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The role of the nasal region in craniofacial growth: an investigation using path analysis

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Running title

Interactions among facial regions in ontogeny

Abstract

This study focuses on the role of the nasal region and its interactions with adjacent facial elements during early ontogeny. A series of linear measurements, areas and volumes were extracted from a collection of 227 medical CT-scans of children from 0 to 6 years of age. These measurements describe aspects of the form of the orbit, maxilla, peri-alveolar (subnasal) region, nasal area, eye, oral region, masseter, and temporal muscles. Hypothesised interactions were then examined using path analysis. Two paths were designed: the first to investigate potential interactions in, and relative contributions of the nasal derivatives and adjacent regions to overall facial growth and development; the second path sees the addition of facial soft tissue measurements and aims to assess their effects on skeletal components, and on overall facial growth and development. The results of the first path indicate a large contribution of the nasal and subnasal regions to facial development. This indicates that the nasal septum and the developing dentition provide an important but variable contribution to facial ontogeny during early years. This result is confirmed in the second path, where the soft tissue elements were added to the diagram. Results of the second path indicate that the soft tissues contribute only locally to the development of some skeletal elements of the face. This indicates that the contribution of skeletal components has a more direct effect on facial height than soft tissue matrices, however there are complex interactions between soft tissues and skeletal elements throughout ontogeny.

KEYWORDS: path analysis, ontogeny, nasal septum, matrices

INTRODUCTION

Human craniofacial ontogeny has been the subject of intensive work in several disciplines. This body of research spans from studies of evolutionary patterns of variation in hominins (O'Higgins et al., 2000; Ponce de Leon and Zollikofer, 2001; Ackermann and Krovitz, 2002; Cobb and O'Higgins, 2004; Bastir et al., 2007), through anthropological analysis of current growth trends in different modern populations (Viðarsdóttir et al., 2002; Gonzalez et al., 2010), to the creation of normative reference data for surgical and clinical studies (Buschang et al., 1983; Waitzman et al., 1992a, 1992b; Landes et al., 2002; Gkantidis and Halazonetis, 2011; Jiang et al., 2015). The common aims are to describe ontogenetic transformations and understand mechanisms that regulate craniofacial growth; how the cranium grows and develops to reach its final size and shape and the major driving forces and constraints acting over ontogenetic and evolutionary time. Many studies have addressed interactions among the cranial base, neurocranium and mandible and their influence on human craniofacial development (Enlow 1975; Lieberman et al., 2002; Bastir and Rosas, 2006; Bastir et al., 2006; Richtsmeier & DeLeon, 2009; Singh et al., 2012; Barbeito-Andrés et al., 2015; Bastir & Rosas, 2016; Zollikofer et al., 2017). These suggest a hierarchy of ontogenetic interactions that impacts on the development of aspects of facial form such as its vertical development, its orientation and prognathism (*e.g.* Lieberman et al., 2002; Bastir and Rosas, 2006; Bastir et al., 2008; Neaux et al., 2015).

Although patterns of craniofacial growth, development and interactions among regions are increasingly well understood, there is a lack of clarity about the hierarchy and modes of these interactions, especially when considering parts (subregions) of the face (Bastir and Rosas, 2004; Martinez-Abadias et al., 2009; Barbeito-Andres et al., 2011; Butaric and Maddux, 2016; Esteve-Altava, 2017; Maddux and Butaric, 2017). Several attempts have been made to identify the drivers of change in the facial region during ontogeny, with contrasting results supporting either the soft tissue or the (cartilaginous) skeletal components as the principal pacemakers for facial growth and development (McLaughlin, 1949; Scott, 1956; Latham and Burston, 1964; 1970; Wexler and Sarnat, 1965; Moss, 1968; Babula et al., 1970; Diewert, 1985; Delaire and Precious, 1987; Grymer et al., 1989; Grymer et al., 1991; Pirinen, 1995; Verwoerd and Verwoerd-Verhoef, 2007; Wong et al., 2010; Holton et al., 2011; 2012; Al Dayeh et al., 2013; Hall and Precious, 2013; Goergen et al., 2017).

Some authors, based on experimental evidence, posit that, during ontogeny, the skeletal elements act purely as a supporting framework around the so-called capsular (spaces, volumes or organs) and periosteal (muscles, blood vessels, nerves) "functional matrices" (functional matrix model,

Moss and Young, 1960; Latham and Burston, 1964; Moss, 1968; 1997; Moss et al., 1968; Babula et al., 1970; Goergen et al., 2017). Each functional matrix, defined as [...] "non-skeletal cells, tissues, organs, and operational volumes" in the body (Moss, 1997), has an associated skeletal capsule (bone or cartilage) that is subordinate to and supportive of the growth and development of the matrix it encloses. Thus, bone formation and remodelling would be directly genetically controlled only to a minor degree and largely subordinated to the corresponding developing functional matrix. However, much experimental and clinical evidence suggests that the expansion and development of the cranium is mainly driven by actively expanding cartilages, central among them being the nasal septal cartilage (Scott, 1954; 1956; 1962; Pirinen, 1995; Herring, 2008; Wong et al., 2010; Holton et al., 2012; Al Dayeh et al., 2013; Hall and Precious, 2013). Differences in conclusions of these studies may be attributable to differences in the choices of species (so, in the form of sutures, articulations of bones and associated soft tissues) and in approaches and sampling (e.g. by focusing on different areas at different times of development). Plausibly, both soft tissue matrices and cartilages are drivers of change in the facial region during ontogeny with the balance among their influences varying spatially and temporally.

In this paper, growth interactions among facial skeletal components are assessed using path analysis, applied to a large sample of CT-scans with the aim of better understanding the mechanisms and hierarchies of growth and development among facial elements during the first six years of life. Path analysis is a statistical method, first conceived by Wright (1921, 1934) as a means of testing the interactions between multiple variables in a system, to understand the functional relations among them. It has been applied in psychology and social sciences to investigate the proportion of contribution of a series of variables to social outcomes (Duncan, 1966; Pajares and Miller, 1994; Streiner, 2005; Rudasill and Rimm-Kaufman, 2009). More rarely, it has been applied to analyse the developmental and evolutionary hierarchical interactions among anatomical elements based on the *a priori* construction of hypothesised relations (Mooney et al., 1989; Bullmore et al., 2000; Holton and Franciscus, 2008; Zollikofer et al., 2017).

In the present study, hypothesised interactions among developing skeletal facial elements are analysed using path models applied to sequential age stages and over years 0-6. These results are then compared with those from a path that also includes measurements of capsular and periosteal functional matrices as defined by Moss (Moss and Young, 1960; Moss, 1968; Moss et al., 1968; Moss and Salentijn, 1969). The aim of this is to investigate likely interactions among hard tissues, and among these and facial soft tissues. In particular, these analyses will test hypotheses concerning potential drivers of facial growth, first elaborated by Scott (1954; 1956; 1962) and Moss

(Moss and Young, 1960; Moss, 1968; Moss et al., 1968). As applied in this study, path analysis aims to yield information about the proportional contribution of the skeletal and soft tissue variables to the growth and development of facial height in the early years.

The first path (P1, Figure 1) is designed to test the relative contributions of different facial skeletal elements to the vertical growth of the face. Uniquely, it does so by comparing developmental interactions at different age stages, by dividing the sample into annual groups from 0 to 6 years. This path tests the intrinsic growth model, that primary cartilaginous growth centres (i.e nasal septum) drive facial growth. The second path model (P2, Figure 1) assesses the contributions of soft and skeletal tissues to facial ontogeny. This path aims to test aspects of the functional matrix hypothesis, that soft tissues interact with skeletal elements to drive facial growth.

In a path diagram, the relationships and postulated interactions among variables are indicated by arrows. A variable with no arrows pointing toward it indicates an independent (or exogenous) variable, not affected by any of the others. A variable with one or more arrows pointing toward it is a dependent variable that has one or more independent variables hypothesised to act on it. Bidirectional arrows indicate hypothesised two-way interactions between variables (covariation). Note that a variable can act as dependent or independent, depending on the hypothesised interaction that is tested in that analysis. A path can contain multiple exogenous variables, that are not dependent on others. A variable that acts on, and is acted upon by, other variables is an intermediate endogenous variable. The final variable of the path is never independent. A sub-path is a specific route through the diagram, leading from one exogenous variable to the final variable of the path (Stage et al., 2004). After building a path diagram, the strengths of the hypothesised interactions between dependent and independent variables are tested using standardised multiple regressions. Standardised coefficients have a mean of 0 and a standard deviation of 1. The resulting standardised partial regression coefficients, termed β coefficients or path coefficients, indicate the change in the dependent expected when there is a one-unit change in that particular independent variable while holding all the other independent variables constant (Allen, 1997). Additionally, the proportion of the total variance of each dependent variable explained by the independent ones in the path leading to it is assessed by computing the R^2, or the coefficient of determination.

The first path diagram (P1, Figure 1) was designed to test hypothesised interactions among the orbit, the derivatives of the nasal capsule, the maxilla and the peri-alveolar region in the development of facial height, considered as a proxy for overall facial development and total proportions. The first hypothesis uses P1 to test these potential interactions.

Hypothesis 1. *The interactions within the sub-path leading from anterior septal height to facial height are stronger than those in the sub-path leading from orbital height to facial height in all age groups.*

The variables used in the path diagram were selected by considering their function and development; each not only serves a different purpose within the facial complex but is also derived from a different growth centre. Orbital height and medial orbital height were used as proxies for orbital growth and development; the anterior height of the nasal septum was chosen as a proxy for the vertical growth and development of nasal capsule derivatives, specifically the septum; the subnasal and maxillary heights were chosen as proxies of, respectively, peri-alveolar and midfacial growth and development.

In the path P1 (Figure 1), the role of the anterior septal height on facial elements is compared to that of orbital height (proxy for the growth of the orbital region). This first path diagram aims to test Scott's nasal septum hypothesis (1954). In his theory, Scott (1954) states "[…] The cartilage of the nasal septum is an important factor in separating the bony elements which have developed around it and may be regarded as a pacemaker for facial growth. This power of cartilage to separate growing bones at sutures resides in its method of interstitial growth, its turgidity and its ability to resist deforming forces" (Scott, 1954). This position has been supported by Hall and Precious (2013), who, reviewing extensive evidence from *in vivo*, *in vitro* and surgical records, suggest that vertical nasal septum growth is the prevalent force acting on facial growth when compared to other skeletal and soft tissue facial elements. Furthermore, experimental studies in animals, in which vertical facial growth was constrained, show evidence that this restriction causes changes in premaxillary subnasal growth and displacement due to continued nasal septal growth (Holton et al., 2011).

Therefore, in path P1, anterior septal height is chosen as an independent exogenous variable, hypothesised here to not be influenced by the other skeletal variables in the model but rather, acting as a pacemaker for growth of the entire facial skeleton and all its variables. Another hypothesised independent variable in the first path P1 is orbital height. This is because in the early years, the growth and development of the orbit are rapid compared to other facial regions (Barbeito-Andres et al., 2016; Evteev et al., 2018). This plausibly has a major impact on facial morphology in not only largely defining facial form during early stages but also driving the growth, development and changing proportions among other facial elements (Sarnat, 1982; Farkas et al., 1992; Furuta, 2001).

Therefore, in P1, to assess and compare the influence of these two exogenous variables, arrows from nasal and orbital heights point at the intermediate variables of medial orbital height, maxillary and subnasal height and at the final variable of facial height.

Specifically, medial orbital height is potentially influenced by the growth of the maximum height of the orbit, but it could also reflect the development of the adjacent nasal bridge, growth of which is directly proportional and potentially linked to the growth of the nasal septum (Mondin et al., 2005). Therefore, in the path diagram P1 (Figure 1), arrows point at this variable from the nasal and orbital heights.

In addition, the vertical development of the maxilla is potentially influenced by the rapid growth of the orbit during early childhood (Pool et al., 2020). Furthermore, several studies have proposed that the maxillary and subnasal regions are each primarily influenced by the nasal septum, given its central position within the maxilla and its anatomical connections at its inferior border with the palate and the peri-alveolar region (Holton et al., 2011). Therefore, in P1, maxillary height is hypothesised to act as a dependent variable, affected by anterior septal and orbital heights, while subnasal height is hypothesised as being influenced by anterior septal height. In addition, subnasal height is hypothesised as dependent on maxillary height. Indeed, the vertical development of the maxilla has been hypothesised to impact on the development of the adjacent subnasal premaxillary region, in that patients with maxillo-palatal deformities show abnormal premaxillary growth and development (Liao et al., 1998). Therefore, in this interaction, maxillary height is hypothesised to act as independent variable on subnasal height, and through that on facial height. To end the path, all the variables, exogenous and intermediate, act on overall facial growth (facial height).

[Figure 1]

The aim of the second path diagram (P2, Figure 1), is to compare the role of the skeletal and cartilaginous components of the face with that of some of the cranial functional matrices proposed by Moss (1960) in influencing facial height during growth. Therefore, a second hypothesis is tested using P2 to assess interactions among both soft and skeletal tissues during facial ontogeny. This second hypothesis states that:

Hypothesis 2. *The interactions within the sub-paths leading from the soft tissue elements to facial height are greater than those in the sub-paths leading either from orbital or anterior septal height to facial height.*

The second path (Figure 1, P2) considers the masseter and temporal cross-sectional areas (as proxies for muscle forces) and the intra-oral soft tissue and orbital volumes (cube roots) as exogenous variables acting on the maxilla, subnasal, medial orbital and facial skeletal measurements. They do this together with the skeletal exogenous variables of orbital and anterior septal heights. In addition, potential two-way interactions between orbital volume and orbital height are represented by a double-ended arrow.

If the impact of capsular and periosteal matrices (the exogenous variables of the intra-oral soft tissue, globe volume and the masseter and temporal areas) on the intermediate variables representing their skeletal support and on the final facial height variable is bigger than the influence exercised on the same variables by the independent exogenous variables of the septum and orbit, this would support Moss's interpretation of the mechanisms of craniofacial growth and development.

MATERIAL AND METHODS

The sample

The sample used for the skeletal measurements to test the first path (P1) comprises 227 specimens (CT-scans), from the National Scientific and Practical Centre of Children's Health (SCCH), Moscow (Russia) (see Evteev et al., 2018 for details). The use of this dataset was approved by the Independent Ethics committee at the SCCH, Moscow (Russia), and by the Hull York Medical School Ethics Committee, York (UK). A subsample of 46 specimens was used to measure soft and skeletal tissues to test the second path (P2).

For the analyses, the sample of 227 individuals used to test the first path (P1) was divided into age groups as follows: 0 to 1 year (91 specimens), 1 to 2 years (27 specimens), 2 to 3 years (25 specimens), 3 to 4 years (27 specimens), 4 to 5 years (32 specimens), 5 to 6 years (25 specimens) and then combined (0 to 6 years). Due to limitations in sample size, the second path was tested using a limited sample of 46 specimens, which includes: 17 specimens of 0 to 1 years, 8 specimens of 1 to 2 years, 5 specimens of 2 to 3 years, 7 specimens of 3 to 4 years, 3 specimens of 4 to 5 years and 6 specimens of 5 to 6 years.

240

241 **Skeletal measurements**

242 Before acquiring the measurements, the skulls were first oriented to the Frankfort plane axially
243 and along a symmetric midline plane vertically.

244 Linear distances were computed between pairs of landmarks on the 3D surface mesh of the skulls,
245 after segmentation and 3D reconstruction of the CT-scans. Landmarks were acquired using Avizo
246 9.0, the computation of Euclidean distances was performed using R studio.

247 The landmarks and the measurements acquired for the study are described in Table 1 and Figure
248 2.

249

250 [Table 1]

251 [Figure 2]

252

253 **Soft tissue measurements**

254 A series of soft tissue measurements was acquired on the CT-scans. The segmentation and
255 measurements were undertaken using Avizo 9.0. To measure the soft tissues, the skull was first
256 reoriented to the Frankfort plane axially and along a symmetric midline plane vertically.

257 The radius of the eye was measured after selecting the slice with the largest globe width and height
258 in the axial plane (Figure 3, A). The volume of the globe was then estimated using the radius. For
259 the linear regression analysis, the cube root of the globe volume was used.

260

261 [Figure 3]

262

263 The cross sectional areas of masticatory muscles were measured and used as proxies for force in
264 the subsequent path analyses. The cross-sectional area of the temporalis was segmented and
265 measured along the axial plane using the slice at which the zygomatic arch was completely visible
266 when scrolling from the most superior to the most inferior slice in axial view (Figure 3, B). The
267 cross-sectional area of the masseter was segmented and measured in the axial plane by choosing

the slice at the midpoint of the mandibular lingula (Figure 3, C). These muscle measurements followed a standard procedure as defined by Toro-Ibacache et al., (2016) and they represent cross-sectional areas where the muscles are the largest and vary little in size between adjacent slices (Toro-Ibacache et al., 2016).

The intra-oral soft tissues including the tongue, sublingual musculature and the soft palate were segmented in sagittal view along the midsagittal line (Figure 3, D).

The breadth of the tongue was then measured between the buccal fat pads in the coronal plane in the slice located at the angle between the mandibular body and the mandibular ramus. The volume of the tongue and its related musculature which we call the 'intra-oral soft tissue volume' was approximated by multiplying the sagittal area of the tongue and its related musculature by tongue breadth. For the linear regression analysis, the cube root of the intra-oral soft tissue volume was used.

Statistical analysis

To assess the accuracy of the soft tissue measurements, three specimens were measured five times over five weeks. Analysis of variance (ANOVA) was performed to test if measurement replicates were reproducible. The ANOVA was performed using the 5 replicates of the 3 individuals as dependent, and "specimen" as independent. It showed a significant difference between specimens (Df: 1, F: 55.134, p-value: 0.001**) but not replicates, indicating that the measurement replicates are consistent with specimen means.

The extent to which the hypothesised paths are supported by data was assessed by standardised multiple regression analysis, testing the interactions indicated by the arrows in the models. A series of standardised multiple regressions were performed, as structured in the paths and sub-paths, each time considering the effect of one or multiple independent variables on a dependent one. Each standardised multiple regression returned a series of beta coefficients (β- also called path coefficients), indicating the net impact of each independent variable on the dependent one, once the other independent variables, affecting the same component, are taken into account (Holton and Franciscus, 2008; Garson, 2013). For each regression, R^2 indicates the proportion of the variance of the dependent variable accounted for by the regression. Note that if, in a path, all tested associations are significant, by looking at the beta coefficients, it is possible to determine the relative strengths of different sub-paths.

For the first path (P1), the results were obtained by re-running the same path analysis after dividing the sample into age groups. For the second path (P2, Figure 1), due to limited sample size, a single analysis pooling all individuals from 0 to 6 years was performed.

RESULTS

Path 1

Figures 4 to 10 represent the results at different ages for the first path (P1), which hypothesises a cascade of influence of different skeletal variables on facial height.

The results for the path diagram from 0 to 1 year (Figure 4) indicate that each variable makes a significant contribution to facial height, with the exception of medial orbital height. In turn, medial orbital height is influenced by orbital height (β= 0.59***) but not affected by anterior septal height (non-significant). Anterior septal height and orbital height directly interact to similar degrees with facial height (β= 0.24*** and β= 0.21***, respectively). Maxillary height is more dependent on orbital (β = 0.48***) than anterior septal height (β= 0.29*), with half of its variance explained by these two variables (R^2= 0.53). Subnasal height is not affected by anterior septal height but only by maxillary height (β= 0.40**) , however the proportion of the total variance of subnasal height explained by this interaction is low (R^2 = 0.22). Subnasal height makes a significant and strong contribution (β= 0.59***) to facial height and the significant variables in the path collectively explain 94% (R^2= 0.94) of the total variance in facial height. The greatest and most significant β coefficients are found in the sub-path leading from orbital height to facial height through maxillary height. While both nasal and orbital heights both directly and indirectly contribute to facial height, the indirect effect of orbital height is greater, while their direct effects are comparable.

[Figure 4]

The second analysis (Figure 5) assesses the same hypothesised interactions among facial elements, but in infants from 1 to 2 years old. In this, nearly all of the significant β coefficients in the previous model (Figure 4) become larger. However, maxillary height is only influenced by anterior septal height (β= 0.45*) and not by orbital height. In addition, maxillary height no longer directly

contributes to overall facial height but does so indirectly through its influence on subnasal height (β= 0.48*).

[Figure 5]

Thus, after the first year of life, as the growth and development of the orbital region slows, changes in orbital height no longer contribute to the development of maxillary height while anterior septal height continues to influence maxillary height. However, the R^2 of this regression, i.e. the variance of maxillary height explained by anterior septal height, is low (R^2= 0.12). This is also true for the impact of maxillary height on subnasal height (R^2= 0.12). This suggests that other elements not present in the path likely impact subnasal height which, in this age range, has an even stronger standardised partial regression with facial height (β= 0.74***). Overall this path continues to explain a very high proportion of the total variance in facial height (R^2= 0.91), albeit with a different balance of direct and indirect influences of independent variables.

The third analysis (Figure 6) assesses the same hypothesised interactions between 2 and 3 years. Interestingly, none of the indirect beta coefficients is significant, while the direct effects of the independent variables on facial height remain significant (except for maxillary height, which was already non-significant in the path of Figure 5), although reduced in magnitude. It is as if, at this stage, there is a lack of integration among facial elements, and although they grow and change, they do not interact and do not influence the other variables in the path. Despite this apparent difference from earlier stages in development, the direct interactions still account for a large proportion of the total variance in facial height (R^2= 0.80).

[Figure 6]

The fourth analysis (Figure 7) explores the interactions among facial elements from 3 to 4 years. Only subnasal height has a significant influence on facial height (β= 0.94***). The proportion of the total variance in facial height explained by this relationship is large (R^2= 0.82). Uniquely, in this age range, orbital height has a weak, negative relationship with maxillary height (β= -0.37*), explaining a small proportion of its total variance (R^2= 0.17).

[Figure 7]

From 4 to 5 years (Figure 8), facial height is only affected directly by anterior septal and subnasal heights (β =0.28** and 0.77***, respectively), which explain a high proportion of its total variance (R^2= 0.85). Anterior septal height also affects maxillary height (β =0.53**), although it accounts for a small proportion of its total variance (R^2= 0.23). Likewise, orbital height has a significant influence on medial orbital height (β= 0.37*), but explains a small proportion of its total variance (R^2= 0.18). The other variables behave independently and do not interact.

[Figure 8]

From 5 to 6 years (Figure 9) the influence of anterior septal height and subnasal height on facial height remains similar to that in the 4-5 year age group (β= 0.15* and 0.77***, respectively). However, now both orbital height and maxillary height contribute directly to facial height (β= 0.47*** and β= 0.21** respectively). Anterior septal height also manifests a new and negative relationship with medial orbital height. Overall the direct effects (in ascending order) of anterior septal, maxillary, orbital and subnasal heights account for a very high proportion of the total variance in facial height (R^2= 0.93) in this age group.

[Figure 9]

Finally, the path is evaluated for the whole sample, from 0 to 6 years old (Figure 10). Facial height is almost completely explained by the effects of all the variables (R^2= 0.96). Anterior septal height and subnasal height make the strongest and most significant direct contributions to facial height (β= 0.44*** and 0.46***, respectively) while orbital height makes minor direct and indirect contributions. A substantial proportion of the total variance in medial orbital height (R^2= 0.62) and maxillary height (R^2= 0.70) is explained by other variables in the path while only 30% of the variance in subnasal height is explained by its relation with the independent variables. This

indicates that other variables not included in the path have an important role in the development of subnasal height and, through this, on facial height.

[Figure 10]

These results indicate that the relationships among skeletal facial dimensions are not constant during the first few years of postnatal life. Orbital height seems to have a significant role in affecting the growth and development of other facial elements and of overall facial height in the very early stages, while anterior septal height and subnasal height progressively become more dominant in influencing facial height later on and are dominant when analysing the whole sample.

Path 2

The results of the second path analysis (P2) are presented in Figure 11. All of the interactions that were assessed in this path (P2) are illustrated in Figure 1. In Figure 11, to avoid an overly complex diagram, the non-significant relations are not shown. The hypothesised paths among skeletal dimensions are topologically identical to the previous ones, testing the same hypothesised interactions, but this path diagram differs in the addition of soft tissue derived variables.

In this path (Figure 11), anterior septal height and subnasal height have the strongest and most significant direct effects on facial height (β= 0.32*** and 0.38*** respectively), while orbital height plays a smaller but significant role (β= 0.23***).

Anterior septal height does not affect any other variable in the path and so it does not impact on facial height indirectly. This is also the case for orbital height: while it has a significant and strong association with medial orbital height (β= 0.76***, R2= 0.67), the latter, as already seen in most of the analyses of path P1, has no impact on facial height. Maxillary height plays a significant indirect role in influencing facial height via its relationship with subnasal height but it has no significant direct influence. This is similar to Figure 10, in which maxillary height has only a small direct influence on facial height (β= 0.05*) and mainly acts through subnasal height.

When analysing the soft tissue components, not surprisingly, orbital height covaries with globe volume (double arrow, indicating an association rather than dependency of one variable on another, Figure 11, β= 0.54***), however, unlike orbital height, the globe has no direct impact on

facial height. The intra-oral soft tissues influence maxillary height and subnasal height (for both, β= 0.10**). The proportion of total variance in maxillary height explained by intraoral soft tissue volume is substantial (R^2= 0.71) despite the low β. The intraoral soft tissue volume, together with the masseter area, a surrogate for maximum masseteric force, and maxillary height explain a substantial proportion of the total variance in subnasal height (R^2= 0.73).

Masseter cross sectional area (force) significantly affects subnasal height (β=0.30*) but not that of the maxilla (non-significant). The cross sectional area (force) of the temporalis muscle has no significant relationship with any of the variables in the path.

[Figure 11]

In summary, there is a significant impact of the development of the intra-oral soft tissues on the maxilla and subnasal region in the first 6 years, the latter also being affected by the development of masseter cross sectional area (force) as well as the maxillary height. However, it is clear that the strongest and most significant relations lie among the skeletal elements and that facial height is influenced by nasal, subnasal and orbital heights. Interestingly, when the soft tissue elements are inserted in the diagram, anterior septal height no longer manifests a significant partial regression with maxillary and subnasal heights and it appears to act only independently and directly on facial height. The temporalis muscle area (force) does not significantly interact with any facial variable. The volume of the globe, as one might expect, covaries with the vertical height of the orbit but has no other significant relation with the variables in the path.

DISCUSSION

This study examined the interactions among facial elements in children from 0 to 6 years. The aim was to determine the relative contributions of skeletal and soft tissue variables to facial height during growth and development. Thus, alternative hypotheses relating to the potential drivers of facial height are tested by comparing the effects of anterior septal height on facial height with those of other skeletal and soft tissue variables. First, a path diagram was designed to test the hypothesised effects of skeletal variables on each other and their effects on facial height. In this path (P1), the anterior septal height (used as proxy for anterior nasal septum growth) and orbital height were hypothesised to be exogenous variables, acting on the intermediate variables of

maxillary height, subnasal height and medial orbital height. All these variables were then hypothesised to contribute to facial height. The design of this path is based on prior studies, reviewed in the introduction, and aims to test alternative hypotheses of soft and hard tissue interactions.

Hypothesis 1 stated that the interactions within the sub-path leading from anterior septal height to facial vertical height are stronger than those in the sub-path leading from orbital height to facial height in all age groups. The path P1 allowed testing of this.

The results indicate that the interactions among facial components are not constant throughout ontogeny. In the first year of life (0 to 1 year), both orbital and anterior septal heights contribute significantly to overall facial height as well as to maxillary height. All the intermediate variables also make a significant contribution. However, the strongest sub-path is the one leading from orbital height, through its direct impact on maxillary height and its indirect effect on subnasal height via maxillary height, and finally to overall facial height, suggesting the influence of the orbit is dominant in the first year of life.

These relationships rapidly change starting from the second path (1 to 2 years, Figure 5). In this, the orbit still significantly contributes to facial height but has no interaction with the midface (maxillary and subnasal heights). From 0 to 1 and 1 to 2 years old, subnasal height is the variable with the most significant influence on facial height. In turn, subnasal height is not significantly influenced by anterior septal height but is influenced by maxillary height.

Figure 6 (2 to 3 years) suggests a phase of decreased integration, or increased modularity, in which nasal, orbital and subnasal heights all contribute to facial height but do not interact with any other elements in the path. This phase of increased modularity becomes extreme in Figure 7 (3 to 4 years), in which only subnasal height strongly influences facial height.

Between 4 and 6 years, the other variables return to contribute to the dynamics of the paths. Anterior septal height (Figure 8) and orbital height (Figure 9) influence facial height, together with subnasal height. Initially, in this age range, anterior septal height contributes significantly to maxillary height but later this interaction is lost. Finally, considering interactions over the entire sample (0 to 6 years, Figure 10), it is evident that anterior septal and subnasal heights make the largest and most significant contributions to facial height, with orbital height contributing less strongly. Indeed, subnasal height is the main contributor to facial height in all the tested paths.

Overall, interactions among variables change over time with anterior septal and especially subnasal heights showing the greatest and most consistent interactions with facial height.

Considering the link between these two structures, the nasal septum lies in close anatomical relation to the palatine bones and the alveolar maxilla. Holton et al., (2010) found that the nasal septum and premaxilla are highly integrated in animals and that the former influences the growth of the latter, with implications for hominin facial reduction.

However, while our results agree with the nasal septal hypothesis, which sees a dominant role of the nasal septum in facial growth, they also suggest that the subnasal region has a similar impact on overall facial height as the nasal septum. Additionally, we find that there is a large increase in the explained variance of subnasal height when masseteric force and intra-oral soft tissue volumes are included in the path (Figure 11). Thus, soft tissues rather than the anterior septal height primarily affect the growth and development of the subnasal region and its growth is a major contributor to the development of facial height.

Indeed, in this study, our results indicate that subnasal height is influenced intermittently by the nasal septum, as well as by the height of the maxilla and the soft tissue components. In addition, it is interesting to note that subnasal height is especially dominant in influencing facial height during the 2^{nd} to 4^{th} years of life. This could reflect the eruption of the deciduous anterior maxillary dentition, which becomes fully functional around the 3rd year (Dean and Turner, 2016) alongside the developing permanent dentition within the alveolus.

Orbital height also has significant, but progressively less strong interactions with facial height and the other variables. This finding is in line with prior work on orbital growth that found, in children, that the most rapid and significant growth in orbital height occurs in the first year of life (Evteev et al., 2018). Therefore, from the results in Figures 4-10, it is evident that, after the first year, the orbit does not make as important a contribution to facial height as anterior septal height and that anterior septal height has a greater impact on facial height and the intermediate variables over time.

Therefore, while skeletal interactions change over time, the strong and significant relationship of anterior septal height with variables describing adjacent structures and with facial height does not falsify Hypothesis 1. Our results evidence an important but variable contribution of anterior septal height and so, of the nasal septum to the determination of facial height.

Hypothesis 2 was tested to examine the interactions of both soft and skeletal tissues during facial ontogeny. It stated that the interactions within the sub-paths leading from the soft tissue elements to facial height are greater than those in the sub-paths leading either from orbital or anterior septal height to facial height.

For this hypothesis, a path was designed that included the significant parts of the skeletal paths tested in Hypothesis 1 together with variables reflecting the functional matrices of the intra-oral soft tissue, globe, and facial muscles, as defined by Moss (Moss, 1968; Moss et al., 1968). In testing this hypothesis, the aim was to determine if the soft tissue matrices have a stronger influence on facial height than the skeletal measurements. Since data acquisition was limited to a smaller sample of 46 specimens, the path was assessed only for the entire sample, ranging from 0 to 6 years rather than for age subsamples.

Results show that the interactions of skeletal elements with each other and facial height do not change particularly when the soft tissue variables are included (Figure 11). Indeed, among the skeletal components, as already noted in the paths in Figures 4-10, anterior septal and subnasal height most affect facial height, with orbital height playing a smaller but significant role. Maxillary height influences subnasal height, and this is the only significant relationship among the skeletal measurements that does not directly involve facial height. Indeed, nasal and orbital heights only significantly directly influence facial height and have no indirect impact, via maxillary height and subnasal height; instead, the soft tissue variables that are included in the path explain much of their variance (R^2 = 0.71 and 0.73; compare with Figure 10).

Furthermore, there is no significant direct interaction of the soft tissues with facial height, rather they act more locally, particularly on the maxillary and subnasal regions. This is an important result, indicating that the development of masseteric force and of intra-oral soft tissues, rather than of the anterior nasal septum affects the growth and development of the subnasal region.

Therefore, Hypothesis 2, of stronger influence of soft tissues (operating through capsular and periosteal matrices) than skeletal elements on facial height is falsified. Both contribute to aspects of facial growth significantly but only skeletal elements had a significant direct effect on facial height.

CONCLUSIONS

This paper aims to clarify the hierarchies of interactions among facial components in driving the growth and development of the human face in the first years of life. It does so using path analysis, to test hypothesised pathways of interactions among facial sub-regions. In the first path model, growth of the nasal septum is opposed to that of the orbits as a pacemaker for the growth and development of the maxilla, peri-alveolar region, medial orbit and overall vertical facial development. The design of this path is based on competing theories on the role of the nasal septum versus other skeletal elements as principal pacemakers for facial growth and development (Scott, 1956; Mooney et al., 1989, Holton et al., 2011, 2012; Moss, 1968; Babula et al., 1970; Goergen et al., 2017). Analyses are performed after dividing the sample into age classes by year from 0 to 6. Results show that interactions among variables change significantly over time, with anterior septal and subnasal heights showing the greatest and most consistent interactions with facial height. This finding supports the hypothesis that the nasal septum has a significant influence on prenatal and early postnatal human facial growth (Scott, 1956; Verwoerd and Verwoerd-Verhoef, 2007; Wong et al., 2010; Holton et al., 2011; 2012; Al Dayeh et al., 2013; Hall and Precious, 2013; Goergen et al., 2017).

In the second path model, the growth of the soft tissue components of the face is compared to that of the skeletal elements with the aim of comparing their relative influences on the growing elements of the face. Results show that, when soft tissue variables are included in the path model, skeletal components appear to act more independently of each other with the direct effects on facial height conserved, if a little weaker. In addition, soft tissues, particularly those related to mastication, such as the tongue with its associated muscles (intraoral volume) and masseter, tend to act only locally, affecting adjacent skeletal components linked to masticatory loading (subnasal region). Our findings indicate that the nasal septum, together with subnasal height, are the major contributors to the development of facial height, particularly after the first year of life, and that changes in soft tissues contribute relatively less and somewhat indirectly.

These results reflect the findings of both Mooney et al., (1989) and Toro-Ibacache et al., (2016). The former assessed the interactions of skeletal elements and capsular and periosteal matrices on facial growth in foetuses. Their findings support a larger contribution (stronger interactions) of the skeletal elements to the growth and development of the face when compared to the action of orbicularis oris muscle and other facial functional matrices. In addition, Toro-Ibacache et al., (2016) found no significant effect of masticatory muscle force on overall face shape after Bonferroni correction; however, the study was limited by a small sample size.

In conclusion, throughout ontogeny, the balance among cartilaginous and soft tissue influences on facial growth appears to change, reflecting the varying roles and relative contributions of initial developmental patterning, intrinsic growth, spatial interactions and loading. It will be of interest to extend this work into older children and related species to better understand how ontogenetic interactions contribute to the development of adult morphology and diversification.

Data availability statement

The CT data used in the study is the property of the National Scientific and Practical Centre of Children's Health (SCCH), Moscow (Russia), where the individuals were scanned for medical reasons. The SCCH ethics committee has declined to make these original scans publically available without specific application to them because of patient identifiability issues but the corresponding author can make the measurements available upon request.

Conflict of interest disclosure

The authors declare no conflict of interest.

Ethics approval statement

For this study, linear measurements, areas and volumes were extracted from a collection of medical CT-scans of children from the National Scientific and Practical Centre of Children's Health (SCCH), Moscow (Russia), (Courtesy of the Lomonosov Moscow State University). The use of this dataset in this specific study was approved by the Independent Ethics committee at the SCCH, Moscow and by the Hull York Medical School Ethics Committee, York.

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Table legend

Table 1. Linear measurements and landmarks (lm) used to estimate them.

Figure legend

Figure 1. Top: path diagram (P1) of the skeletal variables used to test Hypothesis 1; Bottom: path diagram (P2) of the skeletal and soft tissue variables used to test Hypothesis 2. Red arrows represent the hypothesised direct contributions of the exogenous variables to the final variable of facial height; blue arrows represent all the other hypothesised relations.

Figure 2. Infant skull with the landmarks used to estimate the linear measurements of Table 1.

Figure 3. A: The measurement of the radius of the ocular globe (r) was taken at the point in which the surface area is largest (red, sclera included); B: segmentation of the cross-sectional area (red) of the temporalis muscle. The segmentation and subsequent measurement of the area used the

824 slice at which the zygomatic arch was completely visualised when scrolling from superior to inferior
825 in the axial plane; C: segmentation of the area of the masseter muscle (red). The segmentation
826 and subsequent measurement of the area used the slice at the midpoint of the mandibular lingula;
827 D: the area of the intra-oral soft tissue capsule including the tongue, sublingual musculature and
828 the soft palate (red) was segmented and measured in sagittal view along the midsagittal plane.

829

830 Figure 4. Results of the path analysis for the path P1 in the sample from 0 to 1 years old; the
831 numbers next to the arrows represent the beta coefficients (β), the stars indicate the significance
832 of each standardised multiple regression: *< 0.05, **< 0.01, ***< 0.001. The R^2 values indicate the
833 proportion of the total variance of the dependent variable that is explained by the independent
834 variables that are hypothesised to affect it.

835

836 Figure 5. Results of the path analysis for the path P1 in the sample from 1 to 2 years old; the
837 numbers next to the arrows represent the beta coefficients (β), the stars indicate the significance
838 of each standardised multiple regression: *< 0.05, **< 0.01, ***< 0.001. The R^2 values indicate the
839 proportion of the total variance of the dependent variable that is explained by the independent
840 variables that are hypothesised to affect it.

841

842 Figure 6. Results of the path analysis for the path P1 in the sample from 2 to 3 years old; the
843 numbers next to the arrows represent the beta coefficients (β), the stars indicate the significance
844 of each standardised multiple regression: *< 0.05, **< 0.01, ***< 0.001. The R^2 values indicate the
845 proportion of the total variance of the dependent variable that is explained by the independent
846 variables that are hypothesised to affect it.

847

848 Figure 7. Results of the path analysis for the path P1 in the sample from 3 to 4 years old; the
849 numbers next to the arrows represent the beta coefficients (β), the stars indicate the significance
850 of each standardised multiple regression: *< 0.05, **< 0.01, ***< 0.001. The R^2 values indicate the
851 proportion of the total variance of the dependent variable that is explained by the independent
852 variables that are hypothesised to affect it.

853

Figure 8. Results of the path analysis for the path P1 in the sample from 4 to 5 years old; the numbers next to the arrows represent the beta coefficients (β), the stars indicate the significance of each standardised multiple regression: *< 0.05, **< 0.01, ***< 0.001. The R^2 values indicate the proportion of the total variance of the dependent variable that is explained by the independent variables that are hypothesised to affect it.

Figure 9. Results of the path analysis for the path P1 in the sample from 5 to 6 years old; the numbers next to the arrows represent the beta coefficients (β), the stars indicate the significance of each standardised multiple regression: *< 0.05, **< 0.01, ***< 0.001. The R^2 values indicate the proportion of the total variance of the dependent variable that is explained by the independent variables that are hypothesised to affect it.

Figure 10. Results of the path analysis for the path P1 in the sample from 0 to 6 years old (all sample); the numbers next to the arrows represent the beta coefficients (β), the stars indicate the significance of each standardised multiple regression: *< 0.05, **< 0.01, ***< 0.001. The R^2 values indicate the proportion of the total variance of the dependent variable that is explained by the independent variables that are hypothesised to affect it.

Figure 11. Path analysis using skeletal and soft tissue variables (P2) to test Hypothesis 2 from 0 to 6 years. The numbers next to the arrows represent the beta coefficients (β), the stars indicate the significance of each regression (p-value): *< 0.05, **< 0.01, ***< 0.001). The R^2 values indicate the proportion of the total variance of the dependent variable is explained by the independent variables of each multiple regression.

879 Table 1

Linear measurements of skeletal tissues	**Definition of the landmarks used for linear measurements (Frankfort orientation)**	**Landmarks used to estimate the linear measurements**
Anterior Septal Height	Rhinion- Subspinale	Lm 1-2
Medial Orbital Height	Between the most superior and inferior points on the lacrimal bone	Lm 3-4
Maxillary Height	Between the most superior and inferior points on the Zygomatico-maxillary suture	Lm 5-6
Subnasal height	Subspinale- Alveolar	Lm 2-7
Orbital Height	Most superior point on upper border of the orbit - Zygomatico-maxillary suture at the orbital margin	Lm 5-8
Facial Height	Nasion- Alveolar	Lm 7-9

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882 Table 1. Linear measurements and landmarks (lm) used to estimate them.

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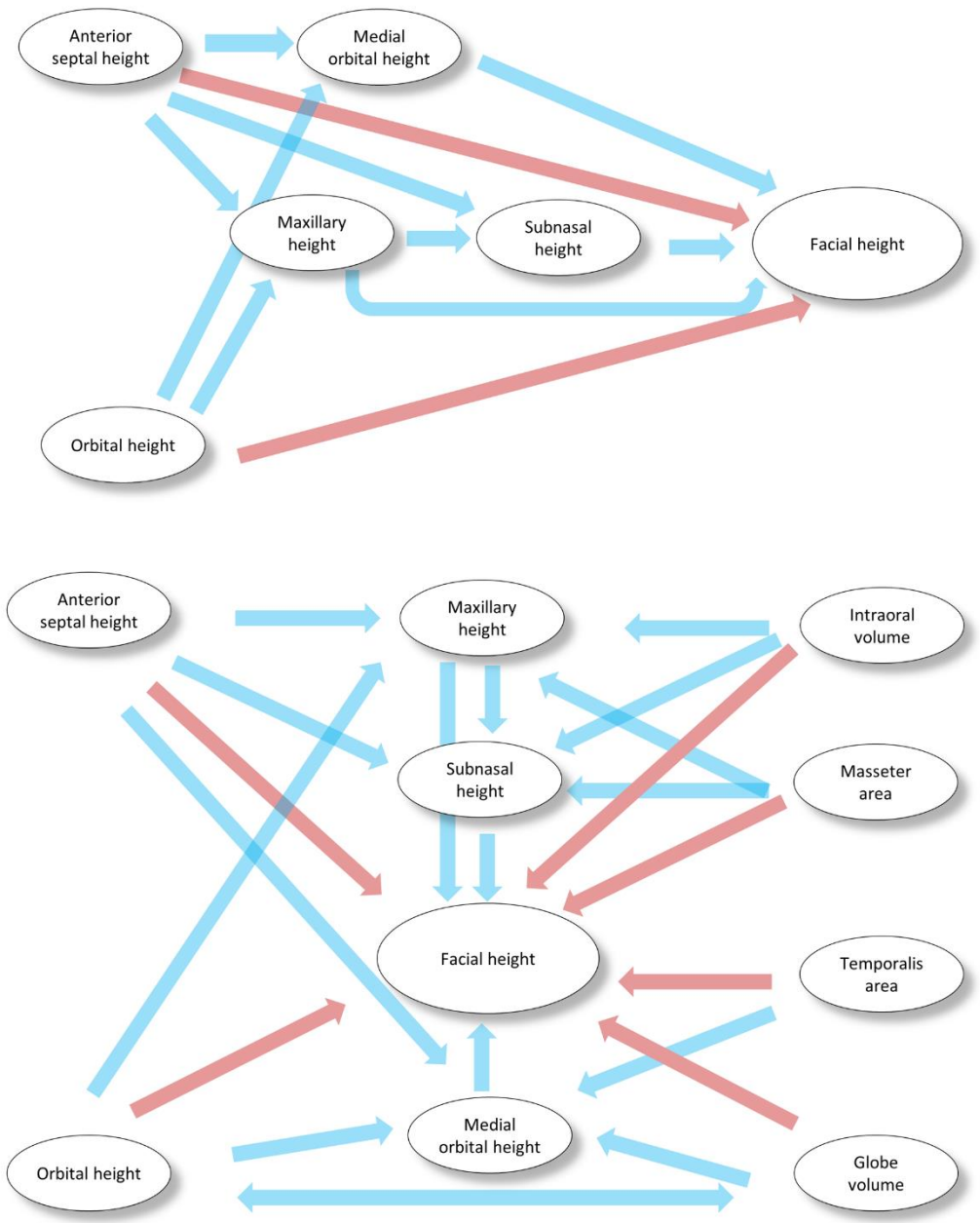
884 Figure 1



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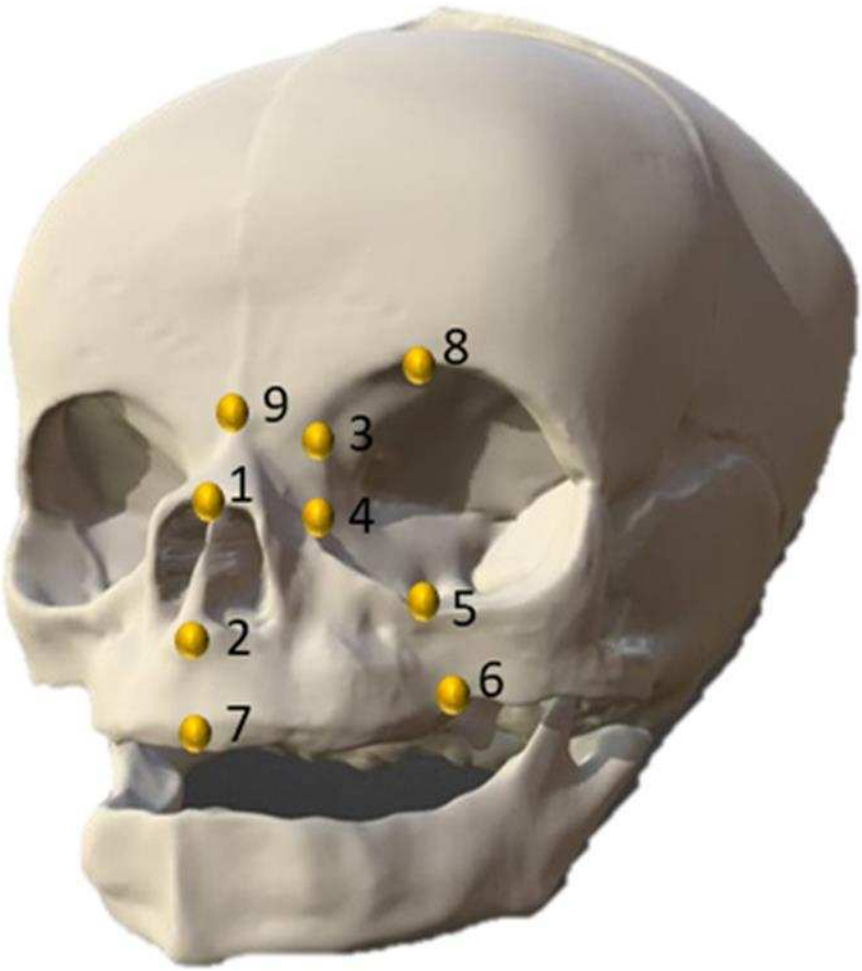
887 Figure 2



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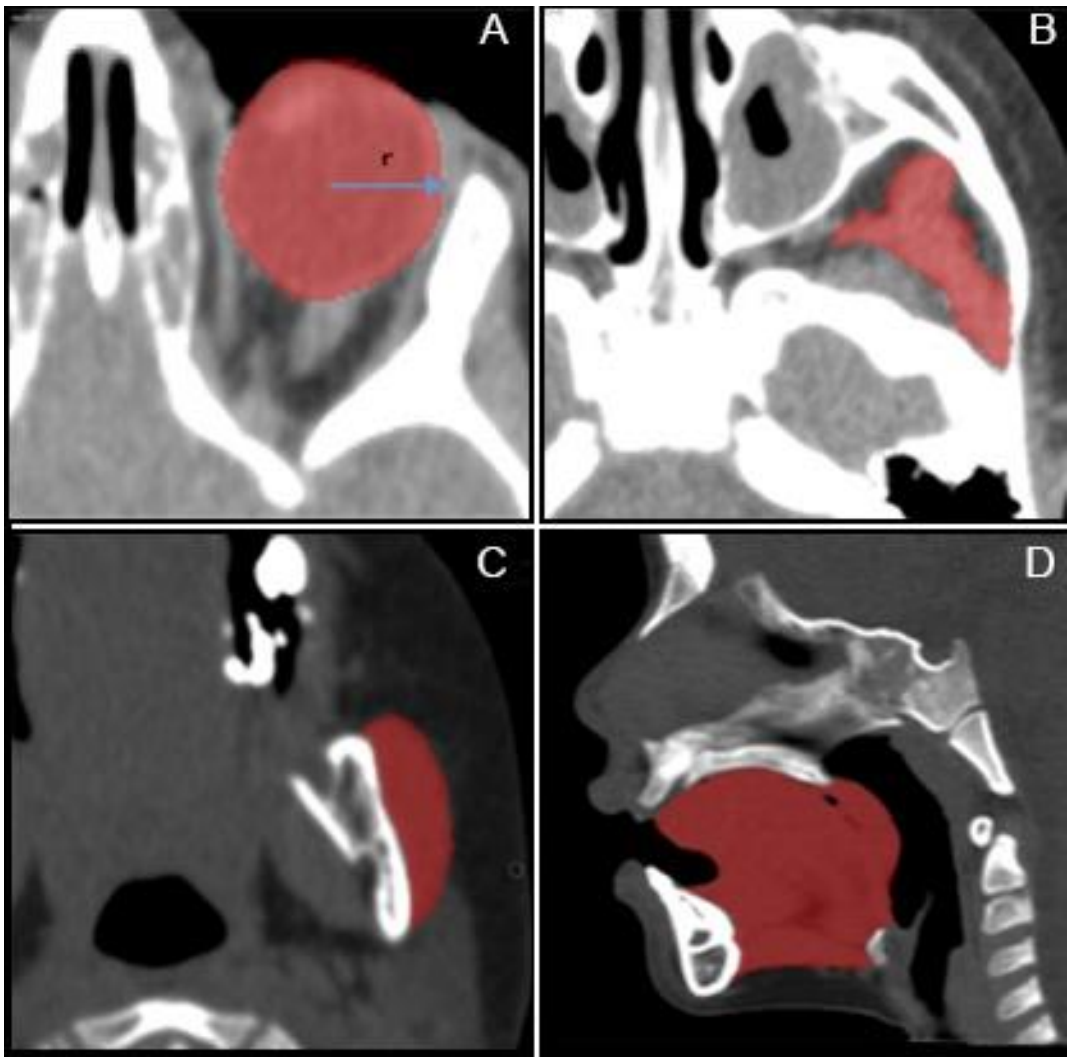
890 Figure 3



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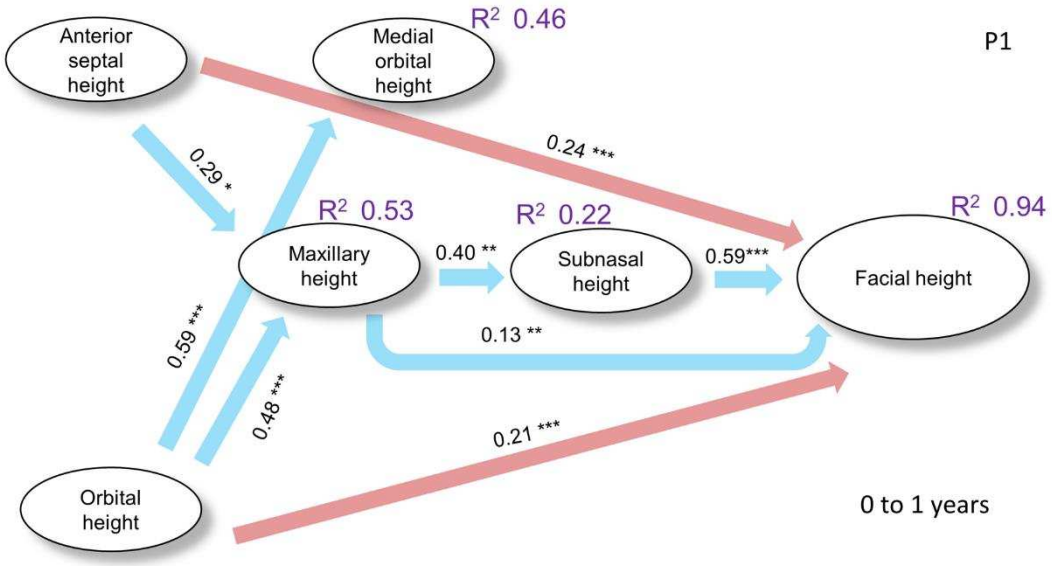
893 Figure 4



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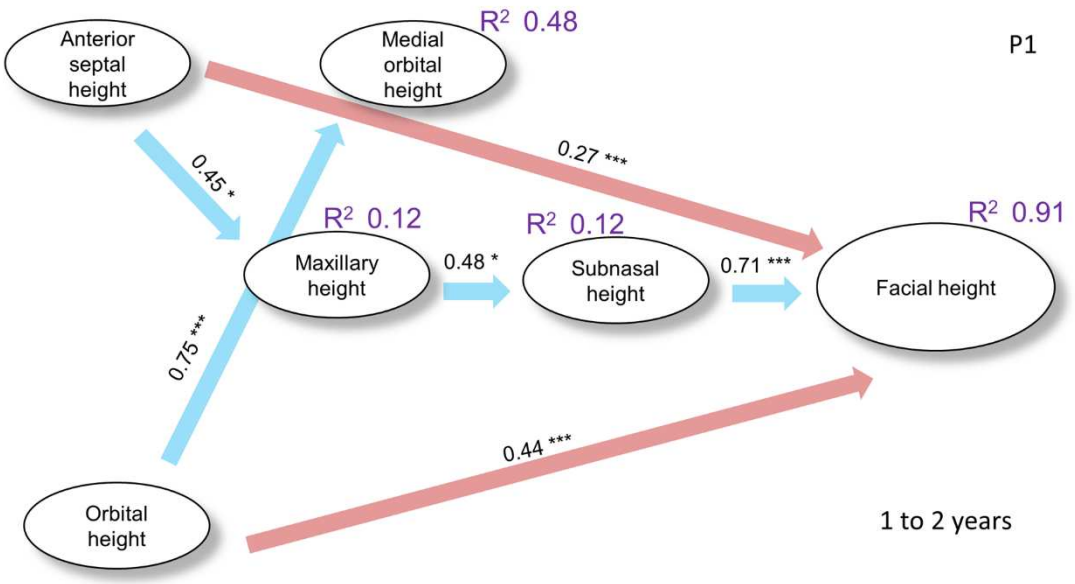
897 Figure 5



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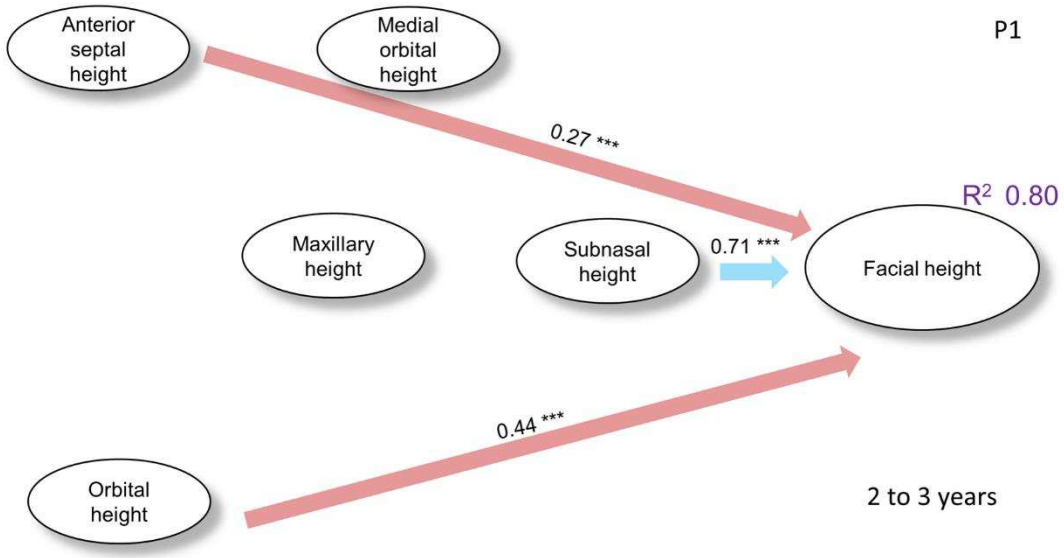
900 Figure 6



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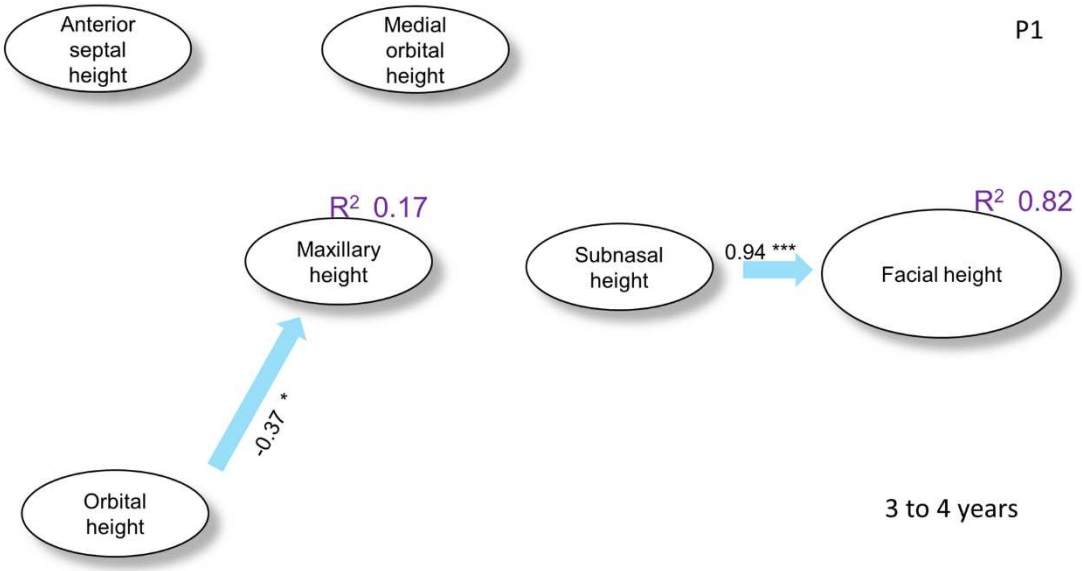
903 Figure 7



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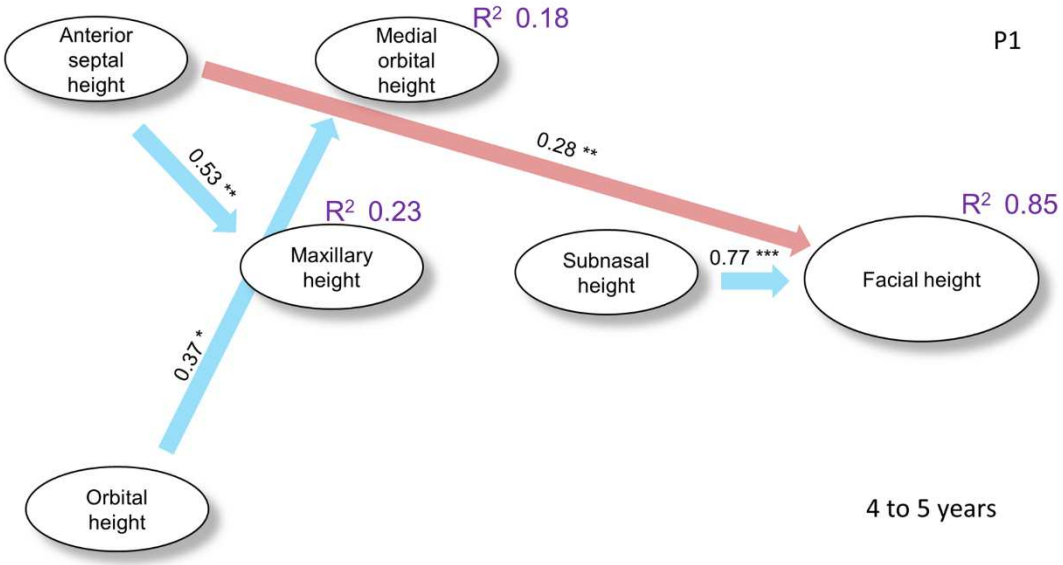
906 Figure 8



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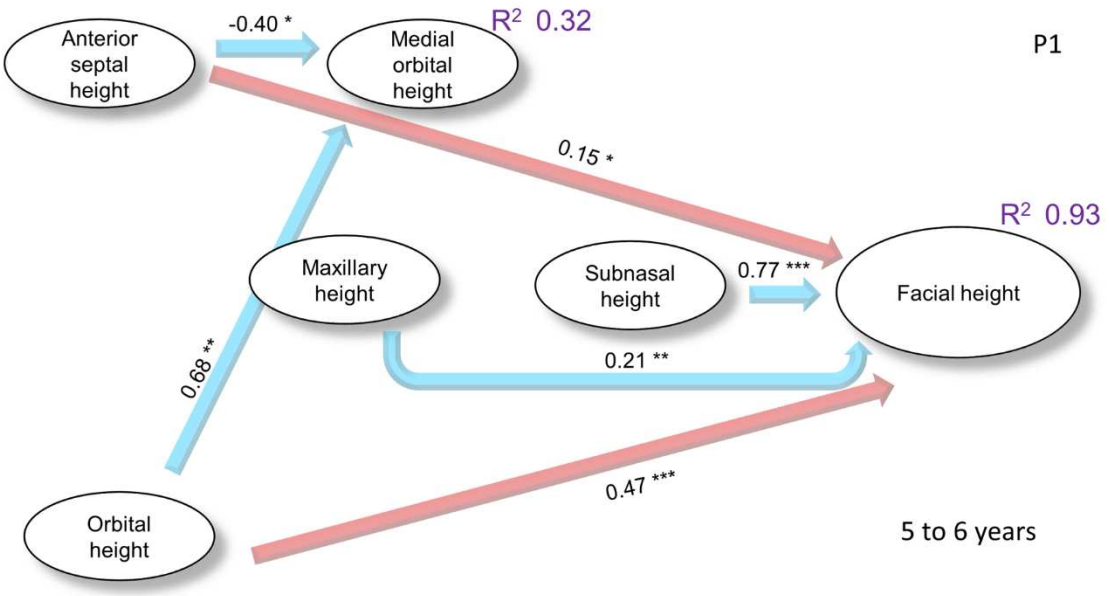
909 Figure 9



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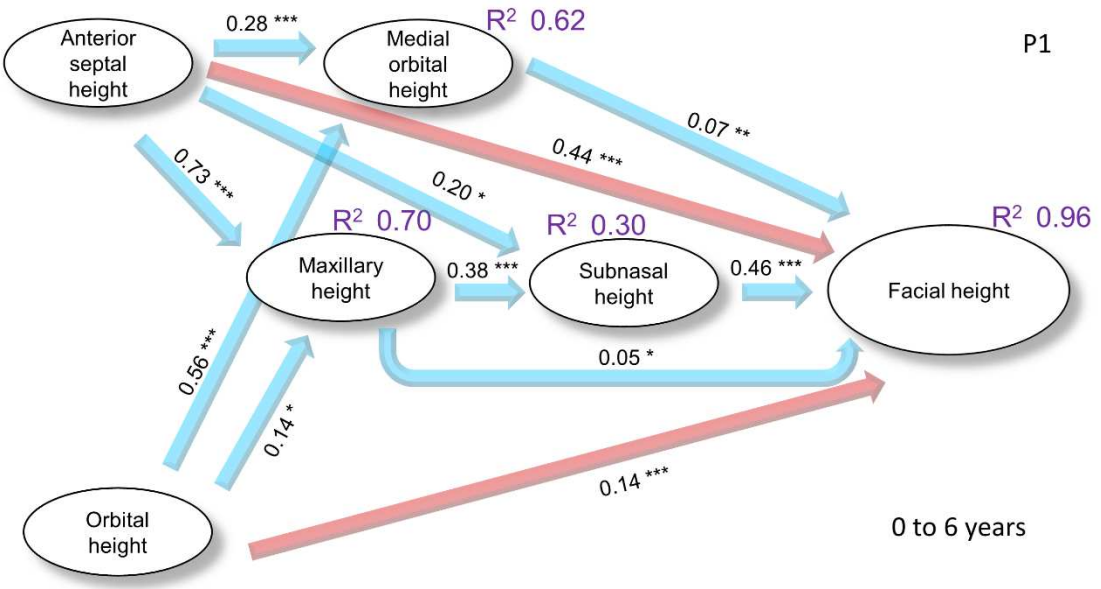
912 Figure 10



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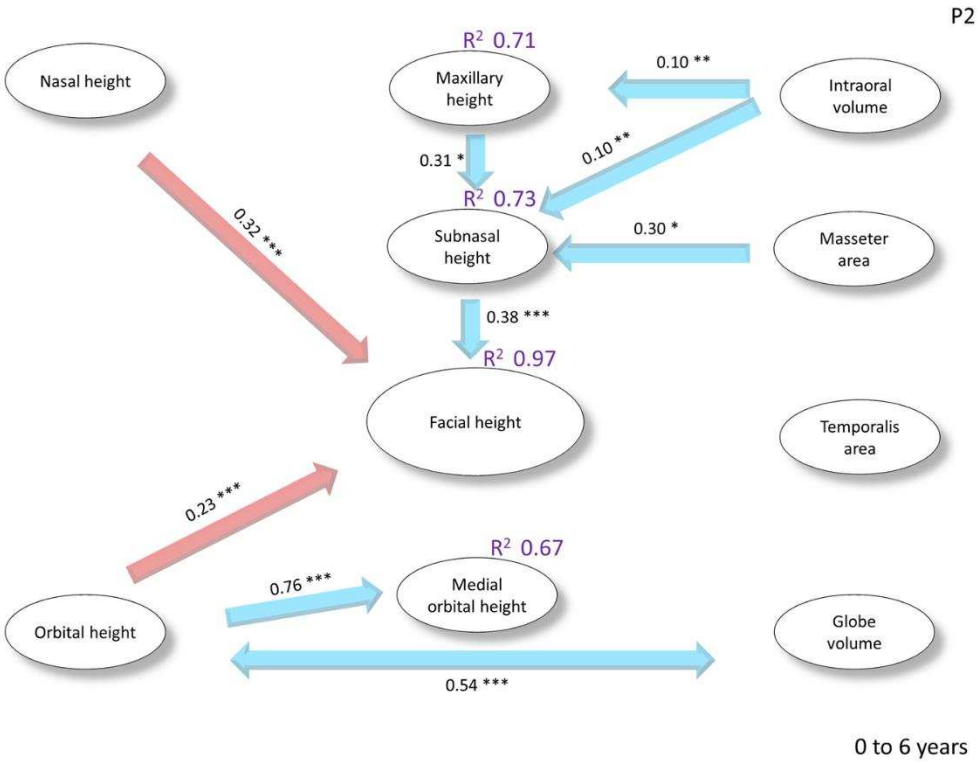
915 Figure 11



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