimposition to assess growth- and/or treatment-related displacement of the upper and lower jaws. Given that it acts as a reference structure, it is essential to know the time of growth cessation of the cranial base.[46,47]

The anterior cranial base length (between the Nasion and Sella landmarks) and posterior cranial base length (between the Sella and Basion landmarks), in addition to the cranial base angle (between the anterior and posterior cranial base), show more growth changes during the first 2 to 3 years of life than any time thereafter.[48]

It is noteworthy that the anterior cranial base grows more and completes its growth earlier than the posterior cranial base, during the postnatal period.[49] In a long-term study, it has been observed that the anterior cranial base reaches almost 90% of its adult size by 4.5 years of age, whereas at this age the posterior cranial base has only reached 80% of its adult size.[49]

Postnatally, the growth of the cranial base is mainly dependent upon the growth of the synchondroses.[13,46] At birth, three synchondroses (inter-sphenoid, spheno-ethmoidal and spheno-occipital) separate the bones in the cranial base. The inter-sphenoid synchondrosis (between the presphenoid and basisephenoid) does not play a role in postnatal growth because it fuses at birth.

Spheno-ethmoidal synchondrosis: The length of the anterior cranial base increases as a result of growth at the spheno-ethmoidal synchondrosis (between the sphenoid and ethmoid bones), in addition to bone apposition. The spheno-ethmoidal synchondrosis is most active in the cranial base growth up to 7 years of age. At about 7–8 years of age, the spheno-ethmoidal synchondrosis loses its cartilage and converts into a suture. Once that conversion takes place, the growth of the anterior cranial base is essentially finished.[46] Thereafter, the length of the anterior cranial base (i.e., the distance between the Sella and Nasion landmarks) continues to increase, up to adulthood, due to the posterior and vertical displacement of the Sella and anterior and vertical displacement of the Nasion. The growth-related displacement of the Sella is due to resorption at the dorsum Sella,[21,46,50] while that of the Nasion is due to drifting of the frontal and nasal bone related to the growth of the frontal sinus[21,50,51]. Between the time of fusion of the spheno-ethmoidal synchondrosis and adulthood, Ford has observed that the frontal bone drifts forward about 6 mm.[51] Radiographical and histological studies have confirmed that, after the age of 7 years, the anterior inner wall of the Sella turcica and the cribriform plate are stable and, therefore, can be used as references for the sagittal and vertical orientations, respectively, in cephalometric superimposition.[21,46,50]

Spheno-occipital synchondrosis: The length of the posterior cranial base increases due to growth at the spheno-occipital synchondrosis (between the sphenoid and occipital bones), as well as bone apposition. The spheno-occipital synchondrosis probably plays a greater role in the changes to the cranial base angle than to its linear growth. Melsen has shown that ossification of the spheno-occipital synchondrosis is initiated at 12–13 years of age in girls and at 14–15 years of age in boys.[46] Once the ossification of the spheno-occipital synchondrosis completed, the growth of the cranial base largely ceases, particularly in the anteroposterior direction, and the changes to the cranial base angle take place due to bone modelling.[46]

Cranial base angle: As the maxillary complex is in close relation to the anterior cranial base and the mandible articulate with posterior cranial base, any changes in the cranial base angle can affect the inter-jaw relation and occlusion.[47] In addition, the cranial base angle is related to the head position (the relation between the head and cervical column). Functional requirements, such as respiration, may represent environmental factors that affect the cranial base angle.[52,53]

Maxillary complex

Postnatal growth of the maxillary complex occurs via intra-membranous ossification, with the exception of the nasal septum. The nasal cartilaginous septum plays a significant role in displacement growth of the maxilla (both forward and downward), particularly during early childhood.[54-60] In addition, the growth in the anterior cranial base contributes to the forward displacement of the maxilla (passive displacement).[31]

The maxilla grows in the downward and forward directions (with an average angle of about 50° to the anterior cranial base) through bone apposition on the circummaxillary and intermaxillary sutures and bone remodelling.[61,62] After birth, the circummaxillary and intermaxillary sutures are available as active sites for bone growth. Downward, forward, and lateral displacements of the maxillary complex give rise to compensatory sutural growth, which accounts for most of the vertical, anteroposterior, and transverse growth-related changes that take place during childhood and adolescence.[13,61]

Vertical dimension: Bone growth at the circummaxillary sutures (e.g., frontomaxillary) and bone remodelling contribute to increasing the height of the maxillary complex (*downward displacement*) between 4 and 20 years of age.[61-63] Björk and Skieller have shown that the downward displacement of the orbital floor from 4 years of age is less than half the magnitude of the sutural downward displacement of the maxillary complex, due to the bone apposition that occurs at the orbital floor.[61] Bone resorption and apposition occur at the nasal floor and palatal roof, respectively, resulting in downward drift of the nasal floor and, consequently, an increase in the height of the nasal cavity. The downward displacement of the nasal floor is due to: downward growth movement of the whole maxilla; and local resorption at the nasal floor.[61-63]

In addition, the alveolar process grows by bone apposition during tooth eruption and is three-fold greater than the downward drift of the hard palate.[61-63] Growth of the maxillary complex continues during childhood and adolescence, with considerably greater increases in the height (double the increase in length).[13,61]

Sagittal dimension: Bone growth at the circummaxillary sutures (e.g., pterygomaxillary) and bone apposition at the maxillary tuberosity contribute to increasing the length of the maxillary complex (*forward displacement*) from 4–20 years of age.[61-63] Bone apposition at the maxillary tuberosity increases the length of the dental arch posteriorly, which in turn provides space for the successively erupting primary molars, and then the permanent molars.[13,61]

Although the anterior surface of the maxilla shows a remodelling process, implant studies have shown that, sagittally, it is quite stable.[62,63]

Transversal dimension: Bone growth at the mid-palatal suture is a major factor in the increase of maxillary width (*lateral displacement*).[61] The transversal dimension of alveolar bone increases owing to the buccal eruption path of the posterior teeth during the tooth eruption phase.[13] It has been observed that between 7.6 and 16.5 years of age, the mid-alveolar (buccally) and bi-jugale widths of the maxilla increase about 3 mm and 6 mm, respectively, while in the same period, the maxillary inter-molar width increases about 3 mm.[64] However, these widths do not increase in the following 10 years.[64] In addition, bone resorption on the lateral walls of the nasal cavity result in further expansion of the maxillary complex.[13]

At about 7 years of age, brain growth is essentially complete, at the same time as the ossification of the spheno-ethmoidal synchondrosis.[46] Thus, displacement due to cranial base growth is an important part of the forward growth of the maxilla up to about 7 years of age. Thereafter, circummaxillary sutural growth is the only mechanism for displacement of the maxilla. The maxillary complex continues to grow skeletally in the downward and forward directions during adolescence.

The maxillary complex increases primarily in height, then in depth, and to the least extent in width, and growth at the sutures continues until they are no longer separated. While the premaxillary suture closes at about 3 to 5 years of age, Melsen has shown that the mid-palatal suture continues with transversal growth up to 16 and 18 years of age in girls and boys, respectively.[65] Therefore, prior to closure of the mid-palatal suture, one can take advantage of the possibility to open the suture using a rapid maxillary expansion device, to treat a narrow maxilla. Closure of the circummaxillary sutures seems to take place slightly later than closure of the intermaxillary sutures.[27] The cessation of maxillary growth considers to take place at 15 and 17 years of age in girls and boys, respectively.[62]

According to the implant study conducted by Björk and Skieller, the anterior contour of the zygomatic process of the maxilla is considered as a stable reference structure that can be used for cephalometric regional superimposition to evaluate maxillary remodelling and movement of the upper teeth.[61]

Maxillary rotation throughout growth: Due to growth and remodelling processes, the two maxillae seem to rotate transversally in relation to each other due to the greater growth observed posteriorly than anteriorly at the mid-palatal suture.[61] Simultaneously, the whole maxilla seems to move (sagittally) forward and rotate (vertically) forward or backward.[61] Forward rotation of the maxillary complex is seen in most children, owing to the more-downward displacement of the posterior than the anterior maxilla. This rotation tends to be obscured by the resorption that takes place on the nasal floor.[61] In addition, there is a certain relationship between the cranial base angle and the prognathism of the maxilla. It has been shown that an acute cranial base angle is associated with prognathism of the maxilla, and that a flattened cranial base angle is associated with retrognathism of the maxilla.[18,47]

Mandible

At birth, a fibrous suture separates the two halves of the mandible at the mid-line (the symphysis), which fuse at the end of the first year of life. Thus, it is impossible to expand the mandible in the suture in the same way as the maxilla. Each side of the mandible is represented anatomically by a condyle, a ramus that provides insertions for the muscles of mastication and a corpus (mandibular body) that forms a base for the lower dental arch.

For mandibular growth, both endochondral (condylar cartilage) and intra-membranous (periosteal) ossification are necessary. Postnatally, the mandible shows the largest amount of growth among the craniofacial bones and it displays the largest individual morphological variation.[19,20,47] Similar to the maxilla, the mandible displays downward and forward growth-related displacement in relation to the cranial base.[13]

The mandibular condyle plays an important role in the growth of the mandible during most of the first two decades of life.[66-68] The development of specific facial and mandibular growth patterns relies on the extent and direction of the condylar growth, as observed in previous implant studies.[20,63] Condylar growth increases the posterior facial height, anteroposterior facial depth, and transversal width.[20,47,63] According to Patcas *et al.*, the peak velocity of condylar growth occurs at about 13 years of age for both girls and boys, and does not coincide with the timing of the peak velocity of body height.[69] It is advantageous to plan the orthodontic treatment (growth modification) of Class II malocclusion to coincide with the peak velocity of condylar growth. The growth of the condyle was observed to terminate on average age at about 19 and 17 years of age in boys and girls, respectively.[3,19] Subsequently, the facial height continues to increase, albeit at a reduced rate, into adulthood.[7,43,44]

In addition, the mandibular condyle is essential for normal TMJ function and movements of the mandible.[66]

Secondary displacement of the mandible created by cranial base growth, which moves the temporomandibular joint, plays an insignificant role in the growth of the mandible.

Vertical dimension: The ramus grows in height (primary displacement) as a result of endochondral bone formation at the condyle. The entire mandible is displaced in the downward and forward directions, and simultaneously increases in size through upward and backward growth.[20,63]

The increase in the posterior facial height is dependent to a great extent upon the growth of the ramus. Between 4 and 17 years of age, the ramus exhibits the largest increase in height (distance between the Condylion and Gonion landmarks), with increases of about 14 and 17 mm for girls and boys, respectively.[70] Measuring the ramus height between the Gonion and Condylion landmarks will significantly under-estimate the real condylar growth, due to the bone resorption that normally occurs at the Gonial region.[21] For each 3 mm of upward growth of the condyle, there is about 1 mm of resorption at the Gonion.[71]

The mandible is usually displaced downwards, more so than the maxilla, with the resulting space being occupied by the erupting teeth. The greatest growth-related changes within the corpus are appositional growth of the alveolar bone related to tooth eruption.

Sagittal dimension: Forward growth of the mandible (primary displacement) occurs through periosteal remodelling at the ramus, due to the bone apposition on the posterior border and simultaneous bone resorption of the anterior border of the ramus. Consequently, the ramus is repositioned backwards and the body of the mandible and the dental arch grow longer.[13] The increased length of the lower dental arch provides space for eruption of the lower posterior teeth.[72]

Between 4 and 17 years of age, the mandible exhibits the largest increase in total length (distance between the Condylion and Menton landmarks), with increases of about 25 mm and 30 mm for girls and boys, respectively. At the same time, the mandibular corpus exhibits the largest increase in length (distance between the Gonion and Pogonion landmarks), with increases of about 18 and 22 mm for girls and boys, respectively.[70]

During postnatal growth, no bone remodelling occurs at the chin, and it is considered to be the only site on the whole surface of the mandible that remains stable.[19,73]

Transversal dimension: As the two rami attain a diverging V-shape, the mandible increases in width due to bone remodelling according to the V-principle.[72] Considering the bone apposition on the buccal side of the mandibular body and simultaneous bone resorption and endosteal bone formation on the lingual side, the body of the mandible is drifted buccally.[13,74] Owing to the synostosis of the symphyseal suture, postnatally, the symphysis contributes little or nothing to mandibular growth, in terms of either width or length.[13] Thus, a slight change occurs at the front of the mandible. The width of the mandible (measured between the left and right Gonial landmarks) increases by about 12 mm (from 7.5 to 16.5 years of age) and by about 3 mm (from 16.5 to 26.5 years of age).[64] However, the mandibular inter-molar width increases about 1.5 mm (from 7.5 to 13 years of age) and does not increase later (from 13 to 26.5 years of age).[64]

Mandibular rotation throughout growth: As a result of proportionally larger growth at the posterior than at the anterior parts of the two corpii, the mandible seems to rotate in the transversal direction. Growth-related downward movement of the maxillary complex will move the anterior part (tooth-bearing) of the mandible, while the condylar growth will move the posterior part of the mandible.[47] Unequal lowering of these anterior and posterior parts will result in a rotational component in the mandibular displacement.[47] When the growth-related lowering of the anterior and posterior mandibular parts is equal, there will be a pure mandibular translation without a rotational component. If condylar growth occurs in the upward and forward directions relative to the base of the mandible, the lowering of the mandibular posterior part will surpass that of the mandibular anterior part. The resulting mandibular rotation is called 'anterior (forward) growth rotation'.[20,75] However, this type of mandibular growth rotation will result in a basal deep bite if there is no occlusal contact at the anterior teeth.[47] In contrast, when the condyle grows in a more backward direction relative to the mandibular base or when the condyle grows only to a small extent, the lowering of the mandibular anterior part becomes greater than that of its posterior part. The resulting mandibular rotation is called 'posterior (backward) growth rotation'.[75] In this type of rotation, occlusal contact between the anterior teeth can be preserved by increased eruption of the incisors, otherwise an open bite will result.[47]

Most individuals display upward and forward growth of the condyle.[20,47] Thus, the downward displacement of the posterior part of the mandible usually exceeds the anterior part and the mandible will mainly exhibit forward rotation.[20,47]

There is periosteal remodelling along the inferior margin of the mandible, which corresponds to the different growth direction of the condyle.[19,21] In most individuals, where the condyle exhibits a forward growth direction, the mandibular lower border shows obvious resorption under the Gonial angle and bone deposition under symphysis, which means that about one-half of the mandibular true rotation is reduced.[19,21] There is no resorption, although there may be bone deposition under the Gonial angle and there may be formation of the antegonial notch in individuals with condylar growth in the backward direction.[19]

Analysis of mandibular growth changes and the changes caused by orthodontic treatment can be made by superimposing cephalograms or tracings on stable structures. Considering this growth-related remodelling (bone resorption and deposition), superimposition on the lower border of the mandible will result in incorrect assessment of growth- and treatment-related tooth movements.[47] However, in their implants studies, Björk and colleague identified specific bone structures that serve as stable references for cephalometric regional superimposition and that allow evaluations of mandibular remodelling and lower teeth movement; these structures include the anterior contour of the chin, internal cortical surface of the symphysis, contour of the mandibular canal, and lower contour of a mineralised molar germ before root formation has started.[21,73]

Facial soft tissue

The growth of the facial soft tissues is not entirely analogous to the growth of the underlying skeletal tissues.[76] Bishara and co-workers have observed that the most-prominent changes in the soft tissue profile occur earlier in women (at 10–15 years of age) than in men (at 15–25 years of age).[77]

At about 10 years of age, the growth of the nasal bone ceases. Thereafter, the growth of the nose depends on the growth of nasal cartilage and soft tissues. The nose grows in the forward-downward direction, especially during the growth spurt.[78] Although the nasal height increases at a slower rate before adolescence, pubertal growth-related accelerates this rate between 14 and 17 years of age. On the other hand, a moderate, growth-related increase of the nasal depth is seen between 7 and 16 years of age.[76]

Lip incompetence (lip separation) at rest is greatest in childhood, while it decreases in adolescence. In addition, the length and thickness of the lips increase between 7 and 18 years of age, after which the lip thickness begins to decrease and flattens during adulthood.[7] However, lip length continues to increase with age, particularly the length of the upper lip, resulting in decreased upper incisor display and increased lower incisor display.[76] Therefore, the display of upper incisors is considered a youthful feature.[79]

As the nose and chin become more prominent after puberty, the lips become less prominent.[3,76,77] Moreover, the position of the lips is influenced by the position and inclination of the upper and lower incisors and is, therefore, responsive to orthodontic treatment.[3,76] This is why it is important to decide how much lip support should be provided by the incisors during orthodontic treatment.[3]

Forward growth of the mandible results in a less-convex facial profile, as observed from 15 years of age.[3,77]

Dentoalveolar development

The occlusal relationship between the maxilla and mandible depend on growth of the jaws and tooth eruption.[47] The dentoalveolar complex has the possibility to compensate for small deviations in the development of the jaw relationship. This dentoalveolar compensation depends on normal tooth eruption, the forces of the soft tissue envelope, and the effects of adjacent teeth.[20,21,47]

On the other hand, it has been demonstrated that disturbed functioning of breathing and/or the orofacial muscles influence the development of the dental arch.[80-82]

Dental arches development

Postnatally, the lengths of the upper and lower dental arches continue to increase until the ages of 13 and 8 years, respectively, with the greatest increase occurring during the first 2 years of life.[1] The length of the posterior dental arch decreases, by 1 mm and 3 mm in the upper and lower arches, respectively, between 7 and 13 years of age, owing to the differences between the mesiodistal width of the primary molars and the permanent premolars (Leeway space).[2] After the age of 13 years, the reduction of the posterior arch length continues.[1,2] The length of the anterior dental arch increases, by 6 mm and 4 mm in the upper and lower arches, respectively, between the ages of 5 and 10 years, owing to the growth-related increase in anterior arch width and to the proclination of the erupting incisors.[2] After the age of 10 years, the length of the anterior arch continues to decrease.[1,2]

The upper and lower arch depths increase until the age of 13 years, due to eruption of the incisors in the proclined position; thereafter, there is a continuous reduction of arch depth, indicating physiological mesial migration of the posterior teeth.[2]

Considering the width of the dental arch, the upper inter-canine width increases by 4 mm until 16 years of age. The lower inter-canine width increases by 4 mm until 10 years of age and thereafter continues to reduce.[2] The inter-molar width in the upper arch increases by about 3 mm between 7.6 and 16.5 years of age, and does not increase thereafter.[64] The inter-molar width in the lower arch increases by about 1.5 mm (from 7.5 to 13 years of age), and does not increase thereafter.[64]

Relationship between jaw rotation and tooth position

Growth-related jaw rotations have an effect on the amount and direction of tooth eruption and on the anteroposterior position of the incisors.[20,21] Björk and co-workers have shown compensatory sagittal and vertical changes of the tooth position, which often correlated with growth rotation of the jaws.[20,21]

Sagittal position of the teeth: The eruption path of the upper teeth is downward and slightly forward. Forward rotation of the maxilla, which usually occurs during normal growth, tips the incisors anteriorly and increases their prominence, while backward rotation of the maxilla tips the incisors posteriorly and decreases their prominence.[20] On the other hand, the path of eruption of mandibular teeth is upward and slightly forward. The normal growth-related forward rotation of the mandible results in lingual tipping (upright position) of the incisors and mesial migration of the molars. This physiological mesial migration of the molars will result in normal reduction of the dental arch length.[20,21] Considering that the growth-related forward rotation of the mandible is greater than that of the maxilla, the normal reduction in lower arch length is to a certain degree larger than the reduction in upper arch length.

In addition, the backward rotation of the mandible results in labial tipping of the incisors, pressing them against the lip and resulting in a slight lingual repositioning of the incisors. This in turn decreases the arch length and leads to crowding.[21]

In both orthodontically treated and untreated subjects, there is a greater risk for lower incisor crowding when the mandible continues to grow after other growth has essentially ceased.[83]

Vertical position of the teeth: Björk and Skieller have observed that subjects with the greatest eruption also have the highest level of vertical growth.[20] In addition, it is noticeable that subjects with short and long facial heights have smaller and larger dentoalveolar heights, respectively.[84]

Thus, the relationship between jaw growth and eruption is confirmed.

Furthermore, jaw rotation during growth affects both the vertical and the sagittal positions of the incisors in subjects with short or long facial heights. Forward jaw rotation associated with the short-face growth pattern tips the incisors lingually and results in a deep bite. On the other hand, backward rotation of the jaw associated with the long-face growth pattern can result in an anterior open bite if the incisors do not erupt over a long distance.[20,21]

Age-related dental arch changes

The natural dentoalveolar changes continue throughout life. The age-related changes in the occlusion and dental arch dimensions are unpredictable and pose a challenge for orthodontics, prosthodontics and orthognathic surgery.[1,2,22]

Longitudinal studies of changes in normal occlusion up to adulthood reveal a decrease of inter-canine width, particularly in the lower arch.[2,9,85,86] Moreover, the length and depth of the dental arch decrease from adolescence to late adulthood, as shown in follow-up studies of untreated subjects.[1,8,9,86,87] Consequently, the anterior teeth, especially in the lower arch, exhibit an increase in age-related crowding.[1,8,9,87,88]

Tsiopas *et al.* have studied dentoalveolar changes in 18 Swedish untreated dentists over a 45-year period, starting at 20 years of age, and have shown that dentoalveolar changes occur as an ongoing process during adulthood, with the changes including decreased inter-canine distance and increased anterior crowding with unchanged overjet and overbite.[9]

Studies have shown that the overbite and overjet are quite stable throughout life,[9,85] while Massaro *et al.* have reported a reduction in overbite in a 40-year follow-up.[86]

Harris and Tsiopas[8,9] have reported that the inter-molar width increases into late adulthood, in contrast to Bishara[89] who observed unchanged inter-molar width.

In addition, studies have shown that even orthodontically treated patients are affected by these age-related dentoalveolar changes.[83,90,91] However, it is difficult to distinguish morphologically between the natural age-related dentoalveolar changes and relapses after orthodontic treatment.[86,92]

Moreover, it has been shown that eruption of the teeth is a continuous process that begins in early childhood and continues into adulthood.[93] In the study of Thilander,[2] a continuous increase in palatal height was observed, indicating slow but continues eruption of the teeth. This continuous eruption of the permanent teeth throughout adulthood explains the infraocclusion of dental implants.[93,94] The dental implants lack the eruption process of natural teeth and the adaptation to growth of the jaws. Thus, the insertion of osseointegrated dental implants is mainly limited to the period after expected jaw growth has finished.[93-95] Follow-up periods as short as 4 years after dental implant installation in adults have shown approximately 1.9 mm infraocclusion of implants, indicating the severity of this problem.[96]

Craniofacial growth mechanisms

Knowledge of the regulatory mechanisms controlling the development and growth of the craniofacial complex remains incomplete. Older theories (i.e., those of Periosteal,[97] Sutural,[98] and Cartilage[59]) related to craniofacial growth control suggested that the development and growth of craniofacial structures are basically the result of intrinsic, hereditary factors that are not mutable to any significant degree. According to these theories, dentofacial orthopaedic treatments cannot affect craniofacial growth.[26,99]

Subsequently, the functional matrix theory shifted the focus from dependence solely on genetic pre-determination, to roles for extrinsic, functional and environmental factors in craniofacial development and growth.[100] This suggested that breathing, muscle function and growth of the brain could explain the mechanisms of craniofacial development and growth.[26,99]

The servosystem theory put forward by Petrovic[38] proposed that a combination of genetic and environmental factors, for example muscle function, regulate craniofacial growth. In addition, this theory suggested the role of hormonal factors in changes to maxillomandibular growth.[26,99] In the late 20th Century, there has been increasing interest in epigenetics as factors of importance for growth and development. Epigenetics refers to changes in gene expression that are not coded by the DNA sequence. These include chemical alterations of the DNA and its associated proteins (histones), which are regulated in turn by the activation of specific enzymes. These changes lead to remodelling of the chromatin, and activation or inactivation of a specific gene. Epigenetic modifications are reversible, and they can also be induced or altered by environmental factors, such as muscle function. In line with this, besides genetic regulation of the craniofacial complex, its development and growth adapt to the epigenetic environment.[101]

The differences in growth mechanisms between bone formed by intramembranous ossification and bone formed by endochondral ossification can be described by the concepts of skeletal growth sites and skeletal growth centres, respectively. Growth centres have tissue-separating abilities, supporting the ability to grow and expand despite the presence of mechanical forces that have the potential to limit or inhibit skeletal growth.[99] Therefore, the epiphyseal and synchondrosal cartilage function as independently growing centres; the nasal septum can also do this, albeit to a lesser degree.[26,99] In contrast, a growth site is a region of skeletal growth that appears secondarily and has no tissue-separating abilities but responds more readily to extrinsic factors. Periosteal bone growth (associated with muscle function) and sutural bone growth (maxillary and cranial vault sutures) are examples of growth sites.[99] It is generally accepted that bone growth at the cranial and facial sutures happens when the bone edges are progressively separated by the expansion of underlying tissues, such as the brain, dura mater, and nasal cartilage.[32]

Cranial base: Endochondral ossification from primary hyaline cartilage tends to be more-strictly programmed genetically than intra-membranous bone ossification. As synchondroses are derived from the primary hyaline cartilage, the growth of synchondroses is controlled by intrinsic factors, including growth factors and cell-signalling molecules that are genetically regulated, and it depends to a lesser extent on epigenetic factors.[99] However, synchondroses can be affected by epigenetic events, such as malnutrition, diseases, and other situations that affect the endocrine functions responsible for bone growth.

Maxillary complex: During childhood, the maxillary complex grows in the forward and downward directions due to the growth of the cartilaginous cranial base and nasal septum.[56,99] The cartilages of the nasal septum and capsule are part of the chondrocranium and appear to have significant intrinsic growth potential. Thus, the nasal capsule cartilage potentially plays a regulatory role in facial suture morphogenesis and patency, in similarity to dural regulation of cranial sutures.[32]

In addition, the maxillary complex is associated with various functional units, including the alveolar process and teeth, the nasal cavity, and the maxillary sinus, which may be involved in the downward and forward displacement of the maxilla during adolescence. The growth of the sutures in the maxillary complex is compensatory and adaptive to the extrinsic factors, for example muscular function, and can be affected directly and indirectly by systemic hormones.[26,80,99,102] The sutures in the maxillary complex also provide opportunities for growth-modifying interventions.

Moreover, several important transcriptional and growth factors that are responsible for suture development have been identified in experimental animal studies. Through exogenous introduction of those factors, experimental research has begun to save the non-growing and even the synostosed sutures.[26,32]

Mandible: The mandible is associated with multiple functional units, including the condyle and alveolar process, as well as the teeth, and all of these have impacts on the growth and morphology of the mandible.[67,103] The forward and downward displacement of the mandible is related to the growth of muscles and other surrounding soft tissues (expansion of the oral, nasal and pharyngeal volume), and this results in new bone being added to the condyle.[80,99,104]

The mandibular condylar cartilage is a secondary cartilage that develops from the periosteum. The growth at the condyles resembles more closely the growth at the maxillary sutures than the growth at an epiphyseal plate.[26,37,38,105]. Although experimental studies have shown that condylar cartilage has some tissue-separating ability,[106,107] the condylar cartilage can be affected by environmental factors, as it has capability for adaptive remodelling in response to changes in the mode of breathing,[104] masticatory function,[80] and condylar repositioning.[108,109] It should be noted that these environmental factors are not in themselves "control mechanisms" for growth but are instead potential effectors of condylar growth. These factors are, thus, non-genomic epigenetic elements that can modulate the control of genes responsible for the expression of molecular factors that in turn affect growth.[26] With significant progress being made in the study of condylar cartilage, it turns out that different growth factors within the condylar cartilage are essential for normal growth of the mandibular condyle.[26,37]

Experiments with growing rats have shown that condylar remodelling, in response to condylar repositioning, is characterised by acceleration of chondrogenesis and subsequent increased bone formation,[110] whereas in adult rats, condylar remodelling is characterised by re-activation of chondrogenesis and subsequent bone formation.[108] However, during growth, dentofacial orthopaedic treatment of Class II malocclusion may to a limited extent affect the growth of condylar cartilage and result in growth remodelling at the TMJ.[105]

The importance of understanding craniofacial growth

Since deviations from the normal developmental processes may cause malocclusions and dentofacial deformity, knowledge regarding craniofacial development and growth is important. Understanding the aetiology of the different skeletal and dental malocclusions enables the orthodontist to make a correct diagnosis and to optimise treatment planning.[24] In addition, in dentofacial orthopaedics, orthognathic surgery, and tooth implantology, it is necessary to take into account the late adult craniofacial growth patterns in terms of treatment timing, post-treatment retention, and relapse.[4]

Moreover, surgeons working in the craniofacial area, e.g., maxillofacial and plastic surgeons, require fundamental knowledge regarding craniofacial growth, to determine the appropriate timing of interventions that will maximise treatment outcomes and minimise iatrogenic consequences.[12]

Methods to evaluate postnatal craniofacial growth

Studies of craniofacial growth are associated with several difficulties due to the long-lasting craniofacial growth period and the structural changes and inherent complexity associated with craniofacial morphology.[111] Nonetheless, several methods have been used to evaluate craniofacial growth.

1. Craniometry

Craniometry was the first method for studying growth, with which physical anthropology began. This method relies on measurements of skulls found among human skeletal remains.[112] Craniometry provides precise measurements of dry skulls, although it has the important limitation that the growth data are cross-sectional.

2. Anthropometry

In anthropometry, different bony landmarks, identified in studies of dry skulls, are used to measure the skeletal dimensions of living subjects using soft tissue landmarks overlaid on these bony landmarks.[113] In spite of the variability of soft tissues, anthropometry makes it possible to follow an individual's growth and can perform the same measurements repeatedly at different times.

3. Cephalometric analysis

Cephalometry is defined as the interpretation of linear and angular measurements between determined anatomical landmarks on a lateral cephalometric radiograph, for descriptive and diagnostic purposes.[114] The cephalometric analysis allows 2D assessments of the sagittal and vertical changes in craniofacial (skeletal and soft tissue) and dentoalveolar structures on lateral cephalometric radiographs. For these reasons, cephalometric analysis has been used widely in orthodontic and orthognathic treatments, as well as in research on craniofacial growth.[115] To improve the accuracy of the cephalometric analysis of the changes that occur over time, cephalometric superimposition is used.[21,116,117] However, cephalometric analysis and superimposition have an inherent limitation in that they provide a 2D description of a 3D object.

4. Metallic implant radiography (Björk's studies)

In the early 1950s, Arne Björk was the first to combine metallic implants and standardised cephalometric radiographs to study facial growth. He inserted metal pins (made of Tantalum) that were rigid, biocompatible and visible on a cephalometric radiograph, into the maxillary and mandibular bones of children, to serve as stable references.[63] This technique increased significantly the accuracy of longitudinal cephalometric analysis of facial growth and provided important information about the growth-related changes in the jaws. At that time, Björk developed his structural method of superimposition based on the implant studies. However, for ethical reasons, this technique is no longer considered.

The implant studies conducted by Björk[20,21] established that the maxilla and the mandible undergo growth-related rotational changes in relation to the anterior cranial base. The mandible exhibits a considerable and real vertical rotation that is greater than the vertical rotation of the maxilla, whereas the maxilla shows a more transverse rotation.

5. 3D techniques

The measurement of 3D craniofacial changes using 2D cephalometric analysis is considered to expose the most significant limitation of the method. The development of cone beam computed tomography (CBCT) provides the possibility to measure 3D changes that are associated with craniofacial growth and orthodontic and orthognathic treatments. However, the radiation dose for a lateral cephalogram is approximately 5.6 µSv, which is equivalent to 0.7 days of background radiation.[118] This can be compared to a low-dose CBCT examination, where the radiation dose is 15–26-times higher.[119-121] Studies of 2D cephalograms re-constructed with CBCT found no significant differences compared to the measurements obtained using conventional cephalogram.[122-124]

In a recent study, an ultra low dose-low dose (ULD-LD) CBCT protocol was used, where the radiation dose was estimated to be reduced by about 87% compared to the standard exposure protocols.[125] However, in that study, a lateral cephalogram (2D) re-constructed from the CBCT examination was used rather than the full 3D examination.[125] Currently, 2D cephalometric analysis is the most commonly used method for longitudinal studies, owing to the absence of 3D cephalometric reference measurements for diagnosis and treatment planning. In addition, it will take many years before a longitudinal study using 3D technique is completed.

Cephalometric analysis

Radiographic cephalometry and superimposition

The ancient Egyptians were probably the first to illustrate an imaginary ideal model of facial proportions in mathematical form and grid. Later, during the Renaissance period, the interest in facial proportions continued when Leonardo da Vinci illustrated the proportions of the face using a grid system.[126] Measurements have been used historically to help artists draw the shape of a human being. In 1768, angular measurements of the facial form were introduced by the Dutch physician and painter Petrus Camper.[127] A facial angle was introduced by Camper that was formed by a line drawn through the wing of the nose and the ear hole and by another line, called the facial line, drawn through the most protruding point on the forehead and the upper anterior alveolar ridge. Camper compared facial angle measurements between infancy and adulthood, and used the longitudinal measurements of this angle to display the time-related changes to the facial profile.[128]

Imaging with x-rays was discovered in 1895 by the German Wilhelm Conrad Roentgen,[129] and soon thereafter x-rays were implemented in medicine, anthropology and dentistry. Radiography made it possible to diagnose internal pathologies in patients and to study growth of the skeleton in humans. Pacini was the first to introduce a standardised technique for exposing the dry skull to lateral x-rays for anthropologic objectives.[129] Thereafter, in 1931, Broadbent introduced the application of the radiographic cephalometer, providing the orthodontist with an instrument for quantitative facial analysis.[130] Longitudinal craniofacial growth studies in living subjects were not feasible prior to the development of the radiographic cephalometer. Broadbent's first longitudinal study of cephalometric radiographs was based on a 5-year analysis of the craniofacial growth patterns of about 1,000 subjects.[131]
Researching craniofacial growth patterns was the primary purpose of cephalometry, and current knowledge of normal craniofacial growth and development has been acquired largely from cephalometric studies. Cephalometric analysis has also found applications in orthodontic and orthognathic treatments, for the diagnosis of malocclusions (skeletal or dental), treatment planning, monitoring of treatment progress and evaluation of treatment outcomes.[132]

In order to assess the contributions of skeletal and dental components in malocclusion, a normal reference group (normal cephalometric data) is required. Downs (1948) was the first to develop a cephalometric analysis based on skeletal and facial proportions of a reference group of 25 untreated subjects, who were selected for their excellent occlusion and facial proportions. Downs analysis confirmed the direction and extent of individual variations in landmark locations that serve as a guide for interpreting the results of cephalometric analyses.[133]

There are two methods to assess the craniofacial changes related to growth and/or treatment.

Conventional cephalometrics

Assessment of craniofacial changes, between different time-points for the same individual, can be performed using conventional cephalometrics. This method depends on a comparison of the numerical values of the linear and angular measurements (obtained between anatomical landmarks on a cephalogram) at different time-points. Conventional cephalometrics is easy to perform and is not time-consuming, particularly if a digital, automated analysis system is used. Nevertheless, conventional cephalometry can give inaccurate measurements due to growth-related positional changes of the chosen landmarks.[134,135] Therefore, superimposition-based cephalometry is required to improve the accuracy of the analysis and to validate the craniofacial changes.[21,117]

Conventional superimposition

In 1931, Broadbent was the first to establish superimposition as a way to study facial growth in living and growing subjects.[130] Cephalometric superimposition refers to a series of cephalograms, taken at different time-points in the same individual, and superimposed using stable structures, such as the anterior cranial base, with the goal of accurately assessing craniofacial changes related to growth and/or treatment. Thus, the location and direction of craniofacial changes in the individual patient can be determined by cephalometric superimposition.

For accurate evaluation of craniofacial changes, a superimposition method should have high reliability (low method error). Furthermore, superimposition should have high validity, i.e., stable (non-growing) anatomical structures should be used for the orientation of serial cephalograms when performing superimposition, so as to detect changes related to growth and/or treatment as accurately as possible.[21,117]

Nevertheless, it takes time to perform a conventional superimposition and it can be difficult to identify stable structures. In addition, conventional superimposition cannot assign numerical values to the changes that occur over time, it can only provide a graphical illustration of these changes.

The aspiration to analyse changes that occur in response to orthodontic or orthognathic treatment and growth has led to the development of several cephalometric superimposition methods.[21,136-138]

Methods for conventional superimposition

1. ***Local maxillary superimposition:*** Superimposition of cephalograms on stable structures in the maxilla revealed growth-related remodelling of the maxilla and treatment-related positional changes of the upper teeth. The anterior contour of the zygomatic process was considered to be the only stable structure for maxillary superimposition, according to Björk's implant study.[61]

2. ***Local mandibular superimposition*:** Superimposition of cephalograms on stable mandibular structures revealed growth-related remodelling of the mandible and treatment-related positional changes of the lower teeth. Björk's implant study revealed a number of stable bone structures in the mandible that could be used for mandibular superimposition, i.e., the anterior contour of the chin, the internal cortical surface of the symphysis, trabeculae related to the mandibular canal, and lower contour of mineralised molar germ before root formation has started.[21,73]

3. ***Cranial base superimposition (General):*** Superimposition of cephalograms on the anterior cranial base revealed overall craniofacial changes (maxilla, mandible and soft tissue profile) related to growth and/or treatment. In addition, cranial base superimposition revealed upper and lower dentoalveolar positional changes. However, dentoalveolar changes assessed by cranial base superimposition include a combination of tooth movement within the jaw (eruption) and tooth movement along with the jaw in which it is embedded (translocation).[93] Cranial base superimposition is usually carried out using either landmarks and planes or Björk's structural method.[21,136,139]

Landmarks and planes for superimposition

SN method

One of the most widely used methods for cephalometric superimposition is superimposition on the Sella-Nasion (SN) plane (Steiner plane), which is registered at landmark Sella.[137] Sella (S) is a geometric centre of the pituitary fossa. Nasion (N) is the most-anterior point on the frontonasal suture. Both S and N are midsagittal landmarks and are easy to identify, which means that they have relatively high reproducibility.[114,140] In a study conducted by Wei to compare the variability of different cephalometric reference lines, the SN plane showed the least variability.[141]

However, the SN plane has certain drawbacks. In particular, the stability levels of the S and N landmarks during growth have been questioned. From the study of Björk[21] and the histological analyses of Melsen,[46] it is clear that Sella undergoes a posterior and vertical displacement due to growth of the pituitary gland and resorption at the dorsum Sella. In contrast, Nasion displaces anteriorly and vertically with growth of the frontal sinuses.[21,50,51] Small variations in either of the landmarks of the SN plane can have significant impacts on landmarks that are far away, for example the displacement at landmark Pogonion can be very large. Thus, the weakness of the validity of superimposition using the SN plane can be attributed to growth-related displacements of landmarks S and N.

NBa method

Ricketts has proposed the use of the NBa plane for the superimposition of cephalograms.[138] The NBa plane consists of the landmark Basion (Ba), which is the lowest point on the anterior margin of the foramen magnum at the base of the clivus, and the landmark N. However, landmark Ba exhibits positional changes due to remodelling of the clivus[46] that may affect the validity of superimposition using the NBa plane.

TW method

Cranial base superimposition can also be performed on the TW plane. The TW plane consists of landmark Tuberculum Sella (T) (also known as Walker's point) and landmark Wing (W) (also known as the Spheno-ethmoidal) (Figure 1). In practice, cephalograms are superimposed on the TW plane, registered at the landmark T. The landmarks T and W are chosen because they attain their stability at an early age.[21,136,142]

Arat and co-workers (2010) compared the TW method with Björk's structural, SN, and Ricketts methods for their capabilities to assess longitudinal growth changes of the cranial base from 12 to 32 years of age.[136] The results of that study indicated that landmark T is stable (100%) in both horizontal and vertical directions and through all stages. This is followed in order of stability by landmark W with 83% stability, whereas the S and N landmarks had 50% and 16% stability, respectively.[136]

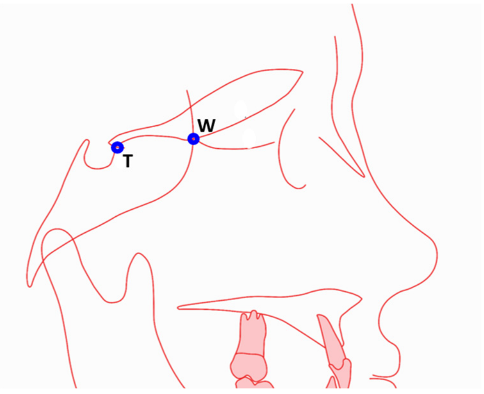

Figure 1. *Illustration of the position of landmarks Tuberculum Sella (T) and Wing (W). Tuberculum Sella is the intersection point of the lower contour of the anterior clinoid process and the anterior wall of Sella turcica. Wing is the intersection point of the middle cranial fossa and the ala major of the sphenoid bone.*

Björk's structural method

Björk conducted longitudinal cephalometric growth studies in which he inserted more than 900 tantalum implants in the upper and lower jaws of more than 200 subjects.[20,21,61,63] The tantalum implants were used as stable markers for serial cephalometric superimposition. The implant studies revealed substantial individual variability of the dentofacial growth patterns. In addition, Björk's investigations have identified natural stable structures in the maxilla, the mandible and the anterior cranial base. Based on these studies, Björk developed the structural method for superimposition.

While it was impossible to insert implants in the cranial base, a histological study conducted by Melsen[46] complemented and clarified the cranial base superimposition suggested by Björk. Björk and Skieller[21] proposed a number of stable anatomical structures in the anterior cranial base that could be used for general superimposition. These include the anterior wall of the Sella turcica, the anterior contours of the middle cranial fossae, Walker's point, the Cribriform plate, the fronto-ethmoidal crests, and the cerebral surfaces of the orbital roofs (Figure 2).

A systematic review carried out by Afrand *et al.*,[50] has confirmed the validity of anterior cranial base superimposition, as determined by Björk. Therefore, based on the evidence from the histological and radiographical studies,[21,46] Björk's structural method remains the most accurate (valid) method for cranial base superimposition.[143,144]

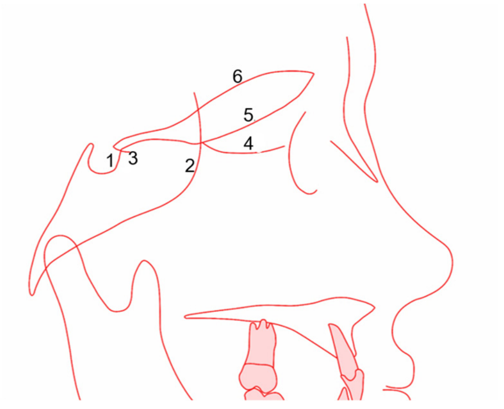

Figure 2. *The positions of stable structures in the anterior cranial base: 1) anterior wall of the Sella turcica; 2) anterior contours of the middle cranial fossae; 3) Walker's point; 4) Cribriform plate; 5) Fronto-ethmoidal crests; and 6) cerebral surfaces of the orbital roofs.*

Subtraction method: To facilitate further the superimposition on the cranial base structures, Björk's method can be combined with subtraction radiography (Björk/subtraction) to improve accuracy.[145,146] Before the digitalisation of x-ray images, it was expensive to work with the subtraction technique because an extra positive (inverted) film copy was needed. In the positive copy, the densities (degree of opacity) are reversed, making the bone appear black. However, the contrast is the same in both radiographs. If the positive copy is developed from the same radiograph that it is superimposed on, and when perfectly matched, the hard tissues appear homogeneously grey, as the structures in the two radiographs cancel out each other. When longitudinal superimposition is performed, growth and remodeling will appear in darker or lighter shades of grey, depending on bone apposition or resorption (Figure 3).

It has been shown that the subtraction method improves the reliability of cephalometric superimposition and enables the optimal use of details in the radiograph.[145] McWilliams compared superimposition with subtraction using anterior cranial base structures with superimposition using the SN method for 15 cases, and with a mean follow-up of 1 year. He found that an approximately 70% improvement in precision was achieved with the subtraction method.[145]

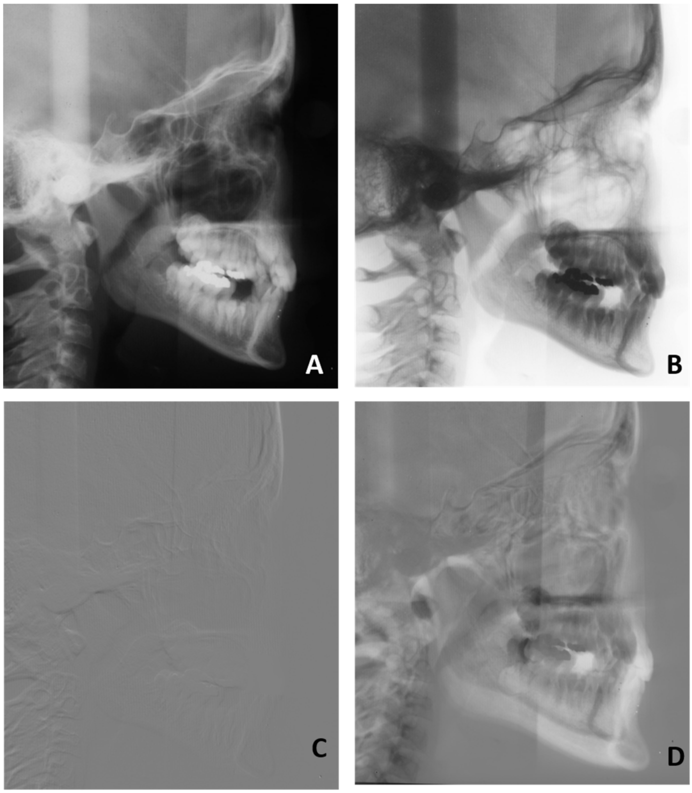

Figure 3. *Lateral cephalograms acquired from the same patient.* ***A)*** *Original cephalogram at 10 years of age.* ***B)*** *Inverted copy of the original cephalogram.* ***C)*** *Superimposition of the original radiograph onto the inverted copy. Unchanged structures are extinguished in this case, resulting in a homogeneously grey image.* ***D)*** *Original inverted cephalogram superimposed onto a cephalogram acquired after 4 years of growth. Changes to the upper and lower jaw are visualised, whereas unchanged structures are extinguished, as in panel* ***C****.*

Validity and reliability of cephalometric analyses and superimposition

For evidence-based medical treatment of patients, clinicians require an accurate method to assess craniofacial changes related to growth and treatment. Since its introduction by Broadbent, cephalometric analysis has been used for more than 90 years and has become a standard tool in orthodontic and orthognathic diagnostics, treatment planning and evaluation.[130] However, two main types of errors can arise in cephalometric analyses and superimposition: projection and identification errors.[115]

Projection errors: These are errors caused by measurements of 3D craniofacial changes in a 2D cephalometric analysis, e.g., the magnification and artefacts due to the x-ray projection and patient positioning.[114] The cephalometric radiographs are subject to magnification errors because the x-rays that generate the radiographical image emerge from a small source and do not radiate in parallel directions. The degree of magnification is dependent upon the ratio of the distance from the x-ray source to the midsagittal plane of the patient's head and the distance from the x-ray source to the detector. The greater the distance between the head and the detector, the greater the magnification.[115] However, Ahlqvist *et al.* have shown that, in cephalometry, the projection errors in linear measurements are not a serious problem.[147] In addition, it has been found that radiographical errors related to the cephalometric equipment can be maintained at an acceptably low level.[148]

Identification errors: These errors are associated with the identification of specific anatomic landmarks or structures on the cephalogram. The magnitudes of identification errors vary between landmarks and are influenced by the density and sharpness of the cephalogram.[114,140] In addition to the necessary quality of the cephalogram, the radiograph should be taken under the same conditions and with the same cephalostat, so as to minimise the source of errors if comparisons between different time-points are planned.[144] Furthermore, the identification of landmarks and superimposition process should be performed carefully, and the identification of each landmark and structure must be done in a single session for each radiograph exposed at a different time-point.[149] The appearance of a double contour in the cephalometric radiograph may depend on the patient positioning and differences in magnification due to the distance to the midline of the patient and the detector; an equidistant contour should be used if there is a double contour.[144]

The validity and reliability of cephalometric superimposition are important for the evaluation of growth- and treatment-related changes over time.[150] The reliability of cephalometric superimposition relates to precision and reproducibility[143] and depends on the quality of the radiograph,[151] the identification of landmarks/structures,[151-153] and the superimposition method,[151-154] as well as the operator's experience regardless of the chosen method.[151-153] Dental landmarks are less-reliable than skeletal landmarks.[114] Errors related to the superimposition protocol can be sufficiently large to influence the interpretation of craniofacial changes.[152,154] In addition, the superimposition may involve a rotational error, where the errors in the linear measurements are exacerbated with increased distance from the centre of rotation.[145] The search for reliability should not obscure the dubious validity of the landmarks and anatomical structures selected for cephalometric analysis and superimposition.[155]

The validity of cephalometric superimposition ensures accurate assessments of true growth-related and treatment-related changes over time. The choice of structures for serial orientation of the radiographs is, therefore, essential in enabling the superimposition to reveal the changes related to growth and/or treatment in a valid manner.[21,46,50]

Many studies have compared different superimposition methods, regarding their validity and reliability, with variable results.[136,139,151,154,156] Some studies have recommended the use of Björk's structural method, relying on its validity.[21,46,136,145,154] Buschang *et al.* compared the reliability of structural superimposition on the cranial base and mandible according to the Björk's method, and showed that structural superimposition on the anterior cranial base was more reliable than other methods.[150]

However, other studies did not observe significant differences between Björk's structural method and the SN method, and have proposed the use of the SN method for cranial base superimposition owing to its reliability and simplicity.[139,156]

Consequently, there are ongoing controversies surrounding the reliability and validity of cephalometric superimposition, and more research is needed to identify a superimposition method that has high reliability and validity levels.

Studies assessing craniofacial changes

Up to early adulthood: In Denmark, Björk conducted his well-known studies of craniofacial growth in the period 1955–1983, in which he used metallic implants as a reference to evaluate craniofacial growth between 5 and 25 years of age.[19-21,61,63,73] Melsen[46] performed an important study on autopsies of subjects aged 0–20 years, where she determined the growth patterns (areas of resorption and apposition) of the cranial base and confirmed the cranial base superimposition proposed by Björk. Thilander, together with Persson and Adolfsson, studied craniofacial changes between 5 and 31 years of age and established cephalometric standards for a Swedish population.[3]

Up to mid-adulthood: In a 20-year follow-up of 30 Swedish dental students aged between 25 and 45 years, Forsberg *et al.* found significant changes in the multiple linear and angular dimensions, including an increase in anterior facial height.[44] Overall, 80% of this increase was located in the lower part of the face. A similar increase in the anterior facial height, especially the lower facial height, was also demonstrated by Bondevik in a Norwegian study of dental students aged from 22 to 33 years.[157] Continuous significant craniofacial changes were noted during the follow-up period of 33–43 years.[43]

Up to late adulthood: Behrents was the first to describe changes in the hard and soft tissues of the face up to late adulthood.[6] However, in Behrents' study, only four subjects were older than 40 years of age. The results revealed significant linear and angular changes in the dentofacial area during the follow-up period until 61 years of age. It was concluded that the changes were similar in type, albeit not of the same magnitude as during adolescence. Significant gender differences were also described in that study.[6] Pecora *et al.* conducted a longitudinal cephalometric study of subjects between 17 and 57 years of age and observed that several significant changes in the craniofacial complex occurred into late adulthood.[7]

In conclusion, very few studies have investigated the craniofacial changes up to late adulthood.[6,7] In addition, the results of the above-mentioned studies challenged on the basis that they used conventional cephalometric measurements[3,43] or with respect to the superimposition method used.[7,44] Therefore, further studies are needed to quantitate craniofacial changes up to late adulthood using cephalometric superimposition.

Dental crowding

Irregularity (crowding) of the teeth affects the appearance of the person and some may find it a less-attractive feature. In recent years, the number of patients attending orthodontic clinics with the chief complaint of dental crowding has increased, mainly due to increased awareness regarding facial aesthetics.[158]

A discrepancy between tooth size and arch dimension is the most common reason for dental crowding malocclusion. However, various factors have been implicated in dental crowding, including the effects of genetic and environmental factors on dental arch width and length, and mesiodistal tooth width.

Conventional methods for creating space to relieve dental crowding usually involve: 1) extraction of teeth, often the premolars, in combination with subsequent orthodontic treatment; or 2) orthodontic expansion of the dental arch.

Treatment of dental crowding

Non-extraction treatments

Dental crowding during mixed dentition, with a space deficiency of <5 mm, can be treated by interceptive orthodontics; e.g., management of the leeway space using a lingual arch.[159] Dugoni *et al.* have concluded that early treatment of mixed dentition using the leeway space to relieve lower incisor crowding yields greater incisor stability.[160] In line with this, a study comparing early and late treatments of crowding concluded that early alignment of incisors might be justified to reduce post-retention incisor irregularities.[161]

In addition, patients who have mild-to-moderate dental crowding during mixed dentition can be treated orthodontically with dental arch expansion sagittally and/or transversally. Transversal dental arch expansion is one of the most common ways to gain space in the dental arch, e.g., rapid maxillary expansion.[159]

Extraction treatments

The extraction of the first premolars with subsequent orthodontic treatment is the strategy of choice for creating space and alignment in the dentition of patients with severe crowding.[162] However, there are a number of clinical situations in which extraction of the second premolars or permanent molars might be considered.

Serial extraction has been used as an interceptive guidance tool for tooth eruption and as a treatment procedure for patients with severe crowding. Kjellgren introduced the term “serial extraction” in the late 1940s,[163] and later Hotz called it “guidance of eruption”.[164] Serial extraction involves the sequential extraction of deciduous teeth (canines and first molars), to facilitate unblocked eruption of the permanent teeth (first premolars), which are extracted once they erupt, so as to allow self-alignment of the anterior teeth.[163,164] Ringenberg has stated that serial extraction may be indicated when there is a space deficiency of ≥7 mm in the dental arch.[165]

The main reported benefits of serial extraction include improved relations of the teeth to the surrounding hard and soft tissues, decreased orthodontic treatment time, and improved stability of the results owing to early self-correction of the crowding.[159,166,167] Serial extraction can reduce or even eliminate the need for subsequent treatment with an orthodontic appliance owing to spontaneous alignment of the dentition. This, in turn, reduces the cost of treatment, reduces the level of discomfort experienced by the patients, and saves time for the patients and their parents.[168]

It has been reported that serial extraction can result in lingual tipping of the lower incisors and increased overbite, in addition to creating unwanted spacing in the dental arches.[165,166,169,170] However, Persson *et al.* have questioned these changes in a longitudinal study of spontaneous changes after premolar extraction.[171] Furthermore, Little has reported no differences in 10-year post-retention stability between a serial extraction group and a matched group with premolars extracted after full eruption, where both groups were treated orthodontically.[90]

Although serial extraction is a good treatment option, extraction of all the suggested 12 teeth in a child to solve a future crowding problem might today be considered unwarranted ethically.

Dentofacial changes in response to premolar extraction

Adults seek orthodontic treatment to improve their dental and facial aesthetics and, hopefully, their popularity and social standing.[10,158] Thus, when planning orthodontic treatment, the position and inclination of the teeth should be determined to plan interventions for counteracting the age-related changes.

Although dental crowding is the most-common malocclusion,[158,172] it is still difficult, in some cases, to choose extraction over the non-extraction alternative to relief crowding, considering the debate about the possible effects of tooth extraction on the dentoskeletal and soft tissue profiles. Space deficiency, incisor inclination, and the facial profile are the most-important factors that are usually analysed to determine the need for premolar extractions in patients with crowded teeth.[173] The nasolabial angle and the distances from the lips to the aesthetic line are two of the facial profile parameters that are commonly used to decide on premolar extraction therapy.[174] Retraction of the upper and lower lips has been shown to occur when orthodontic treatment involves the extraction of the first premolars.[175,176]

Furthermore, it may be necessary to take the facial vertical dimension into account when deciding whether or not to extract teeth, as studies have reported that extractions result in a reduction of the vertical dimension.[177,178] The main reason for suspecting that tooth extractions decrease the vertical dimension is the wedge-effect concept, whereby mesialisation of the molars during closure of the extraction spaces results in anterior rotation of the mandible and reduction of the vertical dimension.[179] However, it has been observed that during closure of the extraction spaces, the direction of the mesialisation of the molars is parallel to the occlusal plane, and not to the maxillary and mandibular planes for the upper and lower teeth, respectively.[180] Muscle balance and function are important factors for determining the vertical dimension.[80,180] Furthermore, several studies have found that extraction of the first premolars does not affect the vertical facial dimension.[181-186] The wedge-effect concept, therefore, has not been proven.

Consequently, craniofacial changes in orthodontically treated patients have been evaluated in short-term and long-term follow-ups. In particular, the effects of extraction and subsequent orthodontic treatment on the soft tissue profile and vertical facial dimension have been investigated.[175-178,185,187-190] Studies have found that premolar extraction can affect the dentoskeletal and soft tissue profiles[175-178], while other studies have shown no significant differences between the extraction and non-extraction treatment outcomes.[174,185,187-190] Proffit has stated, however, that many patients with Class I crowding can be treated adequately with or without premolar extraction if appropriate orthodontic mechanics are used.[162] Thus, it could be considered that the standard orthodontic treatment, following premolar extraction, can reduce the adverse effects of the extraction on the soft tissue profile and vertical dimension.[162,174,191,192] In addition, in short-term studies performed on patients during adolescence, the craniofacial growth that normally occurs during this period may constitute a confounding factor.

It is necessary, therefore, to study the effects on dentofacial structures of premolar extractions, in the absence of subsequent orthodontic treatment. However, in this context, only one relevant study could be found in the literature, which investigated the effects of serial extraction, without subsequent orthodontic treatment, on the soft tissue profiles of subjects who were followed from 13 to 24 years of age.[193] In this '11-year' follow-up, no significant differences were observed in the soft tissue profile between three groups; serial extraction group, serial extraction with subsequent orthodontic treatment group and late premolar extraction with orthodontic treatment group.[193]

Furthermore, long-term follow-up and comparison with untreated control must be considered in order to clarify the possible effects of extraction.

Effects of premolar extraction and orthodontic treatment on age-related lower incisor crowding

The results of several studies on post-retention stability following orthodontic treatment have demonstrated changes in occlusion, indicating the limitations in terms of stability of the orthodontic treatment.[91,194-196] Long-term follow-up studies have shown that such changes in occlusion are not only due to treatment relapse, but also to age-related physiological changes, e.g., continuous decreases in the dental arch length.[9,83,86,91] Studies have shown that the physiological changes and relapse of the occlusion are highly variable and unpredictable.[91,194] However, it is difficult to distinguish between the age-related physiological dentoalveolar changes and relapses that occur after orthodontic treatment.[86,92]

Crowding of the incisors, especially in the mandible, is the most-commonly occurring physiological change with age.[8,9,87,196] Several factors have been considered in relation to the development of lower incisor crowding with age, including mesial migration of posterior teeth, soft tissue pressure, and continuous change to the jaws.[73,87] A previously proposed theory regarding the role of the third molars in the development of lower incisor crowding has been rejected.[20,87,194]

Interestingly, the conclusion made by Little and co-workers is that the lower incisor crowding that develops in treated and untreated cases is similar in nature, albeit to different extents, and is probably linked to the initial occurrence of crowding.[88,194] Consequently, life-long retention of occlusal alignment has been repeatedly suggested.[90,195,196]

A follow-up study up to early adult age of Class I crowding cases, in which spontaneous closure of extraction gaps was allowed without further orthodontic interventions, revealed an improvement in the malocclusion score, to the extent that no difference in scores was noted when compared with a cohort of non-treated normal occlusion cases.[171]

Considering the fact that earlier studies of conventionally treated premolar extraction cases have shown arch length shortening and lower incisor crowding to the same degree, or an even higher degree than in untreated cases,[83,91] it seems logical to investigate whether non-actively closed residual spaces following premolar extraction also lead to similar or more-severe age-related lower incisor crowding.

Aims

The overall aim of this thesis is to study and quantitate the dentoalveolar and craniofacial (skeletal and soft tissue) changes that occur from early to late adulthood.

Specific aims:

I. To evaluate the reliability and validity levels of the traditional superimposition methods and to increase the precision with which growth and treatment can be quantified.

II. To study the craniofacial changes from early adolescence to late adulthood and to establish reference craniofacial data for late adulthood as a supplement to the data already published for the more thoroughly studied earlier age groups.

III. To investigate the impact of premolar extractions on dentoskeletal and facial morphologies up to late adulthood.

IV. To verify whether the extraction of four premolars affects the development of age-related lower incisor crowding, from early adolescence to late adulthood, as compared to orthodontically untreated subjects.

Materials and Methods

KefUm archive

The KefUm archive contains longitudinal research documentation that includes the cephalograms of children in Umeå, Sweden. The archive which also includes photographs, dental casts and somatic data, has been assembled as part of various research projects. At present, three cohorts are included in the archive, including two follow-up studies, performed to late adulthood. All the material has been anonymized and digitized, and is now stored at the Department of Odontology, Umeå University, ensuring availability for research purposes.

The Rune Filipsson-sample (RF-sample)

This sample includes standardized lateral cephalograms and panoramic radiographs. This longitudinal study was conducted by Rune Filipsson to examine the somatic development of orthodontically untreated children in Umeå, Sweden from the mid-1960s to the early 1970s.[197] The radiographs were acquired annually from randomly selected school children between the ages of 9 and 16 years, at the Department of Odontology, Umeå University, in an attempt to explore dentofacial changes during the pubertal growth spurt. The material consists of approximately 1,200 lateral cephalograms of 190 children, including 5–6 annual cephalograms for each child. Prior to the present study (Table 1), a selection of the cephalograms was used in Christer Ekström's study of facial growth in relation to somatic maturation.[198]

The normal sample (N-sample)

This sample, which includes about 50 children in the age range of 12–13 years, was established in the 1960s at the Department of Odontology, Umeå University, Sweden. The inclusion criteria were Angle Class I dental occlusion and a normal soft tissue profile without any malocclusion, to supply normative data for dental and skeletal variables.[199] In total, 30 subjects, who were still living in the region of Västerbotten County Council were documented at the ages of 15 and 30 and, recently, at the age of 62 years. The documentation includes dental casts and photographs, as well as lateral and posteroanterior skull radiographs (Table 1).

The premolar extraction sample (PX-sample)

This sample was collected in the 1960s at the Department of Odontology, Umeå University, Sweden and consisted of 44 children. The inclusion criteria were Angle Class I malocclusion with severe crowding, but without other malocclusions. At the age of 11, these children had all four first premolars extracted to allow spontaneous alignment of their dental arches.[171] Subsequent treatment with an orthodontic appliance was not implemented due to a lack of resources at the time. Follow-ups with documentation were conducted at 15 and 30 years of age for 43 of the patients. At the age of 62 years, only those patients who were still alive and lived in the region of Västerbotten County Council were documented (N=30). The documentation included dental casts, photographs, and lateral and posteroanterior cephalometric radiographs (Table 1).

Table 1. *Descriptions of the studies in this thesis.*

	Study I	Study II	Study III	Study IV
Study design	Methodological study	Prospective longitudinal study	Longitudinal case-control study	Longitudinal case-control study
KefUm archive	RF-sample	N-sample	N-sample PX-sample	N-sample PX-sample
Study material	Cephalograms	Cephalograms	Cephalograms	Dental casts and cephalograms
Follow-up period	10–15 years of age	12–62 years of age	12–62 years of age	12–62 years of age
Number of included subjects	40 (20 girls and 20 boys)	30 (19 girls and 11 boys)	60 (30 PX samples and 30 N-samples)	45 (24 PX samples and 21 N-samples)
Sample collection period	Mid-1960s to early 1970s	Early 1960s to Mid-2010s	Early 1960s to Mid-2010s	Early 1960s to Mid-2010s

All the lateral cephalograms in the abovementioned samples for subjects from early adolescence to early adulthood were exposed using the same cephalostat, the Philips Super Rotalix x-ray tube (Philips, Germany), using a magnification factor of 1.1 (at the midline). For subjects in late adulthood, the Cranex cephalostat (Soredex, Helsinki, Finland) was used with digital image plates as the detector, also with magnification factor of 1.1. All the cephalograms were taken in habitual occlusion and with the lips relaxed. The analogue cephalograms acquired up to early adulthood were scanned with the Epson Perfection V750 Pro scanner (Epson Europe B.V.) with a resolution of 250 dpi (0.092120 mm/pixel). Thereafter, the cephalograms were imported as JPEG files into the FACAD ver. 3.9.2.1133 cephalometric software. During scanning, each cephalogram had included a calibration ruler for calibration of the magnification. The cephalometric analysis and superimposition were performed digitally on all the chosen cephalograms in the four studies included in this thesis by one orthodontist (NA).

Ethical considerations

Early documentation, in the 1960s and 1980s, was performed after permission was obtained from the parents and the subjects, respectively, to participate in the study and to use their materials for research.

The recent documentation on subjects during late adulthood was carried out after approval by the Regional Ethical Board in Umeå, Sweden (registration no. 2012-410-31 M). In addition, written informed consent was obtained from all participants recruited in the 2010s.

Study I

Materials

This study entailed two cephalograms (RF-sample) selected from 40, for growing and untreated subjects, one baseline cephalogram (T1), and one follow-up cephalogram (T2), taken with a mean time interval of 5 years (Table 2). There were 20 subjects with Class I, 13 with Class II and 7 with Class III skeletal malocclusions. Most of the subjects had normal vertical growth, although four subjects exhibited posterior mandibular rotation.

***Table 2**. Description of the subjects in Study I.*

Time-point	T1		T2	
Gender	Girls	Boys	Girls	Boys
N	20	20	20	20
Mean age (SD) in years	9.6 (± 0.69)	10.3 (± 0.83)	14.9 (± 0.69)	15.3 (± 0.84)
Total	40		40	

Methods

Cephalometric landmarks and reference lines

Nine cephalometric landmarks and two reference lines were used in Study I (Figure 4). These landmarks were chosen because their positions are important for most useful cephalometric angular and linear measurements. In order to perform tracing accurately before superimposition, the identification of each landmark was made in parallel at T1 and T2, in one session for each cephalogram.[149]

After identification of the landmarks, the Nasion-Sella line (NSL) and a perpendicular line through the Sella landmark (NSLP) were drawn (only on the T1 cephalograms) as a horizontal and vertical reference line, respectively (Figure 4). The S and N landmarks were used as references. Since we planned to evaluate 5 superimposition methods, 5 digital copies of each cephalometric tracing for all 40 subjects (at T1 and T2) were made, to eliminate landmark identification errors between methods (see Flowchart for Study I).

Cephalometric variables

In total, 15 linear and angular variables were used in Study I, and they were measured in relation to the reference lines and landmarks. The following seven variables describe the vertical changes: vertical distances of five landmarks (N, A, B, Pog and Me) to the horizontal reference line NSL, the anterior facial height (N-Me), and the mandibular plan angle (ML/NSL). Eight variables describe the sagittal relation: horizontal distances of five landmarks (N, A, B, Pog and Me) to the vertical reference line NSLP, in addition to three angles describe the sagittal jaw relation (SNA, SNB, and ANB) (Figure 4).

The measurements of the 15 variables on the T1 cephalograms, performed in relation to the T1 reference landmarks (S and N) and lines (NSL and NSLP), were designated as $T1C^{REF1}$. The measurements of the 15 variables on the T2 cephalograms, performed in a similar way but in relation to the T2 reference landmarks and lines, were designated as $T2C^{REF2}$. Cephalometric measurements performed in this way are referred to as ‘conventional cephalometric measurements’ (Study I, Figure 2a).

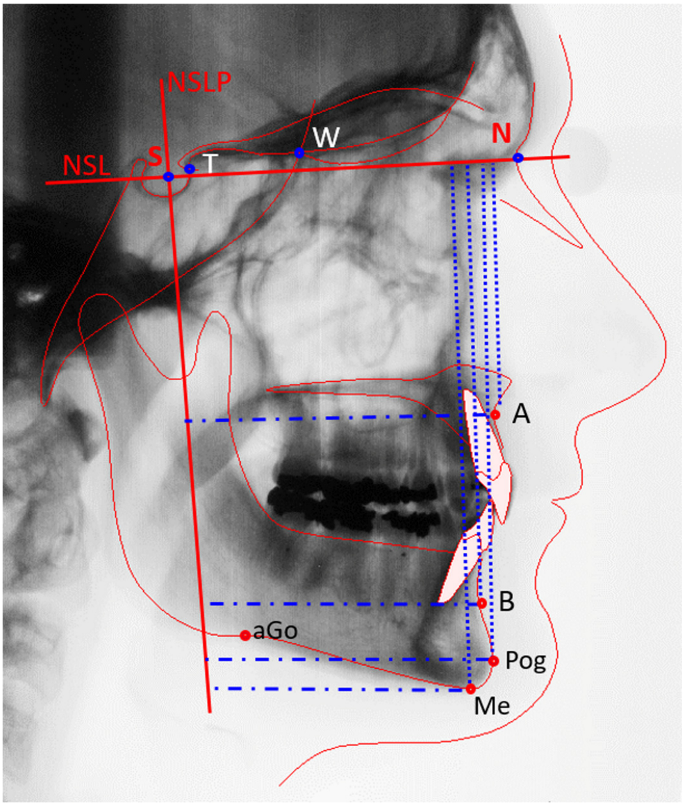

Figure 4. *Inverted lateral cephalogram showing the reference landmarks (S, Sella and N, Nasion), reference lines (NSL and NSLP), and other landmarks used in Study I: T, Tuberculum Sella (Walker's point); W, Wing point (Spheno-ethmoidal); A, A-point; B, B-point; Pog, Pogonion; Me, Menton; and aGo, anterior Gonion. Vertical distances of the landmarks (N, A, B, Pog and Me) to the horizontal reference line NSL. Horizontal distances of the landmarks (N, A, B, Pog and Me) to the vertical reference line NSLP.*

Superimposition-Based Cephalometrics (New Method)

The superimposition of cephalograms T1 and T2 was performed according to Björk's structural method (for details, see Study I). After superimposition, the reference landmarks S and N and reference lines NSL and NSLP were transferred digitally from cephalogram T1 to cephalogram T2 and designated as S^T, N^T, NSL^T, and $NSLP^T$, respectively. Thus, each T2 cephalogram, in addition to having its own references S, N, NSL, and NSLP, also had S^T, N^T, NSL^T, and $NSLP^T$ references with the same original positions that they had in T1. The digital software enabled measurements of the 15 variables on each T2 cephalogram in relation to these transferred landmarks and reference lines (designated as $T2S^{REF1}$). Since the measurements of the 15 variables at T2 were performed in relation to the reference lines and landmarks at T1 after superimposition onto stable anatomical structures, we refer to this as 'superimposition-based cephalometrics'. Changes related to the growth from T1 to T2 were calculated as the difference between the 15 variables ($T2S^{REF1}$ –$T1C^{REF1}$) (Study I, Figure 2c; Appendix Figure A1).

Assessment of the Superimposition-Based Cephalometric Method

The measurements of the five vertical and sagittal variables (ML/NSL, N-Me and SNA, SNB, ANB) were estimated using the conventional cephalometric method ($T2C^{REF2}$) and the superimposition-based cephalometric method ($T2S^{REF1}$), on the same occasion (T2).

In addition, the growth-related positional changes of landmark N were assessed (T1–T2), using the $T2S^{REF1}$ measurement.

Assessment of the different Conventional Superimposition Methods

To identify a valid, reliable and feasible superimposition method, the following three cranial base superimposition methods were evaluated in Study I (Study I; Appendix Figure A2):

- SN plane method[137]
- TW plane method[136] (Figure 1)
- Björk structural method[21]

We used three different techniques to perform Björk's structural method: direct, tracing template, and subtraction techniques (Figure 3). Superimposition (according to Björk's structural method) was performed for each of these three different techniques, on three chosen stable structures in the cranial base: the anterior part of the Sella turcica was used for the horizontal orientation, while the Cribriform plate and Ethmoidal crest were used for the vertical orientation of the superimposed cephalograms (Figure 2).[21,46]

To assess the validity of the SN and TW methods compared with Björk's methods, evaluation of the growth-related facial changes of the 40 subjects (T1–T2) were performed using these three superimposition methods. Thus, the superimposition-based cephalometric measurements ($T2S^{REF1}$) of 15 variables for each T2 cephalogram were compared between the three methods.

The superimposition-based measurements ($T2S^{REF1}$) for each superimposition method were performed on the 40 subjects by a single orthodontist (NA) on two separate occasions with a 3-week interval, to assess the intra-observer reliability (Study I, Table 4). To determine the inter-observer reliability of each method, the measurements using all the methods were performed by another orthodontist (AW) at a single sitting on 10 randomly selected cephalograms (Study I, Table 5).

Error of method
The intra- and inter-observer reliability levels of the used cephalometric measurements were assessed by calculating the intra-class correlation coefficients (ICCs) with 95% confidence intervals. The intra- and inter-observer reliabilities of the measurements were considered to be excellent, as the ICCs were in the ranges of 0.96–0.99 and 0.91–0.99, respectively.[200]

Studies II and III

Materials

The material in Study II consisted of cephalograms from 30 untreated subjects (N-sample) at 4 time-points (Table 3).[199]

The inclusion criteria were: Angle Class I normal occlusion, normal overjet and overbite, normal transversal relation, up to 1 mm space deficiency in each jaw and a harmonious soft tissue profile.

The exclusion criteria were: orthodontic treatment, maxillofacial surgery, missing teeth anterior to the second molar, craniofacial anomalies, and using mandibular advancement devices for treatment of snoring during the observation period.

The material in Study III consisted of cephalograms from the following two study groups at four time-points:

Extraction group. This group included 30 patients from the PX-sample (Table 4). At 11 years of age (T1), these patients had harmonious soft tissue profiles and Angle Class I occlusions with severe crowding (mean space deficiency of 7 mm in each dental arch), without other malocclusions. The mean values for the overjet and overbite were 3.9 mm and 3.8 mm, respectively. In these patients, all the first premolars had been extracted to relieve crowding at a mean age of 11.5 years.[171] Our intention was to exclude from the analysis those subjects who did not participate at the age of 62 years. However, to include as many subjects as possible in the Control group and to maintain a similar sample size in both groups at the age of 62 years, we included 3 patients in the Extraction group who participated at T1, T2 and T3, but not at the age of 62 years.

Control group. This was the same group as used in Study II, and included 30 untreated subjects from the N-sample (Table 3).[199] Study III had the same exclusion criteria as Study II.

Table 3. *Description of the subjects in Study II.*

Time-point	N	Man	Women	Mean age (SD) in years
Early adolescence (T1)	30	11	19	12.8 (±0.3)
Late adolescence (T2)	29*	10	19	15.7 (±0.4)
Early adulthood (T3)	30	11	19	30.8 (±0.4)
Late adulthood (T4)	22#	9	13	61.6 (±0.4)

* One exclusion due to missing cephalogram.

\# Eight exclusions due to: 4 had missing molars, 3 had moved, and 1 was deceased.

Table 4. *Description of the subjects in Study III.*

Time-point	N	Man	Women	Mean age (SD) in years
Early adolescence (T1)	27*	14	13	11.7 (±1.7)
Late adolescence (T2)	25**	12	13	14.5 (±1.5)
Early adulthood (T3)	30	16	14	30.5 (±1.4)
Late adulthood (T4)	25#	15	10	62.8 (±1.4)

* Three exclusions due to missing cephalograms.

** Five exclusions due to missing cephalograms.

\# Five exclusions due to: 2 had missing molars, 1 had moved, 1 was deceased and 1 declined to participate.

Methods

Cephalometric analysis

The cephalometric landmarks and reference landmarks and lines used in Studies II and III are shown in Figure 5, with the exceptions of landmarks Basion and Articulare, which were used only in Study II.

In Study II, 53 angular and linear parameters were used to describe the craniofacial changes over time (Table 5), and 28 of these parameters were measured according to the superimposition-based cephalometric method.[201] The conventional cephalometric method (independent of the superimposition) was used to measure the remaining 25 parameters (Study II, Figure 3).[201]

In Study III, 42 angular and linear parameters were used to investigate the effects of premolar extraction on the dentoskeletal and soft tissue morphologies over time (Table 5). Twenty two of these parameters were measured according to the superimposition-based cephalometric method.[201] The conventional cephalometric method (independent of the superimposition) was used to measure the remaining 20 parameters.

Superimposition-based cephalometric method

Two landmarks (Sella and Nasion) were used as reference landmarks, and two lines (Nasion-Sella line NSL) and a perpendicular line through the Sella (NSLP) were used as reference lines in the T1 cephalogram. The TW plane method was used to perform cranial base superimposition.[201] Thereafter, reference lines NSL and NSLP and landmarks S and N were transferred digitally from the T1 cephalograms to the T2, T3, and T4 cephalograms in Studies II and III. The FACAD software enabled measurements of the parameters (28 parameters in Study II and 22 parameters in Study III) for each of the T2, T3, and T4 cephalograms in relation to these transferred reference lines and landmarks from the T1 cephalograms (Study I, Figure 2c; Appendix Figure A1).

Study III

Similarities in dentoskeletal and soft tissue morphologies between the Extraction and Control groups were necessary at the base line (T1), to exclude the impacts of confounding factors on the results. In addition, to assess the effects of premolar extraction on the dentoskeletal and soft tissue morphologies, the changes in 42 parameters from T1 to T2, T2 to T3, and T3 to T4 were compared between the Extraction and Control groups.

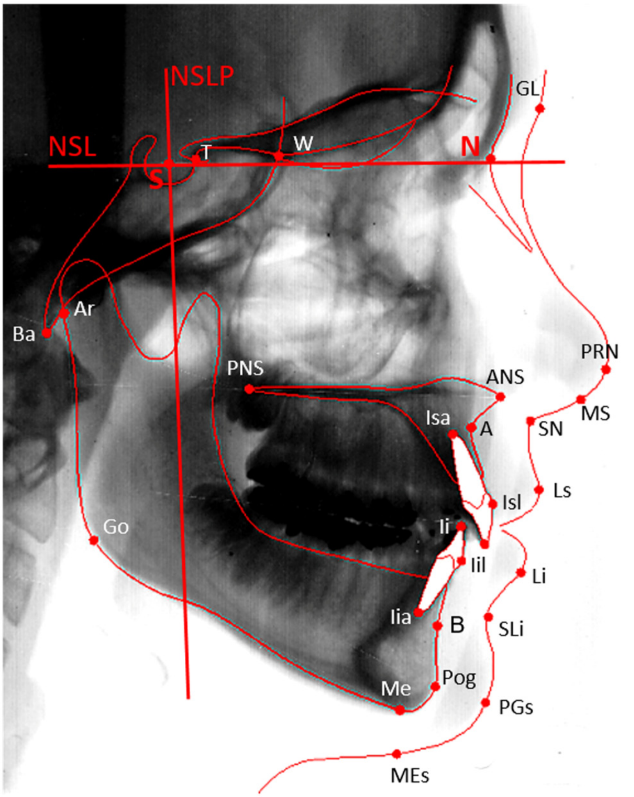

Figure 5. *Inverted lateral cephalogram showing the reference landmarks (S, Sella and N, Nasion), reference lines (NSL and NSLP), and other landmarks used in Studies II and III: T, Tuberculum Sella (Walker's point); W, Wing point (Spheno-ethmoidal); A, A-point; B, B-point; Pog, Pogonion; Me, Menton; ANS, Anterior nasal spine; PNS, Posterior nasal spine; Go, Gonial; Ar, Articulare; Ba, Basion; Is, Upper incisor tip; Isl, Labial surface of upper incisor; Isa, Upper incisor apex; Ii, Lower incisor tip; Iil, Labial surface of lower incisor; Iia, Lower incisor apex; GL, Soft tissue Glabella; PRN, Pronasale; MS, Columnella tangent point; SN, Subnasale; Ls, Upper lip; Li, Lower lip; Sli, Sulcus labial inferior; PGs, Soft tissue pogonion; and MEs, Soft tissue Menton.*

Table 5. *Description of the parameters measured in Studies II and III, with the exceptions of parameters marked with an asterisk (*), which were not measured in Study III.*

Parameter	Description of the parameter
Cranial base relation	
*NSBa (°)	Angle between the Nasion, Sella and Basion, describing the cranial base angle
*NSAr (°)	Angle between the Nasion, Sella and Articulare, describing the cranial base angle
*N-Ba (mm)	Distance from the Nasion to the Basion, describing the length of the cranial base
*S-N (mm)	Distance from the Nasion to the Sella, describing the length of the anterior cranial base
Skeletal sagittal relations	
SNA (°)	Angle between the Sella, Nasion and A-point, describing the sagittal relation of the maxilla to the anterior cranial base
SNB (°)	Angle between the Sella, Nasion and B-point, describing the sagittal relation of the mandible to the anterior cranial base
ANB (°)	Angle between the landmarks A-point, Nasion and B-point, describing the sagittal jaw relation
SNPog (°)	Angle between the Sella, Nasion and Pogonion landmarks, describing the sagittal relation of the chin to the anterior cranial base
*N-NSLP (mm)	Horizontal distance between the Nasion and vertical reference line NSLP
A-NSLP (mm)	Horizontal distance between the A-point and vertical reference line NSLP
B-NSLP (mm)	Horizontal distance between the B-point and vertical reference line NSLP
Pog-NSLP (mm)	Horizontal distance between the Pogonion landmark and vertical reference line NSLP
Me-NSLP (mm)	Horizontal distance between the Menton landmark and vertical reference line NSLP
Skeletal vertical relations	
ML/NSL (°)	Angle between the mandibular plane and NSL line, describing the rotation of the mandible in relation to the anterior cranial base
NL/NSL (°)	Angle between the maxillary plane and NSL line, describing the rotation of the maxilla in relation to the anterior cranial base
ML/NL (°)	Angle between the maxillary and mandibular plane, describing the vertical jaw relation
N-Me (mm)	Vertical distance between the Nasion and Menton landmarks, describing the anterior facial height
ANS'-Me (mm)	Vertical distance between the ANS` and Menton landmarks, describing the lower anterior facial height
S-Go (mm)	Vertical distance between the Sella and Gonion landmarks, describing the posterior facial height
PNS'-Go (mm)	Vertical distance between the PNS` and Gonion landmarks, describing the lower posterior facial height
*N-NSL (mm)	Vertical distance between the Nasion and horizontal reference line NSL
A-NSL (mm)	Vertical distance between the A-point and horizontal reference line NSL
B-NSL (mm)	Vertical distance between the B-point and horizontal reference line NSL
Pog-NSL (mm)	Vertical distance between the Pogonion landmark and horizontal reference line NSL
Me-NSL (mm)	Vertical distance between the Menton landmark and horizontal reference line NSL
Jaw dimensions	
*ANS-PNS (mm)	Distance from the anterior to the posterior nasal spin, describing the length of the maxilla
*Pog-Ar (mm)	Distance from the Articulare to the Pogonion, describing the total length of the mandible
*Me-Go (mm)	Distance from the Gonion to the Menton, describing the mandibular body length
*Ar-Go (mm)	Distance from the Gonion to the Articulare, describing the ramus height
Ar/Go/Me (°)	Gonial angle between the Articulare, Gonion and Menton landmarks, describing the angle of the mandible
Dental relations	
Isa-Is/NL (°)	Angle of the long axis of the upper incisor to the maxillary plane, describing the incisor inclination to the maxilla
Iia-Ii /ML (°)	Angle of the long axis of the lower incisor to the mandibular plane, describing the incisor inclination to the mandible
Isa-Is/Iia-Ii (°)	Inter-incisal angle between the long axes of the upper and lower incisors

Parameter	Description of the parameter
Isl-NSLP (mm)	Distance from the labial surface of the upper incisor to the vertical reference line, describing the protrusion of the incisor
Iil-NSLP (mm)	Distance from the labial surface of the lower incisor to the vertical reference line, describing the protrusion of the incisor
Ii-APog (mm)	Distance from the lower incisor edge to the A-Pog line, describing the protrusion of lower incisor to the A-Pog line.
Is-NL (mm)	Distance from the upper incisor edge to the maxillary plane, describing the extrusion of the upper incisor
Ii-ML (mm)	Distance from the lower incisor edge to the mandibular plane, describing the extrusion of the lower incisor
Soft tissue profile	
*MS-NSL (mm)	Distance from the Columnella tangent point to the horizontal reference line NSL, describing the nasal length
GL/PRN/PGs (°)	Angle between the Pronasale, soft tissue Pogonion and soft tissue Glabella landmarks, describing the total facial convexity
GL/SN/PGs (°)	Angle between the Subnasale, soft tissue Pogonion and soft tissue Glabella landmarks, describing the facial profile angle
MEs-NSL (mm)	Vertical distance from the soft tissue Menton to the horizontal reference line NSL, describing the anterior soft tissue facial height
MEs-NL (mm)	Vertical distance from the soft tissue Menton to the maxillary plane, describing the lower anterior soft tissue facial height
MS/SN/Ls (°)	Nasolabial angle between the Columnella tangent point, Subnasale and upper lip
Li/Sli/PGs (°)	Mentolabial angle between the lower lip, Sulcus labial inferior and soft tissue Pogonion
Ls-EL (mm)	Horizontal distance between the upper lip and Aesthetic line, describing the relation of the upper lip to the Aesthetic line
Li-EL (mm)	Horizontal distance between the lower lip and Aesthetic line, describing the relation of the lower lip to the Aesthetic line
Isl-Ls (mm)	Horizontal distance between the upper incisor labial surface and upper lip, describing the thickness of the upper lip
Iil-Li (mm)	Horizontal distance between the lower incisor labial surface and lower lip, describing the thickness of the lower lip
Ls-NSLP (mm)	Horizontal distance between the upper lip and vertical reference line NSLP, describing the protrusion of the upper lip
Li-NSLP (mm)	Horizontal distance between the lower lip and vertical reference line NSLP, describing the protrusion of lower lip
Ls-NSL (mm)	Vertical distance between the upper lip and horizontal reference line NSL, describing the upper lip length
Li-NSL (mm)	Vertical distance between the lower lip and horizontal reference line NSL, describing the lower lip length

Error of method in Studies II and III

To assess the intra-observer reliability of the cephalometric measurements, a single orthodontist (NA) repeated the measurements of the parameters (53 parameters in Study II and 42 in Study III) in 20 randomly selected cephalograms on two occasions, with a 4-week interval in Study II and a 3-month interval in Study III.

In Study II, the inter-observer reliability of the cephalometric measurements was assessed. A second orthodontist (AW) performed cephalometric tracings onto the same 20 cephalograms.

The intra-class correlation coefficients (ICCs) with 95% confidence intervals were estimated for the intra-observer and inter-observer reliability values.

In Study II, the intra- and inter-observer reliability levels of the cephalometric measurements were excellent, with ICCs in the range of 0.91–0.99 for all of the parameters. The intra-observer reliability was good, with an ICC of 0.81, for the distance between the Menton landmark and the vertical reference line (Me-NSLP) (Table 6), and the inter-observer reliability was good for the Me-NSLP and the mentolabial angle, with ICCs of 0.85 and 0.89, respectively.[200]

Table 6. *Reliability of the cephalometric measurements of 53 parameters (Study II) for 20 randomly selected radiographs performed by a single observer on two occasions with a 4-week interval.*

Parameter	ICC	Lower 95% CI	Upper 95% CI
NSBa	0.96	0.91	0.99
NSAr	0.98	0.94	0.99
N-Ba	0.99	0.99	1.00
S-N	0.99	0.97	1.00
SNA	0.97	0.92	0.99
SNB	0.97	0.94	0.99
ANB	0.95	0.89	0.98
SNPog	0.98	0.96	0.99
N-NSLP	0.99	0.97	1.00
A-NSLP	0.96	0.90	0.98
B-NSLP	0.94	0.85	0.97
Pog-NSLP	0.92	0.82	0.97
Me-NSLP	0.81	0.59	0.92
ML/NSL	0.99	0.97	1.00
NL/NSL	0.97	0.93	0.99
ML/NL	0.99	0.97	0.99
N-Me	1.00	1.00	1.00
ANS`-Me	0.99	0.99	1.00
S-Go	0.99	0.98	1.00
PNS`-Go	0.99	0.98	1.00
N-NSL	1.00	1.00	1.00
A-NSL	0.94	0.87	0.98
B-NSL	0.97	0.94	0.99
Pog-NSL	0.99	0.97	1.00
Me-NSL	1.00	1.00	1.00
ANS-PNS	0.96	0.90	0.98
Pog-Ar	0.99	0.98	1.00
Me-Go	0.91	0.80	0.97
Ar-Go	0.99	0.97	1.00
Ar/Go/Me	0.98	0.96	0.99
Isa-Is/NL	0.96	0.91	0.99
Iia-Ii /ML	0.96	0.90	0.98
Isa-Is/Iia-Ii	0.96	0.91	0.98
Isl-NSLP	0.98	0.95	0.99
Iil-NSLP	0.97	0.94	0.99
Ii-APog	0.95	0.87	0.98
Is-NL	0.98	0.94	0.99
Ii-ML	0.98	0.95	0.99
MS-NSL	0.99	0.98	1.00
GL/PRN/PGs	0.98	0.96	0.99
GL/SN/PGs	0.99	0.98	1.00

Parameter	ICC	Lower 95% CI	Upper 95% CI
MEs-NSL	1.00	0.99	1.00
MEs-NL	0.99	0.97	1.00
MS/SN/Ls	0.96	0.91	0.99
Li/Sli/PGs	0.94	0.86	0.98
Ls-EL	0.99	0.98	1.00
Li-EL	1.00	0.99	1.00
Isl-Ls	0.99	0.98	1.00
Iil-Li	0.95	0.89	0.98
Ls-NSLP	0.99	0.98	1.00
Li-NSLP	0.98	0.96	0.99
Ls-NSL	0.99	0.99	1.00
Li-NSL	0.99	0.98	1.00

In Study III, the intra-observer reliability level of the cephalometric measurements was excellent, with ICCs in the range of 0.92–0.99 for all of the parameters, with the exception of the intra-observer reliability values for the Me-NSLP and nasolabial angle, with ICCs of 0.84 and 0.88, respectively.

Study IV

Materials

The material in Study IV consisted of dental casts and cephalograms acquired at 3 time-points from 45 subjects, including 24 patients from the PX-sample and 21 untreated subjects from the N-sample (Table 7).

Study IV had the same inclusion and exclusion criteria as Study III. In addition, subjects with prosthodontic replacements were excluded.

Table 7. *Description of the subjects in Study IV.*

	Number of subjects			Mean age (SD) in years		
	Total	**Man**	**Women**	**T1**	**T2**	**T3**
Extraction group	24	14	10	11.4 (±1.6)	30.4 (±1.6)	61.8 (±1.4)
Control group	21	9	12	13.0 (±0.3)	31.5 (±0.5)	61.7 (±0.5)

Methods

Lower incisor crowding was assessed using the variables of Irregularity Index[202] (Figure 6) and space deficiency (tooth size-arch length discrepancy; TSALD)[85]. TSALD was measured for the whole lower dental arch mesial to the first molars (TSALDtot) and for the lower six anterior teeth (TSALDant).

Dentoalveolar changes were assessed using the following eight variables: sagittal relation, overjet, overbite, sum of the lower incisor widths, total lower arch length between the first molars (arch length), lower arch depth to first molar line (arch depth), lower inter-molar arch width at first molars (inter-molar width), and lower inter-canine arch width (inter-canine width) (Figure 7). Linear measurements on the dental casts were performed by one orthodontist using a digital sliding caliper (Velleman, 0.01 mm).

The changes in these variables from T1 to T2, T2 to T3, and T1 to T3 were compared between the Extraction and Control groups.

Little's Irregularity Index = A + B+ C + D + E

Figure 6. *Little's definition of the Irregularity Index (mm) as the summed displacement of the adjacent anatomical contact points of the six lower anterior teeth.*

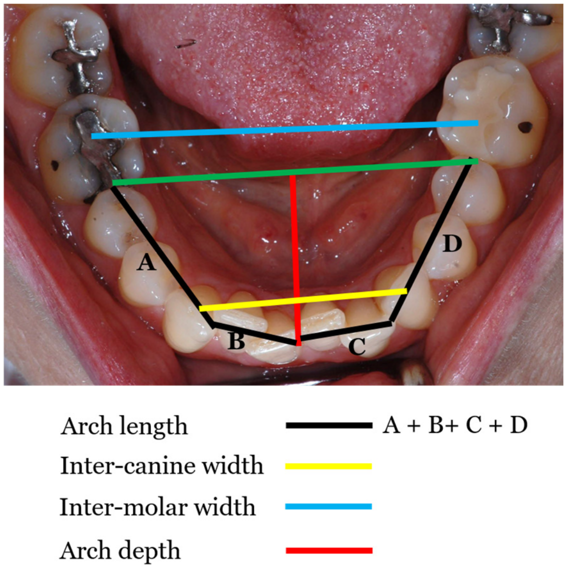

Figure 7. *The dentoalveolar variables used in Study IV.*

Cephalometric changes

Four cephalometric parameters were measured on the cephalogram, including the lower incisor inclination in relation to the mandibular plane (L inc/ML), the distance from the lower incisor to the A-Pogonion plane (L inc-A-Pog), the anterior facial height (N-Me), and the posterior facial height (S-Go). The changes in these parameters from T1 to T2, T2 to T3, and T1 to T3 were compared between the Extraction and Control groups. The cephalometric analysis and superimposition were performed according to Studies II and III.

Error of method

To verify the intra-observer reliability of the measurements made on the dental casts, the measurements for the dental casts from the Extraction group at T1 were repeated on two occasions with a 2-month interval. The reliability level was estimated by Dahlberg's formula, with a mean value of 0.43 mm for all the linear measurements. The mean error of the TSALDtot measurements was 0.43 mm, and that of the Irregularity Index measurements was 0.52 mm.

Statistical analysis

The statistical significance level was set at $p<0.05$ for the four studies included in the thesis. The statistical analyses in Studies I and II were performed using the SPSS for Windows software. In Studies III and IV, the statistical analyses were performed using the R ver. 4.0.0 software (R Core Team 2020).

Study I

A paired *t*-test was used to verify the significant differences in the sagittal and vertical measurements between $T2C^{REF2}$ and $T2S^{REF1}$.

To assess the validity of the methods, the systematic differences between the superimposition methods were estimated using repeated-measures ANOVA, which was used to compare the mean differences for the 15 variables ($T2S^{REF1}$–$T1C^{REF1}$) between the various methods applied. A post-hoc test was made using Tukey's honest significant difference test to adjust for pairwise comparisons of the results obtained with the different superimposition methods.

The intra- and inter-observer reliabilities of the superimposition methods were evaluated by the intra-class correlation coefficients (ICC) with 95% confidence intervals, which were calculated using one-way and two-way random effects models, respectively.

Study II

The mean values and standard deviations were estimated for all 53 parameters for the four time-points (T1, T2, T3, and T4). A paired *t*-test was used to establish if there were significant differences in the changes observed between the different time-points.

Study III

Independent samples *t*-tests were used to verify significant differences in the skeletal, dental and soft tissue patterns between the Extraction and Control groups at T1.

Tests of differences, of the dentoskeletal and soft tissue changes, between the Extraction and Control groups were performed using the independent samples *t*-test.

To maximize the use of the information available in the dataset, the analyses of differences between time-points were performed using a pairwise deletion approach rather than list-wise deletion. Thus, if a subject had measurements that allowed the calculation of a change between two time-points, this data-point contributed to the analyses regardless of whether data were missing for some other time-points for that subject.

Study IV
Statistical tests of crowding and dentoalveolar changes with age within the groups were tested using the non-parametric Wilcoxon signed-rank test, as several of the variable recordings followed a skewed distribution.

Tests of differences between the groups were performed using the Mann–Whitney *U*-test.

Associations between incisor crowding (Irregularity Index and TSALDant) and arch length, width, and depth were assessed using mixed effects models with "age period" as a fixed factor and "subjects" as random effects.

Results and Discussion

Assessing craniofacial changes over time with high precision

Study I was conducted to identify an easy, reliable and valid superimposition method that can accurately quantitate the craniofacial changes related to growth and/or orthodontic and orthognathic treatment. In Study I, it was observed that the superimposition-based cephalometric method provided numerical data for the craniofacial changes occurring over time. In addition, we observed that the TW method had a level of validity similar to that of Björk's structural method, and levels of reliability and feasibility similar to those of the SN method. Thus, the TW method is considered to be the most-suitable method for cranial base superimposition.

Superimposition-based cephalometrics

There is consensus among researchers that landmarks Sella and Nasion are easy to identify.[114,140,141] In addition, the most-used sagittal and vertical cephalometric parameters depend on these landmarks.

Thus, the question in Study I was how to keep landmarks S and N sufficiently stable so as to obtain valid craniofacial measurements. This was solved by transferring landmarks S and N from the initial cephalogram (T1) to the follow-up cephalograms (T2, T3, etc.) after superimposition onto stable structures. Thereafter, all the cephalometric measurements containing landmarks S and N were measured in the follow-up cephalograms (T2, T3, etc.), in relation to these transferred S and N landmarks (Study I, Figure 2c). In this way, the growth-related positional changes of landmarks S and N were excluded. We refer to this method as 'superimposition-based cephalometrics'.

To verify the significance of this method, the measurements generated by superimposition-based cephalometrics were compared with conventional cephalometric measurements in Study I. The changes observed in the sagittal and vertical relations (SNA, SNB, ANB, ML/NSL and N-Me) from 10 (T1) to 15 (T2) years of age were measured with these two methods. We observed that the measurements generated by the superimposition-based method differed significantly from the conventional cephalometric measurements (Study I, Table 1). Importantly, using this new method, the obtained numerical data reflected the graphical illustration of the superimposition, in contrast to using conventional cephalometric measurements.

Furthermore, with the superimposition-based method, positional changes of most of the useful landmarks (e.g., A, B, Pog and Me) can be measured in relation to the vertical and horizontal reference lines drawn through the transferred landmarks S and N. This enables accurate quantitation and interpretation of the sagittal and vertical changes of the jaws.

It has been observed that the growth-related resorption at the dorsum Sella and the growth of the frontal sinus result in posterior and vertical displacement of landmark S[21,46,50] and anterior and vertical displacement of landmark N,[21,50,51] respectively. Thus, the length of the anterior cranial base (i.e., the distance between landmarks N and S) continues to increase with age. This was confirmed in Study I, as landmark N showed significant anterior and vertical displacement (Study I, Table 2). The growth-related displacement of landmark N explains the significant differences observed between the superimposition-based and conventional cephalometric measurements. With conventional cephalometric measurements, the downward or upward displacement of landmark N results in an under-estimation or over-estimation of the vertical craniofacial changes, respectively. In contrast, the usual forward displacement of the N results in an under-estimation of the sagittal craniofacial changes.

Validity and reliability levels of the superimposition methods

The validity (accuracy) and reliability (precision and reproducibility) of cephalometric superimposition is important for evaluations of growth- and treatment-related changes over time.[143,150]

Validity of the methods: There is evidence that certain structures in the cranial base are stable from an early age.[21,46,50] Therefore, using these structures for cranial base superimposition according to Björk's structural method provides a high level of validity[136,143,144]. This method has, therefore, been used as the gold standard when comparing the validity levels of the superimposition methods in Study I. As Björk's structural method can be performed through direct, tracing template or subtraction techniques, all three techniques were compared with the SN and TW methods.

Study I showed that the measurements generated by the SN superimposition method differed significantly from those obtained with the other superimposition methods (Study I, Table 3). Some studies have shown no significant differences between Björk's structural method and the SN method.[139,156] However, in those studies, other criteria were used for material selection, statistical analysis, follow-up times, and evaluation. You and Hägg compared Björk's maxillary and mandibular (local) superimposition method with the cranial base (general) SN superimposition method, to evaluate treatment with the Herbst appliance; this can be considered as an important limitation.[156] Lenza and co-workers evaluated only the linear measurements and used a one-way ANOVA test, ignoring the repeated measurements of the same subjects, which increase the risk of type II errors.[139]

The results from Study I showed no significant differences between the TW method and Björk's three techniques for any of the measurements (Study I, Table 3). Consequently, cranial base superimposition using TW plane is as valid as Björk's structural method. This is consistent with the finding of a study performed by Arat *et al.*[136]

Reliability of methods: The reliability of cephalometric superimposition depends on the operator's experience, the accurate identification of landmarks/structures,[151-153] the quality of the radiographs,[151] and the superimposition method used.[151-153]

The levels of reliability of superimposition obtained for the TW method and Björk's three techniques have been compared with that for the SN method, since superimposition with the SN method has previously shown high reliability.[117,151] The results showed that all the studied superimposition methods, SN, TW and Björk's three techniques, have high levels of reliability (ICC >0.95), while the SN and TW methods have remarkably high ICC values (Figure 8).

Landmarks T and W sometimes exhibit a double contour, which could affect their levels of reliability. However, Study I indicated that the tracing of an equidistant point, when landmarks T and W have a double contour, does not seem to affect the reliability of the TW method.

In a recent systematic review, the reliability of cephalometric superimposition on the cranial base has been evaluated.[203] According to this review, there is at present no superimposition method that can provide accurate results due to the methodological limitations of the evaluated studies, and there is a need for further research in this area. However, this review evaluated only 17 studies published up to November 2020.

Simplicity of methods: Study I demonstrated that it was easier to identify landmarks T and W and to perform the superimposition digitally with the TW method, as compared to superimposition with one of Björk's techniques. Superimposition according to Björk's method is time-consuming, when identifying the stable structures and orienting the cephalograms. If one of Björk's techniques is to be used, we recommend the subtraction technique.

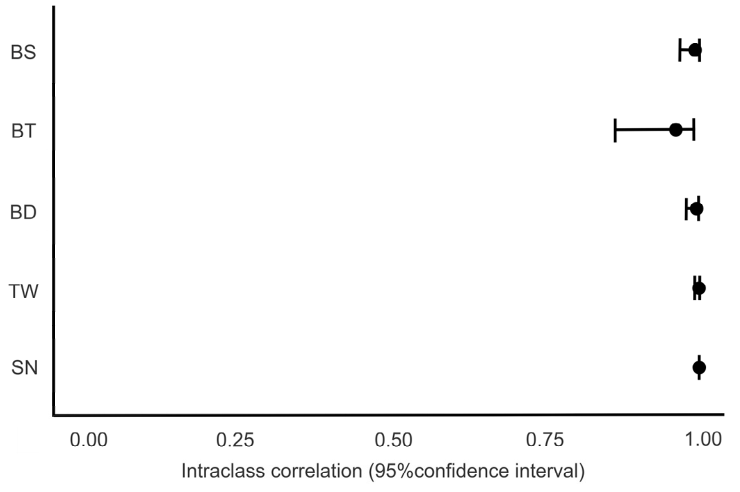

Figure 8. *Reliability levels of Björk's three techniques (BS, BT and BD), as compared with the SN and TW methods.*

Clinical implication
The superimposition-based cephalometric method can be used to quantitate accurately growth- and/or treatment-related craniofacial changes.

Craniofacial changes from early adolescence to late adulthood

Study II was conducted to explore the craniofacial (skeletal, soft tissue, and dental) changes that occur from early adolescence to late adulthood, as well as to establish an age-specific reference material for orthodontic, orthognathic, prosthodontic and forensic anthropological studies.

The material of Study II consisted of cephalograms collected between 1965 and 2015. The cephalograms originated from untreated subjects from a Caucasian Swedish population in the region of Västerbotten County Council, and they had normal occlusion and a harmonious facial profile. The superimposition-based cephalometric method was used to perform the study.[201]

The 50-year follow-up period in this reference group shows that craniofacial changes continue beyond the sixth decade of life. For most of the studied parameters, these changes corresponded to the adolescent growth patterns, albeit with lower absolute values. The exceptions were incisor inclination, sagittal jaw position, vertical jaw relation and inclination, and posterior facial height. Significant changes were also observed for most of the soft tissue parameters throughout the observation period. The vertical changes of the soft tissue parameters corresponded to the vertical changes in the underlying hard tissue. This contrasts with the sagittal changes of the soft tissue parameters. Throughout the observation period, the maxilla showed greater prognathism than the mandible, and the upper incisors exhibited greater retroclination than the lower incisors. From 30 to 62 years of age, we observed significant reductions in the jaw prognathism, posterior facial height, and mandibular height, in addition to a significant increase in the posterior mandibular rotation.

Considering the low number of subjects included in Study II, we could not present the results by gender. Nevertheless, the descriptive analysis has shown that both men and women present almost similar changes during the observation period (Figure 9; unpublished data), as observed earlier.[44,77,204]

Skeletal changes

Cranial base changes: The cranial base angles increased until the age of 30 years (Study II, Table 1 and Figure 3), which indicates continued remodelling of the clivus, which may result in the backward and downward displacement of landmarks Basion and Articulare. The spheno-occipital synchondrosis begins to fuse at the age of 13–15 years of age. Thereafter, the growth of the cranial base largely ceases, particularly in the anteroposterior direction, and the changes in the cranial base angle take place due to bone remodelling.[46]

The cranial base length increases throughout the observation period (Study II, Table 1 and Figure 3), which is in agreement with the results from other studies.[22,43] This can be explained by forward displacement of the Nasion (which is related to the growth of the frontal sinus)[21,50,51] together with backward displacement of the Sella (due to growth-related resorption at the dorsum Sella)[21,46,50] throughout adulthood.

Sagittal changes: During the adolescence period, forward displacements of landmarks A, B and Pogonion, together with increases in the SNA, SNB and SNPog angles, were observed (Study II, Table 1 and Figure 3). These changes indicate anterior growth (prognathism) of the maxilla and mandible, which are in line with results reported in other studies.[6,22] In contrast, from the age of 30 to 62 years, backward displacements of landmarks A, B and Pogonion, together with decreases in the SNA, SNB and SNPog angles, were observed (Study II, Table 1 and Figure 3). These changes demonstrate retrognathism of the maxilla and mandible, and are not in agreement with the results of other studies, which showed a stable sagittal position of the jaws. [7,42,43] The retrognathism of the maxilla and mandible may be explained by age-related remodelling and posterior jaw rotation, respectively, during adulthood.

Vertical changes:
Throughout the observation period in Study II, the four landmarks (A, B, Pogonion and Menton) exhibited more-obvious downward displacements than forward displacements, indicating more-vertical then limited anterior facial growth. The skeletal changes are, therefore, generally more-prominent in the vertical dimension, as compared to the sagittal dimension, and this is in line with previous studies.[6,22,205] However, McNamara has reported that an increase in lower anterior facial height in growing subjects can camouflage a similar increase in mandibular length, as the chin rotates downward and backward.[206]

We found that the anterior and posterior facial heights continued to increase, by a mean of 10.5 mm and 8.5 mm, respectively, until 30 years of age (Study II, Table 1 and Figure 3). The increases in the lower anterior and posterior facial heights were greater than those in the upper ones, indicating more-downward growth of the mandible compared to the maxillary complex. The increases in the anterior and posterior facial heights occur due to continued growth in the condyle and the subsequent eruptions of the upper and lower teeth, and to a lesser extent due to sutural growth of the maxilla.

During growth, it has been shown that downward mandibular displacement, which leads to increased facial height, is mainly due to condylar growth,[66-68] rather than tooth eruption[207]. In addition, the mandibular teeth erupt to compensate for the mandibular growth,[20,47,208] rather than vice versa[207]. However, Forsberg[44] and other studies[6,7,42] provide support for the suggestion that the increase in lower facial height during adulthood is due to tooth eruption and vertical alveolar bone changes.

Up to the age of 30 years, the maxilla and mandible exhibited minimal changes in the vertical inclination in relation to the cranial base. The vertical jaw relation (ML/NL) exhibited a slight deepening (by a mean of

1.6°) in the adolescence period and opening (by a mean of 2.6°) from the age of 30 to 62 years.

From the age of 30 to 62 years, the anterior facial height continued to increase, albeit to a lesser extent, whereas the posterior facial height decreased by a mean of 2 mm, resulting in an increase in the mandibular plane angle of about 3° (Study II, Table 1 and Figure 3). This increase in the mandibular plane angle indicates posterior mandibular rotation, which depends on the reduction of posterior facial height (about 2 mm) and the increase in anterior facial height (about 1 mm) from the age of 30 to 62 years. Some studies have shown posterior mandibular rotation during adulthood,[44,205] although other studies have shown posterior mandibular rotation among women and anterior rotation among men.[6,7] It could be argued that the posterior mandibular rotation observed in Study II from the age of 30 to 62 years is due to the fact that more women than men were included at the age of 62 years. However, according to the descriptive statistics, both men and women showed posterior mandibular rotation from the age of 30 to 62 years (Figure 9).

According to Björk's implant studies, remodelling occurs at the inferior margin of the mandible, which is correlated with the growth direction of the condyle.[19,21] Bone resorption and apposition have been observed below the Gonial angle and symphysis, respectively, in subjects who have normal craniofacial growth and forward condylar growth.[19,21] In addition, remodelling of the craniofacial complex is a biological adaptation to the mechanical forces (e.g., muscle activity, mastication, orthodontic forces) that change the shape and relative position of bones in the craniofacial skeleton.[80,108,209,210] Thus, the variation in growth and shape of the Gonial region may depend on variations with respect to the functions of the masseter and medial pterygoid muscles.[211] Accordingly, it is important to note that age-related bone remodelling (bone resorption) below the Gonial area under-estimates the increase in posterior facial height. This may explain the decrease in the posterior facial height, the posterior mandibular rotation, and the opening of vertical jaw relation from the age of 30 to 62 years, in Study II.

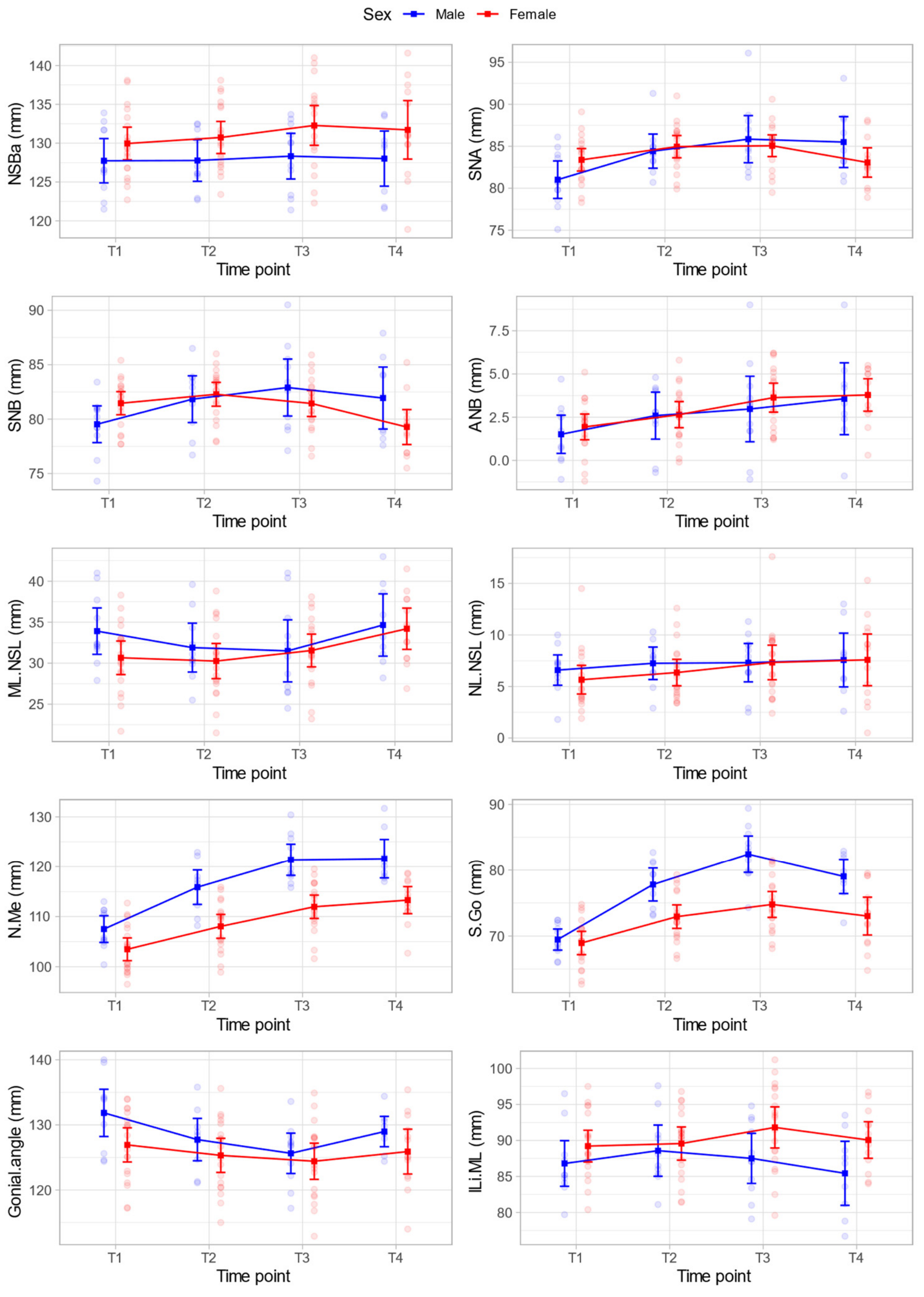

***Figure 9**. Descriptive analysis of 17 parameters selected for men and women showing almost similar changes throughout the observation period.*

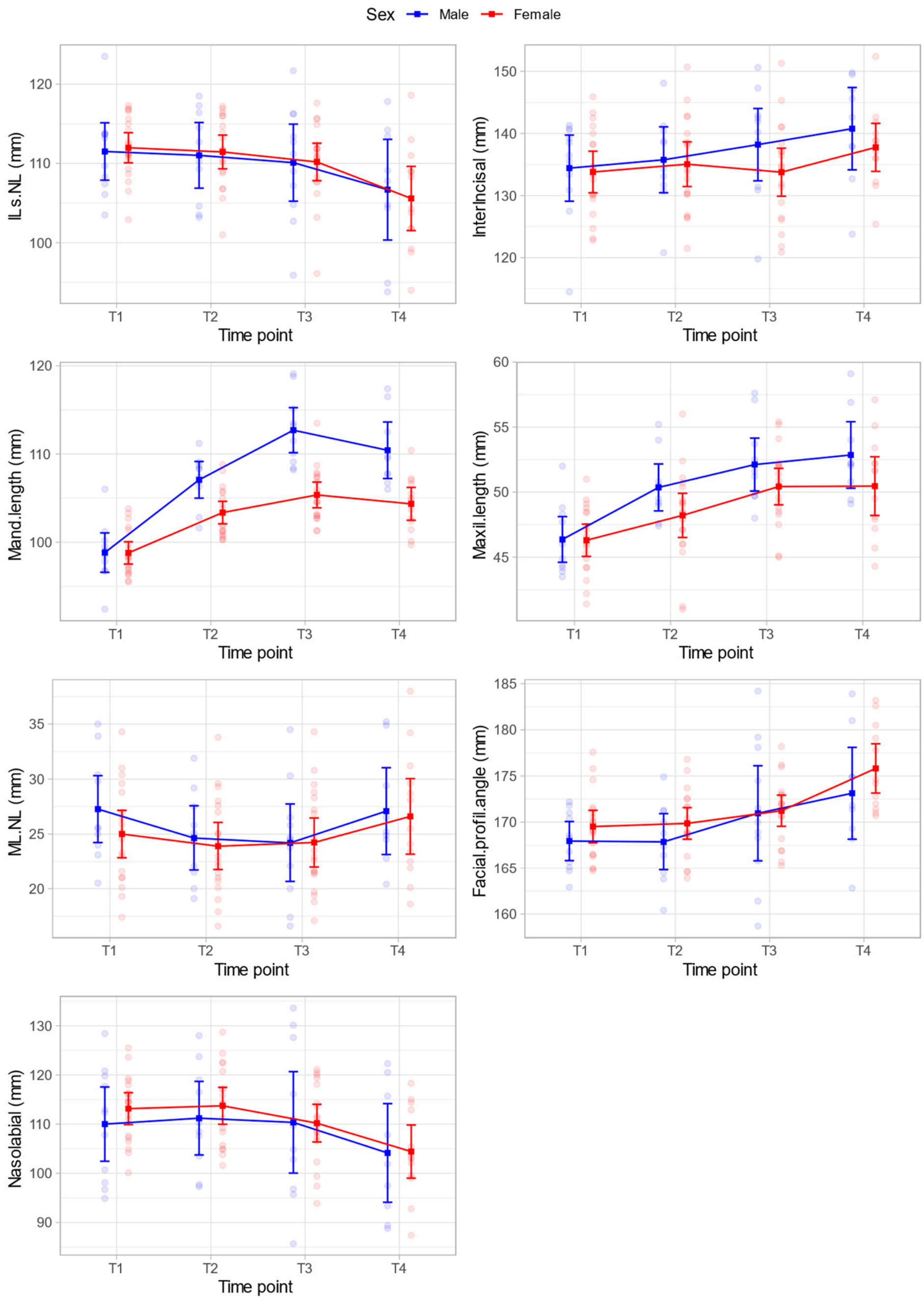

Figure 9. *Continued.*

Jaw dimensions and dental relations

Changes in jaw dimensions: The dimensions of the jaws increased (5-9 mm) up to the age of 30 years (Study II, Table 2 and Figure 4), which is in line with previous studies.[3,7,42] After the age of 30, the lengths of the maxilla and the mandibular body remain stable, and the mandibular length and height are reduced by about 1.2 and 2 mm, respectively. It has been shown that the lengths of the maxilla and the mandible remain stable from early to late adulthood.[7]

Patcas *et al.* observed that the Condylion (Co) landmark is superior to the Articulare (Ar) landmark when it comes to assessment of mandibular growth-related changes.[69] Nevertheless, in the standard closed-mouth lateral cephalogram, the Co landmark is frequently obscured by overlapping structures of the middle cranial fossa. Thus, identification of Co in the closed-mouth lateral cephalogram is technically difficult.[206,212] In addition, it has been observed that the measurement of mandibular length from landmark Ar agrees with the measurement taken from landmark Co.[212,213] As a result, landmark Ar was used instead of Co to measure the length and height of the mandible in Study II.

The total length and height of the mandible, in Study II, were measured between landmarks Ar and Pogonion (Ar-Pog) and between Ar and Gonion (Ar-Go), respectively. However, we have to consider that using landmark Ar may under-estimate the mandibular length and height owing to growth-related rotation of the condyle,[21] as well as growth-related remodelling of the clivus[46]. In addition, as the cephalometric measurements on a cephalogram are performed between landmarks in the mid-sagittal plane, measurement of changes in mandibular length, related to growth and/or treatment, should also be treated with caution. Measuring the length of the mandible, for example between landmarks Ar and Pog, will result in an under-estimation of the mandibular length, since the mandibular anatomy is angulated about 30° to the mid-sagittal plane.[3] Furthermore, age-related bone remodelling (resorption) at the Gonial region[19,21] must be taken into account, as it may under-estimate the ramus height and mandibular body length.

Regarding the Gonial angle, it decreased up to the age of 30 years, which is in agreement with the finding of Thilander *et al.*[3]. This angle reduction may be explained by increased bone formation along the lower than the upper posterior border of the ramus, resulting in more-backward displacement of Go than Ar. On the other hand, the Gonial angle increased from the age of 30 to 62 years owing to age-related bone remodelling (resorption) in the Gonial region, although Pecora *et al.*[7] have demonstrated a relatively stable Gonial angle from 17 to 57 years of age.

Changes in dental relations: The upper and lower incisors showed relatively stable inclination from the 12 to 30 years of age, and significant retroclination from 30 to 62 years of age (Study II, Table 2 and Figure 5). The angle describing the lower incisors inclination (Iia-Ii/ML) was measured between the long axis of the lower incisor (Iia-Ii) and the mandibular plane (ML). The reduction in this angle (Iia-Ii/ML), from the age of 30 to 62 years, was equal to the change in the vertical inclination of the mandibular plane. Thus, the change in the Iia-Ii/ML angle was due to a change in the mandibular plane rather than a change in the incisor inclination. In addition, the value of the upper incisor retroclination from the age of 30 to 62 years corresponds to the increase of the interincisal angle. Consequently, the lower incisors actually have a relatively stable inclination from the age of 12 to 62 years. These results are in line with those of Forsberg, who showed significant retroclination of the upper incisors and stable inclination of the lower incisors from 25 to 45 years of age.[44] The obvious retroclination of the upper incisors after the age of 30 years should be considered before planning extraction in cases with crowding and/or class II malocclusion.

The upper and lower incisors exhibited a slight protrusion in relation to the vertical reference line during the adolescence period and a slight retrusion from the age of 30 to 62 years. These changes in incisor prominence may be related to the changes in the sagittal jaw relation during the corresponding period.

The results from Study II showed a relatively stable distance between the lower incisors and the A-Pog line, especially after the age of 30, indicating simultaneous changes in prominence of the lower incisors and displacements of landmarks A and Pogonion. This is in line with the results of other studies.[6,7]

Moreover, in Study II, from the age of 12 to 30 years, the upper and lower incisors continued to erupt, which is consistent with other studies[6,7,44]. The age-related simultaneous eruption of the anterior and posterior teeth could be confirmed, as Study II showed continued eruption of the incisors up to the age of 30, and Study IV showed non-significant change to the overbite in the corresponding period[214]. The continuous eruption of the upper and lower teeth during adulthood should be taken into account during implant installation, especially in the anterior region.

The assessments of eruption (extrusion) and inclination of the lower and upper teeth are usually performed in relation to the mandibular and the maxillary plane, respectively. However, these assessments should be interpreted with caution because of bone remodelling at the lower mandibular border and the maxillary plane (nasal floor).[21,61]

Soft tissue profile

Throughout the observation period, we observed an increase in the facial profile angle (without the nose), particularly during adulthood, indicating an age-related, straighter facial profile (Study II, Table 3 and Figure 6). This can be explained by thinning of the upper lip and the growth of the soft tissue at the chin and glabella. The anterior soft tissue facial height increased more than the skeletal facial height, especially after the age of 30, and this indicates that besides skeletal growth, there is soft tissue augmentation under the chin (Study II, Table 3 and Figure 6).

In addition, the results of Study II showed that the thicknesses and the prominences of the upper and lower lips increased during the adolescence period and decreased later, particularly from the age of 30 to 62 years. Despite the reduction in the upper lip thickness, the nasolabial angle became more acute, especially from the age of 30 to 62 years, which can be explained by the increase in the length of the nose during the corresponding period. The distances between the lips and aesthetic line increased throughout the observation period in Study II, confirming the age-related thinning of the lips and simultaneous forward growth of the nose and chin.

Furthermore, Study II showed a downward displacement of the upper and lower lips that continued until the age of 62 years, resulting in an age-related decrease in the display of upper incisors.

Nearly all the observed changes in the soft tissue profile (Study II, Table 3 and Figure 6) are in line with the results from other studies.[6,7,77]

The thinning, retrusion and downward positioning of the lips, from the age of 15 to 62 years, must be considered during orthodontic and orthognathic treatment planning.

Comparison with the other longitudinal studies

Some longitudinal studies of craniofacial growth[3,22,43,77] have used conventional cephalometric measurements to describe both the linear and angular changes, whereas other studies[215,216] have used different cephalometric superimposition methods for the linear measurements. However, no study has been carried out to measure angular changes based on superimposition. In our recent study, we used a superimposition-based cephalometric method that provides valid linear and angular measurements, using stable landmarks in the cranial base for superimposition.[201]

Moreover, the superimposition-based method allows interpretations of both the linear and angular craniofacial changes through the assessment of anteroposterior and vertical displacements of the landmarks in relation to the vertical and horizontal reference lines, respectively.

The discrepant results observed in comparisons with other studies (Study II, Table 4) can be explained by the fact that the horizontal and vertical displacements of landmarks Nasion and Sella were not adjusted in the previous studies.[3,6,7,42-44] In addition, the previous studies used different significance levels, landmarks and age intervals than Study II.[7,42,77]

Clinical implication
For successful long-term outcomes, clinicians should be aware of the age-related craniofacial changes in adult patients when planning orthodontic, orthognathic or prosthodontic treatments. Examples of these changes include straighter facial profile, thinning of the lips, retroclination of the upper incisors, and continuous eruption of the teeth. In addition, during adulthood, it is essential to consider the changes in the vertical relationship between the lip and the teeth when planning orthodontic and orthognathic treatments.

Effects of premolar extraction on the dentoskeletal and facial morphologies

Study III was conducted to explore the effects of premolar extractions, without subsequent orthodontic treatment, on the dentoskeletal and soft tissue changes in a group of patients with Class I malocclusion with severe crowding (Extraction group), from 12 to 62 years of age. The dentoskeletal and soft tissues changes were assessed using a superimposition-based cephalometric method,[201] and compared with a matched control group of orthodontically untreated subjects with Class I normal occlusion (Control group).

The comparison of cephalometric measurements between the Extraction and Control groups at the starting point (T1) showed similar dentoskeletal and soft tissue morphologies and, therefore, the groups were considered to be well-matched (Study III, Table 1).

Study III demonstrated that the use of early extraction of four premolars as the only treatment for patients with Class I malocclusion with severe crowding had no effect on the long-term changes to the dentoskeletal and soft tissue morphologies.

As no similar study could be found in the literature, it is difficult to compare our results with others. Only one study has evaluated the effect of serial extraction on the soft tissue profile up to the age of 20 years.[193] As there was no untreated control group in that study and the follow-up was only between 13 and 24 years of age,[193] any comparison with Study III should be approached with caution.

Skeletal changes

Sagittal changes: Throughout the observation period, the Extraction and Control groups showed similar changes in the skeletal sagittal relations, including: the sagittal jaw position (SNA, SNB and SNPog), sagittal jaw relation (ANB), and sagittal positions of the landmarks A, B, Pogonion and Menton (Study III, Table 2). This is in line with the results of short-term studies of orthodontic treatment after premolar extractions.[182,217] Thus, extractions of premolars alone to treat cases of Class I malocclusion with severe crowding have no effect on the skeletal sagittal relations.

Vertical changes: Some studies have reported that dental extractions to relieve crowding may result in a reduction of the vertical facial dimension.[177,178] Therefore, when treating a patient with dental crowding, facial height may be considered in deciding whether or not to extract the teeth. The decrease in the vertical facial dimension after premolar extractions is explained by the wedge-effect concept, whereby mesialisation of the molars during closure of the extraction-related gaps leads to anterior rotation of the mandible and decreases the vertical dimension.[179]

In Study III, the Extraction and Control groups exhibited similar changes in the skeletal vertical relations, including: the vertical jaw inclination and relation (ML/NSL, NL/NSL and ML/NL), and the facial heights, during the adolescence period (Study III, Table 2). Thus, we could not confirm that premolar extractions, without subsequent orthodontic treatment, affect facial heights or vertical jaw relations during adolescence. This is in line with the results of short-term studies that have investigated the physiological drift of the mandibular teeth after premolar extractions without subsequent orthodontic treatment.[184,186] Those studies found no decrease in the mandibular plane angle, since the spontaneous mesial drift of the molars into the extraction sites was associated with extrusion.[184,186] In addition, other studies that have investigated the effects of first premolar extraction and orthodontic treatment on the vertical dimension have found that molar mesialisation after premolar extraction did not reduce the vertical dimension.[181-183,185] Studies have demonstrated that the growth- and treatment-related extrusion of molars during mesialisation prevents reduction of the vertical dimension.[181,185]

From 15 to 30 years of age, there was greater increases in the skeletal facial heights (anterior, lower anterior, posterior and lower posterior) in the Extraction group than in the Control group (Study III, Table 2). This may be related to the extrusion of the molars that accompanies mesial migration, following premolar extraction.[184,186]

Regarding the vertical jaw inclination, no significant differences were noted between the Extraction and Control groups in relation to the maxillary inclination (NL/NSL) during the entire observation period. Nevertheless, there were significant differences between the groups in the mandibular inclination (ML/NSL) from the ages of 15 to 30 and 30 to 62 years (Study III, Table 2). From the age of 15 to 30 years, the Extraction group showed a slight anterior mandibular rotation and a slightly greater degree of deepening of the vertical jaw relation (ML/NL) and Gonial angle, as compared to the Control group. This can be explained by the greater increase in the posterior facial height (4 mm) in the Extraction group during the corresponding period.

From the age of 30 to 62 years, both the Extraction and Control groups showed slight posterior mandibular rotation (ML/NSL) and opening of the vertical jaw relation (ML/NL), albeit with significant differences between the groups. This can be attributed to the age-related remodelling that takes place in the Gonial region in the corresponding period, as shown in Study II.[218]

Therefore, in the clinical context, relief of severe crowding in Class I malocclusion cases by first premolar extractions alone will maintain or even increase the vertical facial heights but will not reduce them.

Dental relations

Throughout the observation period, no significant differences were found between the Extraction and Control groups with respect to the eight studied parameters that describe the inclination and protrusion of the incisors (Study III, Table 3). The Extraction group exhibited a pattern of incisor retroclination during the observation period similar to that of the Control group, reflecting normal age-related changes. Consequently, extractions of premolars alone to treat Class I malocclusion with severe crowding has no effect on incisor inclination and protrusion.

In studies that have investigated the effect of premolar extraction without subsequent orthodontic treatment, it has been shown that the earlier the extraction is performed, the lower the impact on the inclination of the incisors.[184,186] However, the results of short-term studies have shown greater retroclination of the incisors in patients who underwent premolar extractions and orthodontic treatment, as compared to non-extraction orthodontic treatments.[176,182,217]

Soft tissue profile

The nasolabial angle and distances of the lips to the aesthetic line are two of the parameters that are often used to determine the need for premolar extractions in patients with crowded teeth.[173,174] In Study III, throughout the observation period, the Extraction and Control groups displayed similar changes in almost all 14 parameters that describe the soft tissue profile (Study III, Table 4). The Extraction group showed more-pronounced increases in the anterior and lower anterior soft tissue facial heights than did the Control group from 15 to 30 years of age, which is likely due to the more-pronounced vertical skeletal growth observed in the Extraction group. Although few of the soft tissue parameters showed significant differences between the groups in Study III, the premolar extractions had no direct impact on these differences and the differences were small, so they could not be considered clinically important.

Accordingly, the extraction of four premolars alone in patients with Class I malocclusion with severe crowding does not affect the long-term soft tissue profile changes, which include: total facial convexity, facial profile angle, nasolabial angle, lip thickness or length, and lower lip distance to the aesthetic line. Similar findings have been demonstrated in long-term follow-up studies that have investigated the effect of extractions with subsequent orthodontic treatment on the facial profile,[174,189] and by a study that compared changes in the soft tissue profile between serial extraction and late premolar extraction treatments from the age of 13 to 24 years.[193]

Nevertheless, short-term studies have noted that the lip position can be affected by the incisor position following an orthodontic treatment that includes premolar extractions.[175,176,182,217]

Clinical implication

In patients with Class I malocclusion with severe crowding, the space deficiency, rather than the expected changes in skeletal relations, soft tissue profile and incisor inclination, should be the primary concern when deciding on premolar extraction therapy without subsequent orthodontic treatment.

Limitations of Studies I–III

The cephalometric analysis using lateral cephalograms continues to be the gold standard in orthodontic[182] and orthognathic diagnostics and treatment planning. In addition, most of the current knowledge regarding normal craniofacial growth and development is derived from cephalometric studies. However, two main types of errors can occur during the cephalometric analysis and superimposition: projection and identification errors.[115] The main inherent problem with cephalometric analysis and superimposition is that these are analyses of 3D objects on 2D images, which can lead to inaccurate measurements.

However, the 3D technology (e.g., images obtained from CBCT) was not available 50 years ago and it is problematic from the radiation protection and ethical aspects. The radiation dose from a lateral radiograph is low, approximately 5.6 μSv, which is equivalent to 0.7 days of average background radiation.[118] In a low-dose CBCT examination, the dose is approximately 15–26-times higher.[119]

At present, there are no 3D reference measurements for orthodontic diagnosis and treatment planning[125,219] and it will require many years before a longitudinal study with 3D technology can be finalised. Furthermore, to perform longitudinal studies with a 3D technique using today's methods could be questionable from the radiation dose perspective.

Consequently, due to radiation dose restrictions and insufficient studies of normative data, the commonly used 2D cephalometric radiography remains feasible. Moreover, 2D lateral cephalograms can be justified from the radiation safety aspect, and assessments of craniofacial changes can be performed with high precision on 2D cephalograms when the cephalometric measurements are based on superimposition.

Effect of premolar extraction on age-related lower incisor crowding

Treating dental crowding by extracting the first premolars is usually designed to ensure stable incisor alignment.[220] However, the patients who have undergone orthodontic treatment, including premolar extractions, develop more-severe age-related lower incisor crowding than untreated subjects.[88,91,169] It is necessary, therefore, to determine whether patients who initially had incisor crowding and were treated with premolar extractions alone also developed greater long-term incisor crowding. As a result, Study IV aimed to explore the physiological changes that occur in the lower incisor region from the age of 12 to 62 years in patients with Class I malocclusion with severe crowding and who were treated with only premolar extractions (Extraction group), as compared with orthodontically untreated subjects who had normal occlusion (Control group).

In addition, the development of lower incisor crowding has mostly been described using Little's Irregularity index,[202] despite the fact that dental crowding may also be defined as a space deficiency in the dental arch[90,221]. Thus, both the Irregularity Index and tooth size/arch length discrepancy (TSALD) were used in Study IV to assess incisor crowding, given that they represent different aspects of crowding. TSALD describes the space required to align the teeth but does not describe the alignment itself, while the Irregularity index describes the malalignment of the teeth but does not provide information about the available space.[222]

Furthermore, due to late referrals among the patients in the Extraction group, the extractions of the first premolars were not done according to the classic serial extraction[163]. Therefore, in Study IV, there was no potential extraction-related alignment of the anterior teeth, which means that comparisons with previously conducted serial extraction studies[184,186,223] should be undertaken with caution.

Study IV demonstrated that lower incisor alignment basically did not change from early adolescence to late adulthood in patients who had the first premolar extracted as the only treatment for crowding in cases of Class I malocclusion. In contrast, the development of incisor crowding was demonstrated in the subjects with normal occlusion, over a similar period of early adolescence to late adulthood.

General observations

Subjects in the Extraction and Control groups exhibited almost stable Class I molar relations from the age of 12 to 62 years.

The measurements of overjet and overbite were stable in both groups, without significant differences within the group and between the groups, throughout the observation period. The unchanged overjet and overbite noted in Study IV are consistent with the results of earlier long-term follow-up studies of untreated subjects up to late adulthood.[9,85,224]

Slight age-related reduction in total lower incisor width were observed, i.e., -0.4 mm in the Extraction group, and -0.8 mm in the Control group, albeit without significant differences within the group and between the groups over time (Study IV, Table 2). It seems unlikely that these slight and non-significant changes in lower incisor width would affect the values of TSALDant.

Lower incisor crowding

The values of TSALDant and the Irregularity Index in the Extraction group were fairly stable, with no significant changes from the ages of 12 to 30 and 30 to 62 years, indicating stable space and alignment in the lower anterior arch (Study IV, Table 3 and 4). The Extraction group showed large individual variability in terms of the lower arch crowding at the age of 12 years, such that the TSALDtot values were close to zero in a few cases and the indication for extraction in these cases was severe crowding in the upper arch. Significant improvement of the TSALDtot variable was noted in the Extraction group, throughout the observation period, especially from the age of 12 to 30 years due to the premolar extractions. Even from the age of 30 to 62 years, the TSALDtot values did not decrease in the

Extraction group, indicating a stable arch space mesial to the lower first molars (Study IV, Table 3 and 4).

In studies that have evaluated serial extraction, the patients were followed for 2, 3, and 7 years, respectively, and up to 20 years of age.[184,186,223] In contrast to our results in Study IV, Woodside *et al.* showed no significant difference in incisor crowding between serial extraction cases and untreated normal cases at 7 years of follow-up.[223] However, patients who were treated with serial extraction in that study were also given “minor orthodontic treatment".[223]

On the other hand, the Control group, in Study IV, showed significant increases in the Irregularity Index and TSALDtot values, from the ages of 12 to 30 and 30 to 62 years, indicating age-related development of space deficiency and dental crowding in the lower arch (Study IV, Table 3 and 4). This is in line with the findings of previous studies of untreated subjects, and is considered part of the physiological, age-related occlusal changes.[1,8,9,87,225]

Dentoalveolar changes

In Study IV, the Extraction group showed no significant changes in the arch length and arch depth, from the age of 30 to 62, demonstrating the stability of these two variables. In contrast, the Control group exhibited significant reductions in the arch length and depth from the age of 30 to 62 years (Study IV, Table 2). This is in line with the results of previous studies of untreated subjects.[1,8,9,87,225] The apparent reductions in arch length and depth observed in the Extraction group compared to the Control group from the age of 12 to 30 years is dependent upon the extraction of the first premolars. Similarly, the significant differences in the inter-molar width between the groups, from the age of 12 to 30 years, are probably attributable to extraction of the first premolars. Nevertheless, the inter-molar width was stable from the age of 30 to 62 years in both groups, and without significant differences between the groups during this period.

A slight reduction in inter-canine width was observed in the Extraction and Control groups throughout the observation period, with significant reduction seen in both groups from the age of 30 to 62 years, although there were no significant differences between the groups over time (Study IV, Table 2). The age-related reduction of inter-canine width has also been observed in serial extraction cases up to 20 years of age[223] and in other long-term follow-up studies of untreated subjects[9,85].

Cephalometric changes

In Study IV, the anterior and posterior facial heights increased in both the Extraction and Control groups, from the age of 12 to 30 years, although there were significant differences between the groups (Study IV, Table 7). From the age of 30 to 62 years, slight changes in the anterior and posterior facial heights were observed, with no significant differences between the groups. In addition, Study III showed significant differences between Extraction and Control groups in terms of the ML/NSL angle.[226] Post-retention incisor crowding has been considered to be correlated with increased anterior facial height and mandibular plane angle (ML/NSL).[191,221,222] However, in Study IV, we did not study the correlation between skeletal vertical relations and incisor crowding.

Study III and Study IV demonstrated no significant long-term effect of premolar extractions on incisor inclination, as compared to the Control group, from the ages of 12 to 30 and 30 to 62 years. In addition, the results of Study II show that the lower incisors have a relatively stable inclination from the age of 12 to 62 years. Therefore, it is unlikely that the development of age-related lower incisor crowding in the Control group was due to retroclination of the lower incisors. Furthermore, Björk and Skieller have demonstrated that the normal growth-related forward rotation of the mandible results in mesial migration of the molars more than lingual tipping of the incisors, leading to normal reduction of the dental arch length.[20,21] Consequently, we consider that the development of lower incisor crowding in the Control group during the observation period can be explained by the decreases in arch length and depth. This probably occurred due to the mesial migration of the posterior teeth rather than lingual incisor inclination.

On the other hand, in Study IV, the correlations between incisor crowding (Irregularity Index and TSALDant) and arch length, width and depth were evaluated, from the age of 30 to 62 years. Non-significant correlations were found in both groups, when using TSALDant as an independent variable (Study IV, Table 5 and 6). However, only arch depth was significantly correlated with Irregularity Index in the Extraction group, when the Irregularity Index was used as the independent variable. Thus, in the Extraction group, stable arch depth is suggested to be a result of residual premolar extraction gaps, which may accelerate the early mesial migration of posterior teeth and/or diminish the late development of age-related incisor crowding.

A well-known saying in orthodontics is that there is nothing more stable than a malocclusion, which means that external strong enough forces must be applied to teeth to change the natural equilibrium and to induce movement of the teeth into a new position.[227] In addition, it has been shown that patients who have received orthodontic treatment, including premolar extractions, develop more age-related incisor crowding than untreated subjects.[88,91,169] Thus, it has been proposed that orthodontic treatment acts as an accelerator for the age-related physiological occlusal changes.[88,169,225] However, the results of Study IV showed the development of age-related crowding in untreated subjects but not in patients who had Class I malocclusion with severe crowding and who were treated with premolar extractions alone.

Ultimately, it is noteworthy that particular variables need to be analysed to investigate the causes of age-related lower incisor crowding. These variables include: mesial migration of molars[20,21]; late mandibular growth[87], facial height and mandibular inclination[191,221,222] and lower incisor distance to the A-Pog plane[191].

Limitations of Study IV

The described dimensional changes in Study IV are probably not linear and may, similar to changes in the Irregularity Index, vary during the follow-up period. Small changes might occur between the age of 30 and 62 years.

Moreover, it would be worthwhile to have two more groups for comparison: 1) a group with dental crowding treated by premolar extraction and orthodontic appliance finishing with the remaining extraction gaps; and 2) a group with crowding treated with premolar extraction and orthodontic appliance finishing with closed extraction gaps.

Clinical implication

In patients with Class I malocclusion with severe crowding (space deficiency ≥7 mm), the first premolars can be extracted once they erupt, without further orthodontic treatment. However, if alignment of the upper and/or the lower incisors is required with an orthodontic appliance, it may be beneficial to leave the residual extraction gaps open, so as to counteract mesial migration of the molars and subsequent development of incisor crowding in late adulthood.

Conclusions

In the methodological study on superimposition-based cephalometric method to quantitate craniofacial changes (Study I), the following conclusions were reached:

- The suggested superimposition-based cephalometric method can be used to quantitate accurately craniofacial changes.
- The superimposition-based cephalometric measurements reflect the graphical illustration of the superimposed radiographs.
- The TW method is a valid, reliable, and feasible superimposition method that can be used to generate superimposition-based cephalometric measurements.

In the longitudinal study exploring the craniofacial changes from the age of 12 to 62 years (Study II), the following conclusions were drawn:

- From 12 to 30 years of age, the craniofacial changes were greater than those for 30 to 62 years of age, such that:
  The length and inclination of the cranial base increased simultaneously with the increased dimensions of the jaws. The upper and lower jaws exhibited more downward than forward movement, indicating increased facial height. The vertical inclinations of the jaws were relatively stable. The upper and lower incisors showed eruption, although their inclinations remained stable. The soft tissue facial height, nasal length, distances from the lips to the aesthetic line, and downward displacement of the lips increased markedly.
- Between 30 and 62 years of age, the craniofacial changes were less-pronounced as follows:
  The length and inclination of the cranial base were relatively stable, as were the lengths of the jaws. The upper and lower jaws exhibited minor retrognathism, and while the inclination of the upper jaw was stable, the lower jaw showed posterior rotation. The upper incisors showed retroclination, concomitant with straightening of the soft tissue profile and thinning of the lips. The soft tissue facial height, nasal length, distances from the lips to the aesthetic line, and downward displacements of the lips, all continued to increase with age.

In the case-control study investigating the impacts of premolar extractions on dentoskeletal and facial morphologies up to late adulthood (Study III), the following conclusions were made:

- Treatment of patients with Class I malocclusion with severe crowding by extracting the first premolars, without subsequent

orthodontic treatment, generally does not affect the long-term changes in the skeletal relations, incisor inclination and protrusion, and lip support or soft tissue profile, as compared to untreated subjects with normal occlusion.
- In cases of Class I malocclusion with severe crowding, the degree of crowding, rather than changes to the dentoskeletal and facial morphologies, is the essential criterion in deciding on extraction therapy.

In the case-control study investigating whether the extraction of the first premolars affects the development of age-related lower incisor crowding up to late adulthood (Study IV), the following conclusions were made:

- Lower incisor alignment remains mostly unchanged up to 62 years of age in a group of patients with Class I malocclusion with severe crowding who are treated solely with first premolar extraction, in contrast to the significant increase in lower incisor irregularity seen in an untreated group that initially had normal occlusion.
- Significant reductions in arch length and depth are observed only in the Control group. The non-significant changes in the Irregularity Index in the Extraction group correlates with unchanged arch depth.

Future research

For future research in this area, it seems warranted to continue to study in depth the present reference material in relation to the differences between conventional cephalometric and superimposition-based cephalometric measurements in the assessment of craniofacial changes from early adolescence to late adulthood. In this context, we plan to investigate whether there are differences between conventional cephalometric and superimposition-based measurements also in adulthood. Moreover, we want to study the dentoalveolar changes in the digital models of orthodontically untreated subjects who have Class I dental occlusion without any malocclusion from 12 to 62 years of age, as a complement to the previous study of Thilander[2].

In addition, we wish to explore the aetiology of age-related lower incisor crowding using mandibular superimposition and multivariate analyses. This is because the causes of age-related lower incisor crowding are still not well-established. Through the use of local superimposition according to Björk, we plan to study driftodontics, the dentoalveolar changes (molar movement and incisor inclination) after extractions of premolars, without subsequent orthodontic treatment over 50 years, and the sexual dimorphism of normal growth and age-related changes in craniofacial morphology. These proposed future studies emerge from the results of Studies II and III.

It would be interesting to study growth over time for patients with Class II and III malocclusions and to establish a reference material for Class II and III materials.

Furthermore, through the use of the established reference material for Class I and the future results for Class II malocclusions, studying patients with cleft lips and palates and other syndromes.

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