Predicting mandibular growth based on CVM stage and gender and with chronological age as a curvilinear variable

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Abstract

Objective: the aim of this study was to develop a prediction model that combines the information derived from chronological age (analyzed as a curvilinear variable), gender, and the CVM method to predict mandibular growth. **Settings and sample population:** 50 participants (29 females, 21 males) were selected from the AAOF Craniofacial Growth Legacy Collection, the Michigan Growth Study, and the Denver Child Growth study. **Materials and Methods:** In this investigation, 456 lateral cephalograms were analyzed by applying a mixed effect model. The outcome variable was the annualized increment in total mandibular length (Co-Gn) during the year following the lateral cephalogram on which the cervical stage and chronological age were evaluated. The predictive variables were chronological age up to the fifth order, gender, stage of cervical vertebral maturation, as well as interactions between age and gender, age and cervical stage, and gender and cervical stage. **Results:** Cervical stage, chronological age up to the fourth order, gender, and the interaction between age and gender were significant predictors of annualized increments in mandibular length. The annualized increment in Co-Gn was significantly greater for CS 3 when compared to all other cervical stages. Further, annualized increments in Co-Gn for CS 1 and CS 2 were significantly greater when compared to CS 5. **Conclusions:** Cervical stage, chronological age, and gender can be used jointly to predict the annualized increment in mandibular growth. Cervical stage 3 exhibited the greatest annualized increase in mandibular length.

Introduction

The issue of optimal timing in dentofacial orthopedics is linked intimately to the identification of periods of favorable growth that can contribute to the efficient and effective improvement of skeletal problems in the individual patient. For example, it has been shown that the best timing to stimulate mandibular growth effectively in Class II patients with mandibular deficiency is during the pubertal phase of development.[1-3] Cephalometric investigations on longitudinal samples have identified a pubertal spurt in mandibular growth that is characterized by large individual variations in onset, duration, and rate.[4-7]

Several indicators of individual skeletal maturity have been proposed over the years to define treatment timing in orthodontics. The most commonly used indicators of individual skeletal maturity are increase in statural height,[8,9] skeletal maturation of the hand and wrist,[10,11] and the maturation of the cervical vertebrae (CVM method).[12-14] Several studies have investigated the role of the CVM method in predicting the pubertal growth spurt in the mandible.[9, 15-25]

To our knowledge, however, there is lack of information on the predictive power of the CVM method on mandibular growth in growing subjects.[21,22] Thus, the aim of the present study was to develop a predictive model that combines the information derived from chronological age, gender, and the CVM method to predict mandibular growth. In this investigation for the first time to our knowledge, chronological age was used as a curvilinear variable.

Materials and methods

Participants who had not received orthodontic treatment were selected from the records of the Fels, Iowa, Mathews and Oregon Growth Studies that are available through the American Association of Orthodontists Foundation (AAOF) Craniofacial Growth Legacy Collection Project (www.aaoflegacycollection.org). Moreover, the complete records of the University of Michigan Growth Study (after having removed the 30 subjects that were used in the previous study by Baccetti et al[13] to elaborate the CVM method) and of the Denver Child Growth Study were screened.

Inclusion criteria were:

- availability of a series of at least 6 consecutive annual lateral cephalograms from the age of 7 years to 18 years;
- the bodies of the second, third, and fourth vertebrae had to be visible in all films;
- the interval between 2 consecutive cephalograms had to range from a minimum of 6 months to a maximum of 18 months;

- the first cephalogram of the series had to show CVM stages CS 1 or CS 2;[7,8] and,
- the last cephalogram of the series had to show at least CVM stage CS 5.[7,8]

Exclusion criteria were incomplete records, radiographs of poor quality, anomalies in vertebral morphology, and evidence of orthodontic treatment (except when passive space maintainers were evident in the cephalograms). Two operators selected independently the participants from the Growth Studies. A third operator was consulted in case of uncertainties.

Increases in mandibular length (Co-Gn, the linear distance from Condylion to Gnathion) between consecutive cephalograms taken annually were calculated for the entire series of cephalograms for each participant. In that the interval between consecutive cephalograms was not always 12 months, the increases in Co-Gn were annualized. The outcome variable was the annualized increment in mandibular length during the year following the lateral cephalogram on which the cervical stage and chronological age were determined.

Mandibular length was measured on all cephalograms by the same examiner (L.F.) on the digital cephalograms using a cephalometric software (Viewbox 4.0, dHal Software, Kifissia, Athens, Greece). The value of Co-Gn was standardized to 0% enlargement (life size) after adjustment of the magnification factor of the different Growth Studies. Point Gnathion was defined as the most anteroinferior point on the contour of the bony chin. It was determined by bisecting the angle formed by the mandibular and facial (Nasion-Pogonion) planes.

The CVM method used in the present study was the one described by McNamara and Franchi.[8] The intermediate or in-between stages (when the characteristics of two consecutive stages were present in a single image)[8] were included in the more immature stage, i.e. the intermediate CS 3-4 was classified as CS 3.

The predictors used in developing the multivariable prediction model first was chronological age up to the fifth order (the second order, or quadratic term, describes a parabolic curve while the third order, or cubic term, indicates the presence of inflection point in the curve; in general, the higher the order, the more complex the polynomial curve; Fig. 1). Then gender was considered. The stage of development of the cervical vertebrae also was determined as an ordinal variable (CS 1, CS 2, CS 3, CS 4, CS 5, or CS 6). Interactions among these variables also were evaluated. All cephalograms were staged according to the CVM method by a single expert examiner (L.F.).

All participants from the Growth Studies who met all inclusion/exclusion criteria were included in this study. We followed the TRIPOD statement[26] for transparent reporting of a multivariable prediction model. This study was conceived as a Type 1a analysis[26] (development of a prediction model where predictive performance is evaluated directly using the same data).

Statistical analysis

Intra-examiner reproducibility for the CVM stages and for the Co-Gn measurement was calculated on 30 randomly selected cephalograms after 2-week washout period with the weighted kappa coefficient for ordinal data and with the intraclass correlation coefficient, respectively. Random error for the Co-Gn measurement was assessed with Dahlberg's formula.

Descriptive statistics were performed for the following variables: gender, chronological age and CVM stage.

As for inferential statistics, a mixed effect model was applied. As mentioner earlier, the outcome variable was the annualized increment in mandibular length (Co-Gn) during the year following the lateral cephalogram on which the cervical stage and age were determined. Random effect was the participant (random effect is the effect that arises from uncontrollable variability within the sample, and it is usually attributed to the participants). The predictive variables (fixed effects) were chronologic age up to the fifth order, gender, cervical stages (categorical variable - CS 1, CS 2, CS 3, CS 4, CS 5, or CS 6), interactions between age and gender, age and cervical stage, and gender and cervical stage. The interactions and age from second up to fifth order were included in the model only if they were statistically significant. Post-hoc test for CVM stages was evaluated with Tukey HSD. A residual graphical analysis was performed to test model assumptions.

The level of statistical significance was set at $P<0.05$. The statistical computations for the intra-examiner reproducibility and for the mixed model were performed with specific software (MedCalc®, version 19.0.3, MedCalc Software bvba, Ostend, Belgium and JMP ® vers. 13.0.0, SAS Institute Inc, Cary, NC, USA).

Results

From a parent sample of 1151 subjects a final sample of 50 participants (29 females and 21 males) was derived. Six cases (5 females and 1 male) were derived from the Fels Growth Study, 2 (1 female and 1 male) from the Iowa Growth Study, 3 (1 female and 2 males) from the Mathews Growth Study, 24 (15 females and 9 males) from the Oregon Growth Study, 3 (1 female and 2 males) from the XXXXXX Growth Study and 12 (6 females and 6 males) from the University of XXXXXX Growth Study.

The intra-observer reproducibility for the CVM method and for the Co-Gn measurement was "almost perfect"[27] (CVM method: 0.87, 95% Confidence Interval, CI, 0.77-0.96; Co-Gn: 0.99, 95% CI 0.99-1.00). The random error for the Co-Gn measurement was 0.57 mm.

In this investigation, 456 lateral cephalograms were analyzed. The mean number of cephalograms per participant was 9.1 ± 1.2 (minimum 6 and maximum 12 cephalograms). In Table 1, the frequencies of the different CVM stages and the corresponding percentages and annualized increments in Co-Gn are reported. The mean age at the first cephalogram was 8.2 ± 0.5 years (min 7.5, max 9.9 years) while the mean age at the last cephalogram was 16.5 ± 1.1 years (min 14.0, max 20.2 years). The mean interval between 2 consecutive cephalograms was 1.0 ± 0.1 years [min 0.75, max 1.49].

As for inferential statistics (Table 2), the model showed a significant effect for cervical stage, for age up to the fourth order, for gender, and for the interaction between age and gender. Cervical stage CS 3 exhibited the greatest annualized increase in Co-Gn. The fact that chronologic age was significant up to the fourth order implied that the annualized increase in Co-Gn varied in a complex manner as a function of age (see the complex curves in Figure 2).

As for gender, the annualized increase in Co-Gn was significantly greater in males. The significant interaction between age and gender indicated, however, that the difference between males and females varied with age. As chronological age increases, the difference between males and females also increased, favoring males. All other interactions and the fifth order for chronologic age were not significant and, therefore, not included in the final model. The analysis of residuals did not show any deviation from assumptions of the model.

Figure 2 was constructed based on the estimates of the mixed effects model reported in Table 2. Two examples of how to derive two points for the curves in Figure 2 are reported at the bottom of Table 2.

Table 3 reports the comparisons for the annualized increments in Co-Gn for each cervical stage. The annualized means were adjusted for age and gender. The annualized increment in Co-Gn was significantly greater for CS 3 when compared to all other cervical stages. Also, the annualized increments in Co-Gn for CS 1 and CS 2 were significantly greater when compared to CS 5.

Discussion

The aim of the present study was to develop a predictive model for mandibular growth using chronological age, gender, and the CVM method as predictive variables.

A unique feature of this study was entering chronological age in the predictive model as a curvilinear variable (polynomial curve up to the fifth order or degree, Figure 1). Using age as a curvilinear variable is important when analyzing mandibular growth changes with age. If age is entered as a linear variable (Fig. 1A), this means that we expect that mandibular growth should increase or decrease linearly along with age. We know, however, that mandibular growth is not linear with age but rather follow a curvilinear trend that is characterized, particularly during adolescence, by an acceleration that reaches a peak, followed by a deceleration in mandibular growth rate until the end of active growth.

In the literature, there is controversy on the reproducibility of the CVM method assessment. Some studies have reported poor reproducibility of the CVM method,[28] whereas other studies have reported the agreement for CVM staging to be substantial.[29] Reasons for the poor reliability have been attributed to the level of training, clinician experience, and methods of assessment.[29] In the current study the assessment of the CVM staging was performed by an expert examiner and the intra-observer reproducibility was almost perfect.

Summary of the findings

The results of the present study showed that the maturation of the cervical vertebrae, gender, and chronological age are related to mandibular growth in a significant manner. In particular, the greatest annualized increment in mandibular growth was found during the year following the appearance of CS 3. The smallest increases were found to occur after stages CS 5 and CS 6.

As for gender, in general, the increases in mandibular growth in male subjects were greater than in females. This difference can be visualized easily in Figure 2 where all the growth curves for males were higher than those for females for all CVM stages. At the age of 8-9 years all subjects were either in CVM stage CS 1 or CS 2 and the increases in mandibular growth were similar in males and females. From the age of 9 years onward, females already can be in stage CS 3, and they showed greater mandibular increases than males who are still in CS 1 or CS 2. In general, therefore, females tended to grow more than males during the early ages, while males showed longer and higher growth increases than females during later ages.

It is interesting to note that the curves CS 1 and CS 2 in females and males started from higher values at 8 years, then they reached a minimum around the age of 9 years followed by an acceleration of growth. This observation confirms the existence of a prepubertal minimum in mandibular growth that has been described previously.[4,5,7] The greatest increase in mandibular growth occurred at CS 3 for both females and males with annualized values of 3.2-3.3 mm at 12-13 years in females and with annualized values of 4.1 mm at 13-14 years in males.

The curves for stages CS 4, CS 5, and CS 6 were characterized by growth deceleration that is typical of the postpubertal growth phases. Our data also confirmed that mandibular growth diminishes substantially earlier in females (around 16-16.5 years) than in males (around 18-19 years).

Comparison with other papers

The results of the present study differ from those reported by Engel et al.[21] and Gray et al.[22] Engel et al.[22] assessed the performance of the CVM method in predicting mandibular growth in female subjects with Class II malocclusion selected from the Nijmegen Growth Study. A linear mixed model was applied in order to determine potential associations between increments mandibular growth (evaluated in a 6-month interval) and average across observers CVM scoring after adjusting for age.

A major limitation of the above-mentioned studies is that the CVM stage was considered as a continuous variable rather than a qualitative variable and that chronological age was evaluated as a continuous linear variable (implying that mandibular growth changes linearly along with age). In contrast to the present study, Engel et al.[21] concluded that there is no evidence to support the hypothesis that the CVM method can predict the amount of craniofacial growth in girls with Class II malocclusion. Our findings do not agree with this conclusion.

Grey and coworkers[22] analyzed the CVM method and its relationship to observed changes in mandibular length during growth. Mixed model analyses were used to determine the relationships between mandibular length, gender, CVM stage, and chronological age. Mandibular length represented the response variable, with gender and CVM stage entered as covariates. The interaction between CVM stage and gender also was assessed. The results showed that mandibular length was associated with chronological age and to a marginal extent with gender. No significant association was found between mandibular length and cervical stages. It should be noted, however, that the differences with the present study were that the outcome variable was mandibular length and not mandibular growth increments and that chronologic age was evaluated as a continuous linear variable.

Limitations of the study

It should be noted that the lateral cephalograms were collected in the various Growth Studies from the 1930's to the 1980's. Thus, these data could be affected by secular trends. [30,31]

The final sample was relatively small with respect to the parent sample analyzed. Moreover, small samples were gathered from diverse independent growth studies.

Another limitation was the lack of validation of the prediction model. Unfortunately, it was not possible to validate the prediction model on a different sample because all eligible subjects available through the AAOF Craniofacial Growth Legacy Collection Project, the University of Michigan Growth Study, and of the Denver Child Growth Study were included in this study. No other growth study was available.

Clinical implications

The results of the current study showed that CS 3 corresponds to the stage that precedes the year with the greatest annualized increase in total mandibular length in both males and females. Our data supports the recommendation that CS 3 represents the ideal stage to begin functional jaw orthopedics in Class II patients, as has been suggested previously by other investigations.[1-3] When a patient starts treatment at CS 3, after 2 years of functional jaw orthopedics followed by fixed appliances or aligners, it is likely that he/she will show a postpubertal stage CS 4-CS 5. This aspect works in favor of a better long-term stability. [3] On the contrary, if treatment with functional jaw orthopedics is started before puberty (CS 1- CS 2) the patient shows a temporary acceleration of mandibular growth that is followed by a relapse during the posttreatment period with an overall long-term effect that is similar to untreated Class II subjects.[3] Therefore, If the aim is to produce effective skeletal mandibular changes, the start of treatment with removable functional appliances should be postponed until puberty. On the other hand, if the correction of the Class II problem requires mainly dentoalveolar changes, treatment can be initiated before puberty.[3]

Conclusions

The present study developed a prediction model that combined the information derived from chronologic age, gender, and the CVM method to predict mandibular growth.

It was demonstrated that:

- Cervical stages, age up to the fourth order, and gender, were significant predictors for the annualized increments in mandibular growth.
- The annualized increment in Co-Gn was significantly greater for CS 3 when compared to all other cervical stages.

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Conflict of Interest Statement

None of the authors declare any conflicts of interest.

Authors' contributions

Lorenzo Franchi: conception and design, writing of the manuscript.

Michele Nieri: data analysis and interpretation of data.

James A. McNamara Jr.: conception and design, editing of the manuscript.

Veronica Giuntini: conception and design.

Data availability

Data are available on request from the authors.

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Figure legends

Figure 1: In the prediction model, chronologic age was considered as a polynomial up to the fifth order or fifth degree. Graphical representations of polynomials. A. First order or first degree polynomial (linear polynomial or linear function). B. Second order or quadratic term or second degree polynomial is represented graphically by a parabolic curve. C. Third order or cubic term or third-degree polynomial has a single inflection point, (a point where the function changes from being concave to convex, or vice versa) and 2 extrema (maximum or minimum). D. Fourth order or quartic term or fourth degree polynomial has 2 inflection points and 3 extrema. E. Fifth order or quintic term or fifth degree polynomial has 3 inflection points and 4 extrema.

Figure 2: Annualized increments of Co-Gn (y axis) as of function of age (x axis), gender and cervical stage.

Table 1: Frequencies and percentages of the CVM stages with correspondent mean and standard deviation of the annualized increment in Co-Gn

Vertebral Stages	Frequency (n)	Percentage	Annualized increment in CoGn (mm)	
			Mean	SD
CS 1	140	31%	2.3	0.9
CS 2	62	14%	2.4	0.9
CS 3	86	19%	3.5	2.0
CS 4	57	12%	1.8	1.5
CS 5	72	16%	1.0	1.0
CS 6	39	9%	1.1	0.9
Total	456	100%	2.3	1.5

Table 2: Mixed effect model. Outcome variable: annualized increment in CoGn. Predictive variables: CVM stage, age up to the fourth order, gender and interaction age*gender. In presence of CS6 the estimate is 0. For male subjects the estimate is 0. Age^5 was not statistically significant.

Variable	Estimate	Standard Error	P value
Constant (intercept)	64.9905	25.54	
CS1	0.9211	0.43	
CS2	0.9660	0.44	
CS3	1.8190	0.39	<0.0001
CS4	0.3245	0.37	
CS5	-0.0984	0.37	
Age (years)	-21.2229	8.55	0.0135
Age^2	2.5398	1.05	0.0161
Age^3	-0.1286	0.06	0.0223
Age^4	0.00233	0.001	0.0347
Gender F	-0.6640	0.12	<0.0001
(Age-11.87)*gender (F)	-0.1556	0.05	0.0037

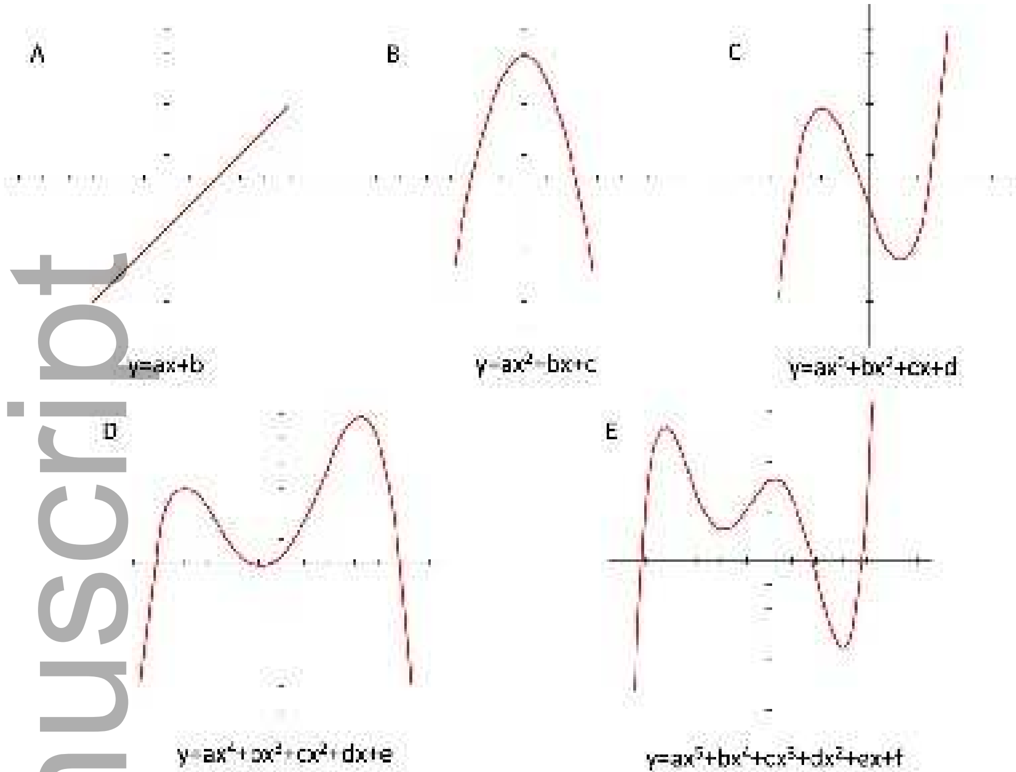
Formula for CS3 Female subject at 12 years: $64.9905 + 1.81890 - 21.2229*12 + 2.5398*12^2 - 0.1286*12^3 + 0.00233*12^4 – 0.6640 – 0.1556\,(12 – 11.8714) = 3.27$

Formula for CS2 Male subject at 10 years: $64.9905 + 0.9660 - 21.2229*10 + 2.5398*10^2 - 0.1286*10^3 + 0.00233*10^4 = 2.41$

Table 3: Statistical comparison between the cervical stages. The mean of the annualized increment in Co-Gn was adjusted for age and gender. The column "Diff from CS3" reports the differences between the CS3 mean and the means for the other CVM stages. The column "Diff" indicates the statistically significant differences between the stages. In the last column stages with a different letter indicate a statistically significant difference.

CVM	Adjusted Mean (mm)	Diff from CS3 (mm)	95%CI Diff from CS3	Diff
CS1	2.4	0.9	0.2; 1.6	B
CS2	2.4	0.9	0.2; 1.5	B
CS3	3.3	-	-	A
CS4	1.8	1.5	0.8; 2.2	BC
CS5	1.4	1.9	1.1; 2.7	C
CS6	1.5	1.8	0.7; 2.9	BC

Diff: Difference



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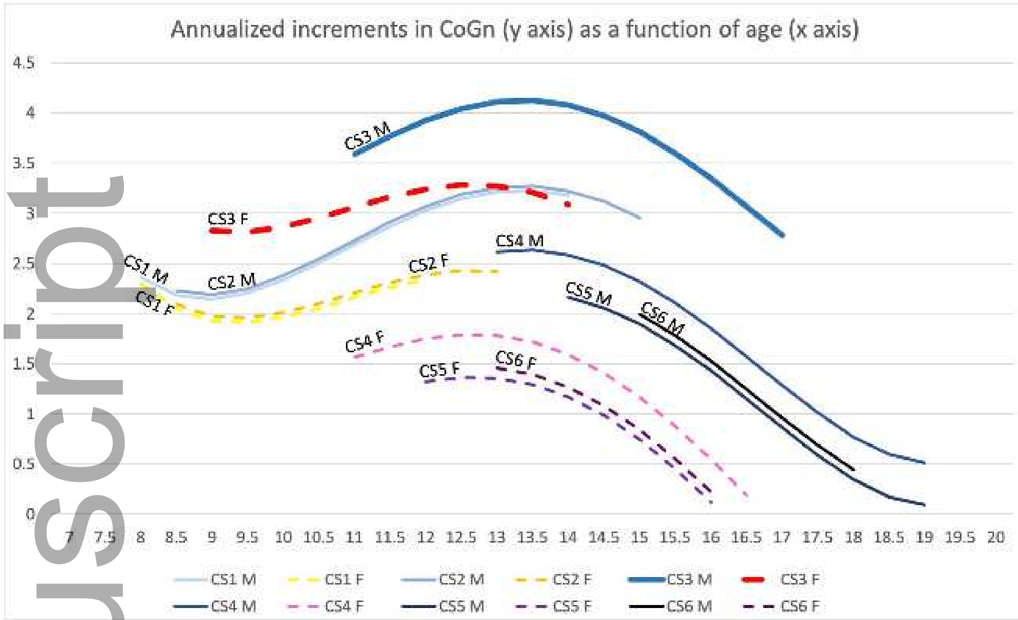

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