A multilevel analysis of craniofacial growth in subjects with untreated Class III malocclusion

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Running Head: Growth in untreated Class III subjects

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Abstract

Objective: To analyze the craniofacial growth of a long-term semi-longitudinal sample of Caucasian subjects with untreated Class III malocclusion.

Setting and Sample Population: 144 Caucasian subjects (of North American and Italian origin) with untreated Class III malocclusion.

Materials and methods: Subjects aged 2 years and 9 months up to 21 years and 7 months were selected. A multilevel model was used to calculate growth curves for ten variables for both each individual subject and for the whole sample.

Results: There was a statistically significant increase for total mandibular length (Co-Gn. T2-T1 = 8.4 mm), midfacial length (Co-A. T2-T1 = 3.4 mm) and lower anterior facial height (ANS-Me. T2-T1 = 3.8 mm). The multilevel analysis showed an acceleration of growth at 11-15 years of age for seven out of ten variables. For Co-Gn and Co-A variables, males presented points of maximum growth delayed by 1 year in comparison to females, with a greater duration (1 year longer) and a greater total growth of about 5 mm. Active mandibular growth continued for a long time after the pubertal spurt: increases in mandibular length ended at about 17 years of age in females and after 18 years for males.

Conclusions: Untreated Class III malocclusion showed a specific growth curve, especially for the mandible, whose excesses added up over time. In males the amounts of mandibular and midfacial growth during the whole observation time were greater and lasted longer than in females.

Keywords: Class III; Malocclusion; Growth; Cephalometrics; Caucasian

Introduction

Although in recent years interest concerning treatment of Class III malocclusion has intensified,[1-3] studies on craniofacial growth of untreated Class III subjects continue to be scarce.[4-8] To date, investigators have found that Class III malocclusion is the dentoskeletal disharmony with the lowest prevalence in the world; a global range varies from 0% to 26.7%.[9] The prevalence of this condition depends on ethnicity and geographic region. In Caucasian populations, the prevalence is relatively low (from 1.9% to 12.2%).[10-13] The highest prevalence is recorded in Southeast Asian populations (in China and in Malaysia the prevalence is between 12.6% and 26.7%).[14-16]

The complexity of this malocclusion is reflected in its etiopathogenesis. Class III malocclusion is the result of both genetic and environmental factors. The former has a strong unfavorable influence on the course of craniofacial development; thus far, multiple models of inheritance have been hypothesized. The autosomal-dominant model with incomplete penetrance and the polygenic inheritance model are two of the most probable explanations.[17,18]

The growth pattern observed in Class III malocclusion is complex. Cross-sectional studies have concluded that its typical craniofacial characteristics already are established at an early age.[19,20] Class III malocclusion is not susceptible to spontaneous improvement during growth. On the contrary, this condition tends to worsen over time, especially in males[4,21-23] with excessive mandibular growth. Growth continues to worsen slightly even after the pubertal phase.[4,23]

Differences have been found in the craniofacial growth of subjects with untreated Class III malocclusion compared to Class I subjects. Cross-sectional studies have shown that the pubertal growth spurt lasts longer in subjects with untreated Class III malocclusion compared to that of subjects with Class I malocclusion (on average 5 months longer).[24] Excessive mandibular growth, the absence of catch-up growth of the maxilla and the vertical direction of facial growth appear to be unfavorable aspects in Class III malocclusion.[4,6] Moreover, the pubertal growth spurt seems to be delayed for a few years compared to individuals with normal occlusion.[23]

Longitudinal studies available on this topic[4-6] have confirmed only a few of these aspects. Furthermore, there is a shortage of longitudinal studies with untreated Class III subjects followed until the end of their skeletal growth. Many studies regarding craniofacial growth have outlined polynomials multilevel models.[25-28] The curvilinear multilevel model can estimate the extent of acceleration (when its regression coefficient is positive) or deceleration (when its regression coefficient is negative).[27]

Only one study regarding craniofacial growth of untreated Class III malocclusion was reported performing a multilevel statistical analysis using a linear model.[6] Linear multilevel models can show growth velocity but cannot consider variations in the subjects and their oscillations during growth.[25,27] Thus, the present study is aimed to describe craniofacial growth in a group of untreated Caucasian subjects (of Italian and North American origin) with Class III malocclusion using cephalometric data elaborated with a curvilinear multilevel model including chronological age up to the fifth order.

Materials and methods

This study was exempted from review by the Medical School Institutional Review Board of the XXXXXX of XXXXXXX (HUM00160285).

This article is structured according to STROBE guidelines for longitudinal studies.[29] The sample consisted of semi-longitudinal cephalometric data of Caucasian subjects with untreated Class III malocclusion. It was derived in part from a database of untreated Class III subjects (41 subjects: 17 males and 24 females) described by Levin et al.,[30] and in part from a database reported by Zionic Alexander et al.[5] (104 subjects: 48 males, 56 females), for a total of 145 subjects. These patients were left untreated because they refused treatment or because their records were derived from historical samples taken from Growth Center Studies conducted in the USA and Canada.

Subjects originally were selected by orthodontists from the United States and Canada in their private practices. Other sources included university-affiliated orthodontic clinics, Growth Center Studies (including the Bolton-Brush Growth Study, the Burlington Growth Center, the University of XXXXXXXXXXX Growth Study and the XXXXXX Growth Study), the Orthodontic Clinic of the University of XXXXXXX and the Orthodontic Clinic of the University of XXXXXXXXXX.[5,30]

For each patient a series of longitudinal lateral cephalograms were available.[5,30] Each subject had at least two cephalometric records related to two different ages, with the films taken at least one-year apart. The distribution of the sample according to the number of cephalometric films for each subject is displayed in Supplementary Table 1. Cephalometric magnification varied originally from 0% (life size) to 12.9%, and it was then standardized to 0%.

Patients with pseudo Class III anterior crossbite were excluded for two reasons: first, in contemporary Class III subjects who refused treatment, the orthodontist reported a functional deviation; second, an increase in the linear distance between the second vertebral body and the posterior border of the mandibular ramus during tooth intercuspation was noted for subjects derived from Growth Center Studies.

The sample that met the inclusion criteria (Table 1) consisted of 145 Caucasian patients with untreated Class III malocclusion. Of these subjects, 1 patient showed cephalometric data typed incorrectly; this subject was eliminated. The final number of subjects was 144 (65 males and 79 females). Patients who derived from Growth Center Studies (Growth Study Group) were 45 out of 144; patients who refused Class III treatment (Non-Growth Study Group) were 99 out of 144.

For each subject, a lateral cephalometric record at T1 (time of the patient's first observation: on average 10.0 ± 3.7 years) was available, and one at T2 (patient's last observation: on average 13.8 ± 2.7 years) (Supplementary Table 2). Patients with observations (cephalometric data) occurring during the post-adolescent age, i.e. from 18 years of age up to 21 years and 7 months, numbered 16 (7 males and 9 females).

Statistical analysis

The method error for cephalometric measurements is described in Levin et al.[30] and in Zionic Alexander et al.[5]

Both descriptive and inferential statistical analysis were performed. For the descriptive analysis, 23 cephalometric variables were examined (11 linear and 12 angular) at T1 and at T2, using a statistical software (JMP®, version 13.0, Cary, NC, USA). Descriptive statistics for the T2-T1 changes for three variables also was calculated for total mandibular length (Co-Gn), midfacial length (Co-A) and lower anterior facial height (ANS-Me). Descriptive statistics and statistical comparisons were performed also for the Growth Study Group vs Non-Growth Study Group at baseline.

An inferential analysis then was performed using a multilevel model at two levels (patient and number of lateral cephalograms). A study of craniofacial growth over time often is performed with longitudinal data across childhood and adolescence.[27] Analysis of longitudinal data usually requires advanced statistical methods that vary according to properties of the data, such as the number of repeated measurements of the subjects or the shape of the growth curves.

To characterize some features in the process of growth changes a classical regression analysis can be used.[31] Regression analysis assume that the observations are independent, but when multiple observations are collected from the same subjects, those observations are correlated. In particular, in this study a multilevel modeling (also known as hierarchical linear modeling) was conducted to take this correlation into account for analyzing longitudinal data.

The advantage of multilevel analysis is that it can show how average growth and individual growth can be characterized.[32,33] Moreover, it uses polynomials that can define growth curves in many shapes; therefore multilevel analysis is versatile.[32] Multilevel analysis also does not require complete longitudinal data, in fact it can manage missing terms easily. The software used in this study was a multilevel modeling software (MLwiN®, version 2.26, University of XXXXXXXX).

Multilevel analysis examined 10 cephalometric variables (3 linear and 7 angular), i.e. Co-Gn, Co-A, ANS-Me, NSBa, SNA, SNB, ANB, ArGoMe, SN-MP, PP- MP to evaluate growth variations of these variables over time (including each cephalometric record available) for the whole sample considered. Males and females were analyzed separately.

Multilevel models used “Age” up to the fifth order as an explanatory variable. “Age^{5}” is “Age” raised to the fifth power. Since growth of the variables does not seem to be linear in the subjects, we have included the term "Age" up to the fifth order (i.e. the quintic term of age) in years. A multilevel analysis up to the first term of age would have involved the creation of a linear multilevel graph; this method could not have allowed the highlighting of variations in the craniofacial growth of the variables.[31] The higher the age orders are, the more accurate is the approximation of the growth curve to the individual observations collected for each patient. Missing values, therefore, can be interpolated with a polynomial method.

The other explanatory variables were “Gender” and the "Age x Gender" interaction. The various terms related to “Age” were left in the model only if significant starting from the polynomial with higher degree. Even the "Age x Gender" interaction was left in the model only if significant. In any case, the simplest model had to present the variables “Age” of order 1 and “Gender”. The level of significance was set at 0.05. The random effects consisted of the “Intercept” (constant) and the variable “Age” of order 1 (the latter only if significant).

Results

Descriptive statistics for the 23 cephalometric variables at T1 and at T2 are reported in Table 2. Regarding T2-T1 changes for the Co-Gn, Co-A and ANS-Me variables, a significant increase in time interval (Table 3) was found. Midfacial length showed a statistically significant T2-T1 mean increase (3.4 mm. 95% confidence interval [CI]: 2.8- 3.9 mm). This increment, however, was about one third compared to that of total mandibular length (8.4 mm. CI: 7.3- 9.5 mm). Moreover, there was a significant increase in the vertical measure ANS-Me in the time interval (3.8 mm. CI: 3.2- 4.6 mm).

Descriptive statistics and statistical comparisons of Growth Study Group vs Non-Growth Study Group at baseline were reported in Supplementary Table 3. No statistically significant differences were found between the 2 groups with the exception of the angle ANB. The difference in the ANB angle was -1.4 degrees (95% confidence interval from -2.1 degrees to -0.6 degrees).

Growth curves of each of the 144 patients were constructed for the Co-Gn, Co-A, and ANS-Me variables at the different ages available. Because this study did not calculate the growth difference of each variable for each age interval considered, the "spurt" of the growth curve corresponded to a steeper variation of the inclination of the multilevel curve.

Multilevel models for ten cephalometric variables are reported in Figures 1 and 2; graphs for multilevel models are presented in Table 4. Longitudinal records by age-class are displayed in Supplementary Table 4.

The growth trends for total mandibular length (Co-Gn) and midfacial length (Co-A) (Fig. 1) for the whole sample were curvilinear, with two growth spikes observed at 3-5 years and 11-15 years. The spike at 3-5 years should be interpreted with caution due to the limited number of subjects for this age range.

For both variables there was significant interaction between age and gender; in fact, females showed spurts occurring slightly before males. The growth spurts ended about 1 year earlier in females, and total growth was about 5 mm smaller compared to males. Total mandibular length growth ceased around 17 years in females. In males a modest continuation of growth of total mandibular length (Co-Gn) until the end of the observation time (21 years and 7 months) was observed (Fig. 1). It should be stressed that the growth estimate occurring the period after 18 years of age should be interpreted cautiously because of the relatively small sample size (16 subjects). Midfacial length growth finished at about 17 years in both males and females. Increases in lower anterior facial height growth also ended at about 17 years in both females and males. There were no gender differences in the observation time, and there were two points of maximum growth at about 3-5 years of age, and 11-15 years of age.

The cranial base angle showed no differences in growth between males and females, and it exhibited no appreciable modifications during growth, describing a linear growth model ("Age" was not significant in the model; Table 4). SNA angle showed mild oscillations over time with no differences between males and females.

The increase in the SNB angle was linear and constant over the age range considered, without differences between males and females. The ANB angle decreased over time, initially with a more marked tendency (from around 3 to 11 years of age) and then increasingly less accentuated until it stabilized at about 20 years of age at a negative value of about -2.5 degrees. The decrease in the gonial angle was curvilinear with two accentuated decreases at about 3-5 years and 12-16 years. Decrements in the gonial angle ended at about 18 years of age.

The growth curve of the inclination of the mandibular plane in relation to the anterior cranial base was curvilinear in both genders, and it was steeper starting from about 11-13 years. There was interaction between gender and age: males had higher values between approximately 3-7 years, with smaller values after 14 years, compared to females. Females showed a less steep decrease in the growth curve over time.

The growth curve of the inclination of the palatal plane in relation to the mandible plane decreased linearly over time (of about 5 degrees overall). There was much interindividual variability in the quantity of growth for eight out of ten variables (see Supplementary Fig. 1 for Co-Gn variable).

Discussion

In the present study, a two-level multilevel analysis was able to delineate growth curves for some cephalometric variables over time. The results of this study largely agree with previous longitudinal studies:[4-6] in fact, a worsening and a lack of spontaneous improvement over time of the skeletal characteristics of Class III malocclusion was described. This lack was particularly evident through a worsening of the ANB angle (associated with a constant increase in the SNB angle), a reduction of the Wits appraisal, and an excessive increase in total mandibular length.

The scarcity of data on the untreated Class III subjects made it necessary to undertake this retrospective study that described craniofacial growth in subjects with untreated Class III malocclusion, using cephalometric data elaborated with a curvilinear multilevel model. Multilevel modeling was originally established to analyze clustered data in which measurements were not independent, such as patients treated by the same clinician or clinicians working in the same clinic.[31,33] Repeated observations can be considered as clustered data with multiple measurements of the same variable made in the same subject, such as repeated cephalometric measurements on the same patient.[27,31]

To evaluate better the growth curve of each variable in each patient, a polynomial curvilinear analysis model was applied to highlight growth variations over time, both in males and females. In fact, the multilevel model can evaluate different growth patterns with the additional variable of "Gender", resulting in a more complex model.[27,31] Moreover, random effects were used also to consent the change in growth velocity to vary across children.[31] Because this type of occlusion invites early intervention and because of the limited prevalence of this malocclusion, data on untreated Class III subjects are increasingly difficult to collect.

In this study, gender differences in the growth curves generated for Co-Gn, Co-A, and SN-MP were observed. Total mandibular length (Co-Gn) demonstrated an increase in growth over time, with an average growth of 8.4 mm between T1 and T2 (T2-T1 min = 0.8 years. T2-T1 max = 11.9 years. T2-T1 mean = 3.8 years, SD = 2.7 years. Supplementary Table 2).

Growth along Co-Gn continued beyond 15-16 years of age, ending at 17 years of age in females. In males, mandibular growth as measured from Co to Gn continued until the end of the observation time (21 years and 7 months). As emphasized already, this result should be interpreted with caution due to the limited number of male subjects after the age of 18 years. The persistence of active mandibular growth, well beyond the circumpubertal phase, had been observed only by previous medium-term cross-sectional studies,[4,23] mostly in males. Previous longitudinal studies revealed that mandibular length had a more pronounced growth in males.[4-6] In the previous multilevel study[6] on growth of untreated Class III malocclusion, mandibular length continued to increase rapidly over time, with a greater amount of growth observed in males, as confirmed by the present study.

Midfacial length (Co-A) evidenced an amount of growth at the end of the observation time which was about one third (3.4 mm, CI: 2.8 - 3.9 mm) of that shown by total mandibular length (8.4 mm. CI: 7.3- 9.5 mm). Maxillary growth deficiency has been confirmed in previous cross-sectional and longitudinal studies[4,23] and in studies in which small groups of untreated Class III subjects, used as control groups, were followed longitudinally.[34,35] Previous studies[4,23] also confirmed gender differences for the Co-A variable. In the study by Wolfe et al.[6] midfacial length was significantly larger in males than in females, and there were no differences in growth of midfacial length of Class III subjects compared to the control group of Class I subjects. In addition, it was not possible to compare the multilevel curve of growth of the Co-A variable because it had not been reported in previous studies.[6]

Compared to prior cross-sectional studies[4] and semi-longitudinal studies,[5,6] in which there was a shorter lower anterior facial height (ANS-Me) in female subjects, the present study did not find gender differences for ANS-Me both in the growth trend and the quantity of growth. A significant increase in this variable during the entire observation interval was detected. This finding is in accordance with those of previous longitudinal studies.[5,6] In the study by Wolfe and co-workers[6] the ANS-Me variable expressed a linear growth increase over time, which, therefore, determined an opening of the mandibular plane angle.

The cranial base angle showed no appreciable changes during growth, both in males and females. The same finding was reached in other longitudinal studies,[5,6] or a slight closure of this angle was described, albeit not significant.[4] In the previous multilevel study on this topic[6] during the observation time (6-16 years of age) there were no significant growth differences between males and females and between Class III subjects and Class I individuals.

The position of the maxilla relative to the cranial base (SNA angle) presented slight but non-significant changes in angulation over time. This outcome suggests that the maxilla was not retruded relative to the cranial base, with respect to normal values.[36] At the same time, the forward growth of the maxilla was deficient compared to the excessive mandibular growth in a forward and downward direction. Moreover, the multilevel growth curve for the SNA variable was not present. Even in that study,[6] the position of the maxilla (evaluated by the SNA angle and Co-A) was not retruded at the end of growth, despite the end of the time evaluated was only 16 years of age.

The position of the mandible relative to the cranial base, measured with the SNB angle, progressed over time without gender differences. Predictably, the increase of SNB angle in the untreated Class III malocclusion was more pronounced than normal,[36] with a total increase of about 6 degrees, on average, during the observation time, both for males and females.

Such a forward growth of the mandible, demonstrated by the increase of the SNB angle, has been described by previous studies on craniofacial growth of untreated Class III malocclusion. Baccetti et al.[4] conducted a longitudinal study in which the increase of the SNB angle was more than double of that of the SNA angle. Wolfe et al.,[6] regarding the SNB angle, reported a statistically significant increase over time, without differences between males and females. The gonial angle showed a reduction in angulation over time.

The same growth trend was demonstrated in the multilevel graphics in the study of Wolfe et al.,[6] but also in the study of Zionic Alexander et al.[5] in which the increments in growth at the 6-16 age intervals were almost always negative (for 16 age intervals out of 21). Similarly, Baccetti et al.[4] described a negative T2-T1 difference of the Ar-Go-Me angle (-2.4 degrees).

The inclination of the mandibular plane in relation to the anterior cranial base (SN-MP) and the inclination of the palatal plane in relation to the mandible plane (PP-MP) were not taken into account in previous longitudinal studies.[4,5] In these investigations, however, the angulation of vertical values (FH to occlusal plane, FH to palatal plane and MPA angle) decreased over time, as reported in the current study. Regarding the study of Wolfe et al.,[6] these two variables (SN-MP, PP-MP) were not considered in the multilevel analysis. The mandibular plane angle, however, was significantly larger in the Class III group at 11 years of age and the growth curve of this variable decreased lightly over time.

Interindividual variability was statistically significant for eight (Co-Gn, Co-A, ANS-Me, SNA, SNB, ArGoMe, PP-MP, NSBa) out of ten variables considered. Variability can be due to a summation of minor effects from a variety of different genes and/or from the influence of epigenetic factors.[37-39]

A limit of this study is that only 28/144 subjects have more than three observations, and 88/144 subjects have only two observations. These results reduce the capacity to correctly understand the longitudinal variation of cephalometric measures within subject.

Another limit of this study was that the reliability of reported outcomes below 6-7 years and above 18 years was reduced due to the few longitudinal observations available.

Conclusions

In summary, it emerged that:

- A growth spike for Co-Gn, Co-A, ANS-Me and increase in the angulation for SNA at 11-15 years of age was found.

- Untreated Class III malocclusion progressively worsened over time and did not show spontaneous improvement.

- Gender differences were found for the Co-Gn, Co-A and SN-MP variables. The spike in growth at 11-15 years was delayed in males by about 1 year in comparison to females, both for the total mandibular length and for midfacial length. In addition, this spike in growth during the circumpubertal growth period continued for about a year longer in males, and there was a greater increase in length of about 5 mm in males compared to females.

- Class III malocclusion had a protruded and larger mandible, while the maxilla was not retruded at the end of growth.

- Significant mandibular growth continued for a long time after the pubertal phase in untreated Class III subjects. In particular, growth in mandibular length (Co-Gn) ended about 17 years of age for females while in males mandibular growth continued after 18 years. Growth in midfacial length finished at about 17 years in both females and males. Growth in lower anterior facial height ended at about 17 years in both genders.

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Figure legends

Figure 1. Multilevel graphs of the whole sample, for Co-Gn, Co-A, ANS-Me, NSBa and SNA cephalometric variables.

Figure 2. Multilevel graphs of the whole sample, for SNB, ANB, ArGoMe, SN-MP and PP-MP cephalometric variables.

Supplementary Figure 1. Individual longitudinal growth variations for Co-Gn for all the 144 subjects analyzed in this study, divided into males and females.

Table legends

Table 1. Sample inclusion criteria.

Table 2. Descriptive statistical analysis for the sample at T1 and T2.

Table 3. T2-T1 difference of the Co-Gn, Co-A and ANS-Me cephalometric variables.

Table 4. Table for the multilevel model of 10 cephalometric variables.

Supplementary Table 1: Distribution of the sample according to the number of consecutive cephalometric films available for each subject.

Supplementary Table 2. Age (years) of the sample analyzed at T1 and T2.

Supplementary Table 3: Statistical comparison between Growth Study and Non-Growth Study Groups at T1.

Supplementary Table 4: Available longitudinal records by age-class.

Table 1. Sample inclusion criteria.

1. European or American ancestry (Caucasian ethnicity)
2. No orthodontic or orthopedic treatment before the first cephalometric record, or between the records, has been performed
3. Initial diagnosis (T1) of:
   - anterior cross-bite (excluding pseudo-crossbite)
   - edge-to-edge incisive relationship, concomitant with one of the skeletal Class III criteria
   - accentuated mesial step relationship of the deciduous second molars
   - mesial Class III relationship of the first permanent molar of at least half cusp
4. Class III skeletal relationship having one or both:
   - a negative Wits appraisal greater than –2.0 mm
   - an ANB angle less than 0°
5. No congenitally missing or extracted teeth
6. No craniofacial syndromes
7. Not less than 9 months and not more than 30 months between consecutive cephalometric films

Table 2. Descriptive statistical analysis for the sample at T1 and T2.

T1						T2					
Variable	Mean	Standard deviation	Median	Min	Max	Variable	Mean	Standard deviation	Median	Min	Max
NSBa	128.2	5.4	128.6	108.0	140.9	**NSBa**	128.5	5.3	128.5	109.6	140.1
NSAr	121.5	5.2	121.9	106.9	135.8	**NSAr**	121.6	5.0	122.0	106.6	132.3
SN	63.8	4.2	63.8	53.8	72.5	**SN**	66.0	4.1	65.8	56.7	75.4
S-Ar	29.3	4.0	28.8	21.9	40.0	**S-Ar**	31.0	3.7	30.5	21.9	41.0
SNA	79.6	3.9	79.7	68.9	89.5	**SNA**	79.7	4.1	79.9	66.7	88.5
SNB	79.9	4.1	79.5	69.1	88.9	**SNB**	81.3	4.3	80.8	70.1	90.2
ANB	-0.3	2.2	0.0	-8.0	6.2	**ANB**	-1.6	2.5	-1.4	-9.1	3.7
Wits	-4.9	2.7	-4.7	-13.8	0.4	**Wits**	-6.1	3.4	-5.7	-16.4	3.0
Co-A	77.8	6.3	78.2	63.8	95.4	**Co-A**	81.2	5.9	81.2	67.2	100.1
Co-Gn	104.3	10.8	104.6	83.1	135.3	**Co-Gn**	112.7	10.2	113.4	90.0	140.4
Co-Go	47.4	7.3	47.3	31.5	72.5	**Co-Go**	52.1	7.3	52.4	37.0	76.4
Go-Gn	72.3	7.7	72.3	55.2	91.9	**Go-Gn**	78.0	6.8	78.0	62.7	97.0
ArGoMe	129.6	6.2	129.9	112.5	145.3	**ArGoMe**	128.0	6.5	128.2	111.7	145.4
SN-PP	8.7	3.6	8.3	-0.5	18.6	**SN-PP**	8.8	3.6	8.7	-1.7	18.9
SN-MP	35.9	6.0	36.9	21.4	52.3	**SN-MP**	34.9	6.5	35.5	20.5	51.1
PP-MP	27.1	5.8	27.6	9.4	41.8	**PP-MP**	26.1	6.2	26.3	9.6	40.4
N-Me	104.5	10.2	104.4	81.7	131.2	**N-Me**	111.9	9.6	112.1	84.9	136.7
ANS-Me	59.2	6.1	58.6	47.1	76.0	**ANS-Me**	63.1	6.5	62.9	47.7	79.7
OVJ	-0.0	2.1	0.2	-7.2	4.0	**OVJ**	-0.5	2.4	-0.4	-8.1	3.9
OVB	0.8	1.6	0.6	-5.1	6.6	**OVB**	0.9	1.6	0.7	-2.9	6.7
U1-PP	109.6	9.1	111.1	85.2	132.0	**U1-PP**	114.4	7.5	114.1	91.0	133.1
L1-MP	83.8	6.9	83.4	63.6	100.5	**L1-MP**	83.1	7.8	83.2	61.6	99.8
Interinc	139.5	11.8	137.8	113.9	167.0	**Interinc**	136.4	10.9	136.2	112.3	169.7

Table 3. T2-T1 difference of the Co-Gn, Co-A and ANS-Me cephalometric variables.

T2-T1	Mean	Standard deviation	Median	Min	Max
Co-Gn	8.4 *CI 95% [7.3; 9.5]*	6.6	6.2	0.3	30.7
Co-A	3.4 *CI 95% [2.8; 3.9]*	3.3	2.0	-1.1	16.1
ANS-Me	3.8 *CI 95% [3.2; 4.6]*	3.7	2.8	-2.1	15.6

Table 4. Table for the multilevel model of 10 cephalometric variables.

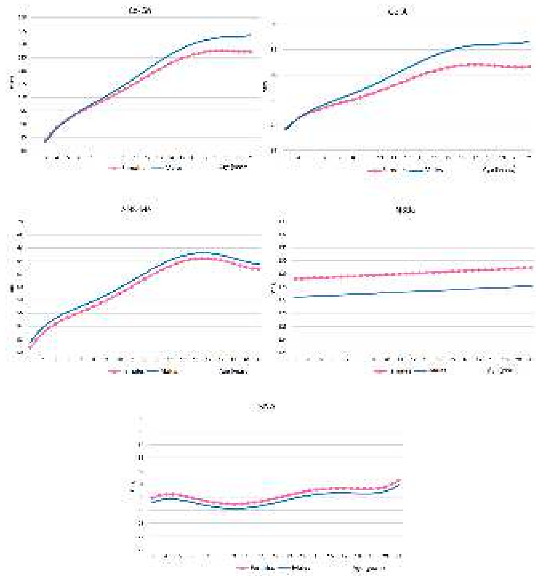
	Co-Gn			Co-A			ANS-Me			NSBa			SNA		
Term	Estimated	Standard error	P-value	Estimated	Standard error	P-value	Estimated	Standard error	P-value	Estimated	Standard error	P-value	Estimated	Standard error	P-value

Fixed effects															
Intercept	48.948	7.194		51.746	4.831		33.857	5.214		127.064	0.859		76.603	4.319	
Age	2.036	1.397	<0.0001	9.793	2.413	<0.0001	10.194	2.613	<0.0001	0.0478	0.0431	0.2674	4.061	2.171	0.0613
Gender (f)	2.036	1.397	0.1451	1.121	1.104	0.3099	-0.843	0.738	0.2533	1.397	0.885	0.1145	0.353	0.652	0.5882
Age x Gender	-0.383	0.117	0.0011	-0.291	0.078	0.0002									
Age^2	-3.140	0.690	<0.0001	-1.785	0.463	<0.0001	-1.901	0.500	0.0001				-0.936	0.417	0.0248
Age^3	0.2883	0.0624	<0.0001	0.170	0.042	<0.0001	0.180	0.045	<0.0001				0.0934	0.0378	0.0135
Age^4	-0.0122	0.00268	<0.0001	-0.0746	0.00181	<0.0001	-0.0784	0.00194	<0.0001				-0.00417	0.00162	0.0100
Age^5	0.000191	0.0000437	<0.0001	0.000121	0.0000296	<0.0001	0.000125	0.0000317	<0.0001				0.0000689	0.0000265	0.0093
Random effects (Variance)															
Intercept	34.944	7.213		26.327	4.651		18.890	3.880		46.291	7.737		18.877	3.390	
Age	0.240	0.051	<0.0001	0.103	0.023	<0.0001	0.164	0.032	<0.0001	0.112	0.028	<0.0001	0.0496	0.0134	0.0002
Covariance (Intercept, Age)	-1.357	0.524		-0.882	0.283		-0.793	0.300		-1.485	0.414		-0.473	0.184	
Rx level	1.425	0.148		0.628	0.066		0.716	0.075		0.960	0.099		0.545	0.0555	
-2loglikelihood	2066.393			1765.865			1816.237			1904.475			1646.329		

Table 4. Continued

	SNB	ANB	ArGoMe	SN-MP	PP-MP

Term	Estimated	Standard error	P-value	Estimated	Standard error	P-value	Estimated	Standard error	P-value	Estimated	Standard error	P-value	Estimated	Standard error	P-value
Fixed effects															
Intercept	75.887	0.599		3.671	0.533		143.133	3.925		37.071	0.999		29.540	0.767	
Age	0.355	0.033	<0.0001	-0.514	0.080	<0.0001	-3.905	1.492	0.0089	0.0473	0.1098	0.6666	-0.255	0.043	<0.0001
Gender (f)	0.857	0.649	0.1868	-0.336	0.371	0.3651	-0.249	0.960	0.7953	-1.724	1.195	0.1491	0.392	0.905	0.6649
Age x Gender										0.154	0.054	0.0043			
Age^2				0.0106	0.0033	0.0013	0.461	0.204	0.0238	-0.01451	0.00468				
Age^3							-0.0260	0.0117	0.0258						
Age^4							0.000531	0.000237	0.0251						
Age^5															
Random effects (Variance)															
Intercept	20.602	3.520		4.605	0.578		28.586	6.447		35.218	4.209		24.208	4.918	
Age	0.080	0.017	<0.0001				0.113	0.035	0.0009				0.110	0.027	<0.0001
Covariance (Intercept, Age)	-0.721	0.211					-0.464	0.395					-0.327	0.295	
Rx level	0.400	0.043		0.746	0.063		1.956	0.194		1.364	0.116		1.089	0.110	
-2loglikelihood	1604.539			1487.465			2092.397			1941.825			1939.348		



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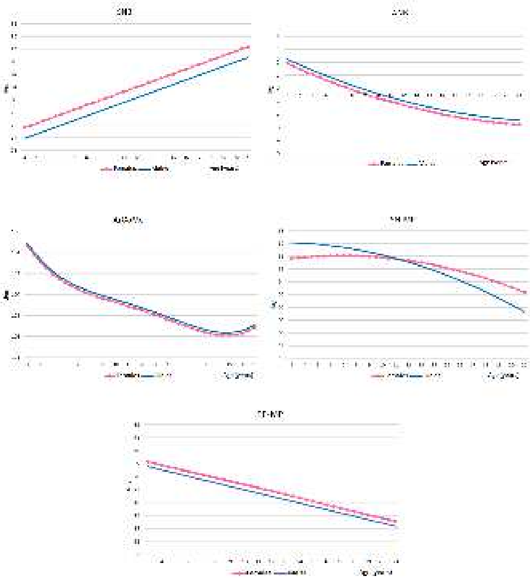

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