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

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24 Running title

25 Interactions among facial regions in ontogeny

26

27

28 **Abstract**

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

46 **KEYWORDS: path analysis, ontogeny, nasal septum, matrices**

47

48 INTRODUCTION

49 Human craniofacial ontogeny has been the subject of intensive work in several disciplines. This
50 body of research spans from studies of evolutionary patterns of variation in hominins (O’Higgins
51 et al., 2000; Ponce de Leon and Zollikofer, 2001; Ackermann and Krovitz, 2002; Cobb and O’Higgins,
52 2004; Bastir et al., 2007), through anthropological analysis of current growth trends in different
53 modern populations (Viðarsdóttir et al., 2002; Gonzalez et al., 2010), to the creation of normative
54 reference data for surgical and clinical studies (Buschang et al., 1983; Waitzman et al., 1992a,
55 1992b; Landes et al., 2002; Gkantidis and Halazonetis, 2011; Jiang et al., 2015). The common aims
56 are to describe ontogenetic transformations and understand mechanisms that regulate
57 craniofacial growth; how the cranium grows and develops to reach its final size and shape and the
58 major driving forces and constraints acting over ontogenetic and evolutionary time. Many studies
59 have addressed interactions among the cranial base, neurocranium and mandible and their
60 influence on human craniofacial development (Enlow 1975; Lieberman et al., 2002; Bastir and
61 Rosas, 2006; Bastir et al., 2006; Richtsmeier & DeLeon, 2009; Singh et al., 2012; Barbeito-Andrés
62 et al., 2015; Bastir & Rosas, 2016; Zollikofer et al., 2017). These suggest a hierarchy of ontogenetic
63 interactions that impacts on the development of aspects of facial form such as its vertical
64 development, its orientation and prognathism (*e.g.* Lieberman et al., 2002; Bastir and Rosas, 2006;
65 Bastir et al., 2008; Neaux et al., 2015).

66 Although patterns of craniofacial growth, development and interactions among regions are
67 increasingly well understood, there is a lack of clarity about the hierarchy and modes of these
68 interactions, especially when considering parts (subregions) of the face (Bastir and Rosas, 2004;
69 Martinez-Abadias et al., 2009; Barbeito-Andres et al., 2011; Butaric and Maddux, 2016; Esteve-
70 Altava, 2017; Maddux and Butaric, 2017). Several attempts have been made to identify the drivers
71 of change in the facial region during ontogeny, with contrasting results supporting either the soft
72 tissue or the (cartilaginous) skeletal components as the principal pacemakers for facial growth and
73 development (McLaughlin, 1949; Scott, 1956; Latham and Burston, 1964; 1970; Wexler and Sarnat,
74 1965; Moss, 1968; Babula et al., 1970; Diewert, 1985; Delaire and Precious, 1987; Grymer et al.,
75 1989; Grymer et al., 1991; Pirinen, 1995; Verwoerd and Verwoerd-Verhoef, 2007; Wong et al.,
76 2010; Holton et al., 2011; 2012; Al Dayeh et al., 2013; Hall and Precious, 2013; Goergen et al.,
77 2017).

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

81 Moss and Young, 1960; Latham and Burston, 1964; Moss, 1968; 1997; Moss et al., 1968; Babula et
82 al., 1970; Goergen et al., 2017). Each functional matrix, defined as [...] “non-skeletal cells, tissues,
83 organs, and operational volumes” in the body (Moss, 1997), has an associated skeletal capsule
84 (bone or cartilage) that is subordinate to and supportive of the growth and development of the
85 matrix it encloses. Thus, bone formation and remodelling would be directly genetically controlled
86 only to a minor degree and largely subordinated to the corresponding developing functional
87 matrix. However, much experimental and clinical evidence suggests that the expansion and
88 development of the cranium is mainly driven by actively expanding cartilages, central among them
89 being the nasal septal cartilage (Scott, 1954; 1956; 1962; Pirinen, 1995; Herring, 2008; Wong et al.,
90 2010; Holton et al., 2012; Al Dayeh et al., 2013; Hall and Precious, 2013). Differences in conclusions
91 of these studies may be attributable to differences in the choices of species (so, in the form of
92 sutures, articulations of bones and associated soft tissues) and in approaches and sampling (e.g.
93 by focusing on different areas at different times of development). Plausibly, both soft tissue
94 matrices and cartilages are drivers of change in the facial region during ontogeny with the balance
95 among their influences varying spatially and temporally.

96 In this paper, growth interactions among facial skeletal components are assessed using path
97 analysis, applied to a large sample of CT-scans with the aim of better understanding the
98 mechanisms and hierarchies of growth and development among facial elements during the first
99 six years of life. Path analysis is a statistical method, first conceived by Wright (1921, 1934) as a
100 means of testing the interactions between multiple variables in a system, to understand the
101 functional relations among them. It has been applied in psychology and social sciences to
102 investigate the proportion of contribution of a series of variables to social outcomes (Duncan,
103 1966; Pajares and Miller, 1994; Streiner, 2005; Rudasill and Rimm-Kaufman, 2009). More rarely, it
104 has been applied to analyse the developmental and evolutionary hierarchical interactions among
105 anatomical elements based on the *a priori* construction of hypothesised relations (Mooney et al.,
106 1989; Bullmore et al., 2000; Holton and Franciscus, 2008; Zollikofer et al., 2017).

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

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

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

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

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

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

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

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

170 Therefore, in path P1, anterior septal height is chosen as an independent exogenous variable,
171 hypothesised here to not be influenced by the other skeletal variables in the model but rather,
172 acting as a pacemaker for growth of the entire facial skeleton and all its variables. Another
173 hypothesised independent variable in the first path P1 is orbital height. This is because in the early
174 years, the growth and development of the orbit are rapid compared to other facial regions
175 (Barbeito-Andres et al., 2016; Evteev et al., 2018). This plausibly has a major impact on facial
176 morphology in not only largely defining facial form during early stages but also driving the growth,
177 development and changing proportions among other facial elements (Sarnat, 1982; Farkas et al.,
178 1992; Furuta, 2001).

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

182 Specifically, medial orbital height is potentially influenced by the growth of the maximum height
183 of the orbit, but it could also reflect the development of the adjacent nasal bridge, growth of which
184 is directly proportional and potentially linked to the growth of the nasal septum (Mondin et al.,
185 2005). Therefore, in the path diagram P1 (Figure 1), arrows point at this variable from the nasal
186 and orbital heights.

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

201

202 [Figure 1]

203

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

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

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

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

224

225 **MATERIAL AND METHODS**

226 **The sample**

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

233 For the analyses, the sample of 227 individuals used to test the first path (P1) was divided into age
234 groups as follows: 0 to 1 year (91 specimens), 1 to 2 years (27 specimens), 2 to 3 years (25
235 specimens), 3 to 4 years (27 specimens), 4 to 5 years (32 specimens), 5 to 6 years (25 specimens)
236 and then combined (0 to 6 years). Due to limitations in sample size, the second path was tested
237 using a limited sample of 46 specimens, which includes: 17 specimens of 0 to 1 years, 8 specimens
238 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
239 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

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

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

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

280

281 **Statistical analysis**

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

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

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

302

303 RESULTS

304 Path 1

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

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

321

322 [Figure 4]

323

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

328 contributes to overall facial height but does so indirectly through its influence on subnasal height
329 ($\beta= 0.48^*$).

330

331 [Figure 5]

332

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

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

350

351 [Figure 6]

352

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

358

359 [Figure 7]

360

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

367

368 [Figure 8]

369

370 From 5 to 6 years (Figure 9) the influence of anterior septal height and subnasal height on facial
371 height remains similar to that in the 4-5 year age group ($\beta = 0.15^*$ and 0.77^{***} , respectively).
372 However, now both orbital height and maxillary height contribute directly to facial height ($\beta =$
373 0.47^{***} and $\beta = 0.21^{**}$ respectively). Anterior septal height also manifests a new and negative
374 relationship with medial orbital height. Overall the direct effects (in ascending order) of anterior
375 septal, maxillary, orbital and subnasal heights account for a very high proportion of the total
376 variance in facial height ($R^2 = 0.93$) in this age group.

377

378 [Figure 9]

379

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

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

389

390 [Figure 10]

391

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

397

398 **Path 2**

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

404 In this path (Figure 11), anterior septal height and subnasal height have the strongest and most
405 significant direct effects on facial height ($\beta= 0.32^{***}$ and 0.38^{***} respectively), while orbital height
406 plays a smaller but significant role ($\beta= 0.23^{***}$).

407 Anterior septal height does not affect any other variable in the path and so it does not impact on
408 facial height indirectly. This is also the case for orbital height: while it has a significant and strong
409 association with medial orbital height ($\beta= 0.76^{***}$, $R^2= 0.67$), the latter, as already seen in most
410 of the analyses of path P1, has no impact on facial height. Maxillary height plays a significant
411 indirect role in influencing facial height via its relationship with subnasal height but it has no
412 significant direct influence. This is similar to Figure 10, in which maxillary height has only a small
413 direct influence on facial height ($\beta= 0.05^*$) and mainly acts through subnasal height.

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

417 facial height. The intra-oral soft tissues influence maxillary height and subnasal height (for both,
418 $\beta = 0.10^{**}$). The proportion of total variance in maxillary height explained by intraoral soft tissue
419 volume is substantial ($R^2 = 0.71$) despite the low β . The intraoral soft tissue volume, together with
420 the masseter area, a surrogate for maximum masseteric force, and maxillary height explain a
421 substantial proportion of the total variance in subnasal height ($R^2 = 0.73$).

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

425

426 [Figure 11]

427

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

438

439 **DISCUSSION**

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

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

452

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

537

538 **CONCLUSIONS**

539 This paper aims to clarify the hierarchies of interactions among facial components in driving the
540 growth and development of the human face in the first years of life. It does so using path analysis,
541 to test hypothesised pathways of interactions among facial sub-regions. In the first path model,
542 growth of the nasal septum is opposed to that of the orbits as a pacemaker for the growth and
543 development of the maxilla, peri-alveolar region, medial orbit and overall vertical facial
544 development. The design of this path is based on competing theories on the role of the nasal
545 septum versus other skeletal elements as principal pacemakers for facial growth and development
546 (Scott, 1956; Mooney et al., 1989, Holton et al., 2011, 2012; Moss, 1968; Babula et al., 1970;
547 Goergen et al., 2017). Analyses are performed after dividing the sample into age classes by year
548 from 0 to 6. Results show that interactions among variables change significantly over time, with
549 anterior septal and subnasal heights showing the greatest and most consistent interactions with
550 facial height. This finding supports the hypothesis that the nasal septum has a significant influence
551 on prenatal and early postnatal human facial growth (Scott, 1956; Verwoerd and Verwoerd-
552 Verhoef, 2007; Wong et al., 2010; Holton et al., 2011; 2012; Al Dayeh et al., 2013; Hall and Precious,
553 2013; Goergen et al., 2017).

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

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

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

576

577

578 **Data availability statement**

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

584

585 **Conflict of interest disclosure**

586 The authors declare no conflict of interest.

587

588 **Ethics approval statement**

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

594

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599

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810 **Table legend**

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

812

813 **Figure legend**

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

818

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

820

821 Figure 3. A: The measurement of the radius of the ocular globe (r) was taken at the point in which
822 the surface area is largest (red, sclera included); B: segmentation of the cross-sectional area (red)
823 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

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

859

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

865

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

871

872 Figure 11. Path analysis using skeletal and soft tissue variables (P2) to test Hypothesis 2 from 0 to
873 6 years. The numbers next to the arrows represent the beta coefficients (β), the stars indicate the
874 significance of each regression (p-value): * < 0.05 , ** < 0.01 , *** < 0.001). The R^2 values indicate the
875 proportion of the total variance of the dependent variable is explained by the independent
876 variables of each multiple regression.

877

878

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 |

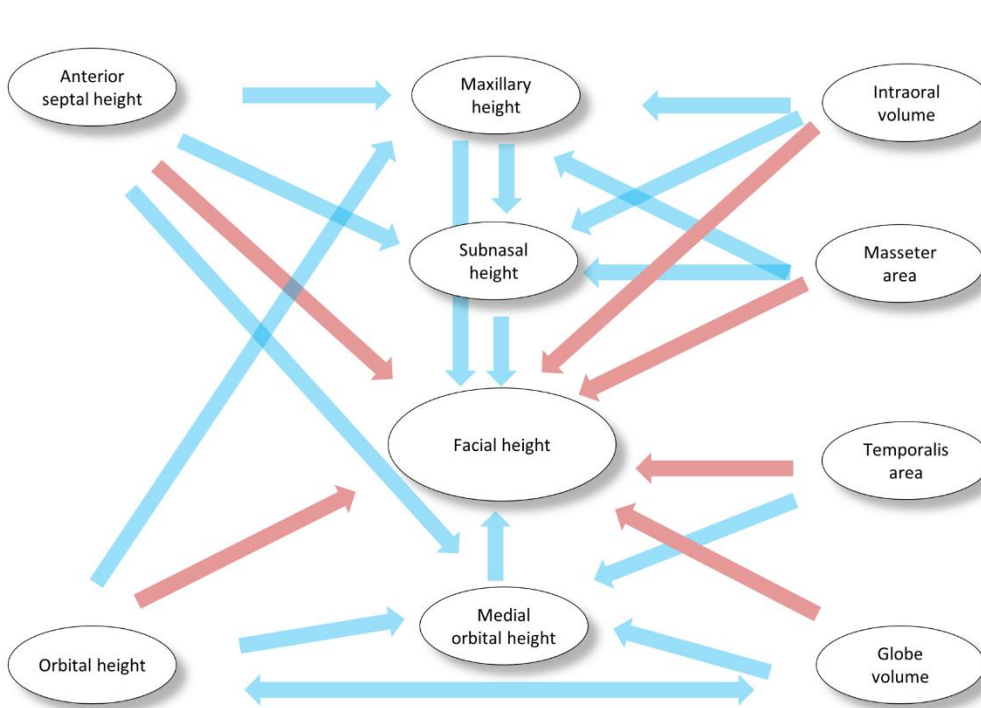
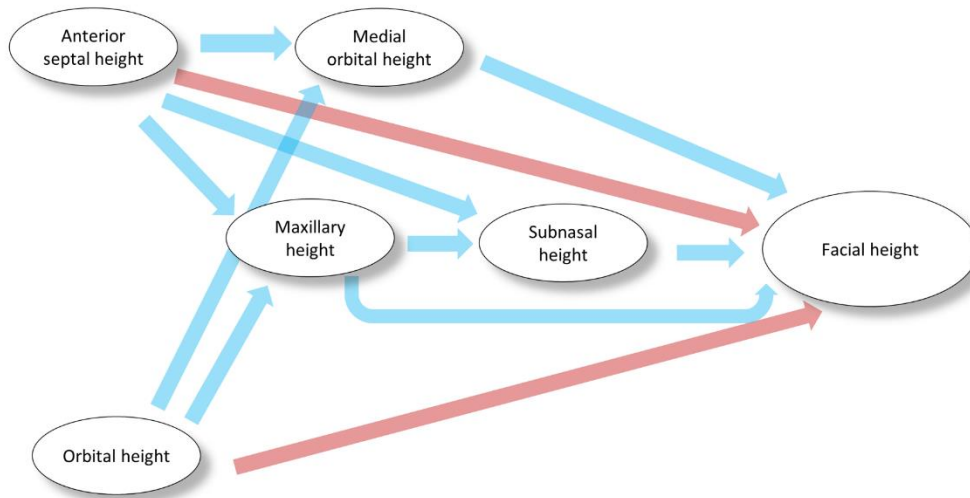
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882 Table 1. Linear measurements and landmarks (lm) used to estimate them.

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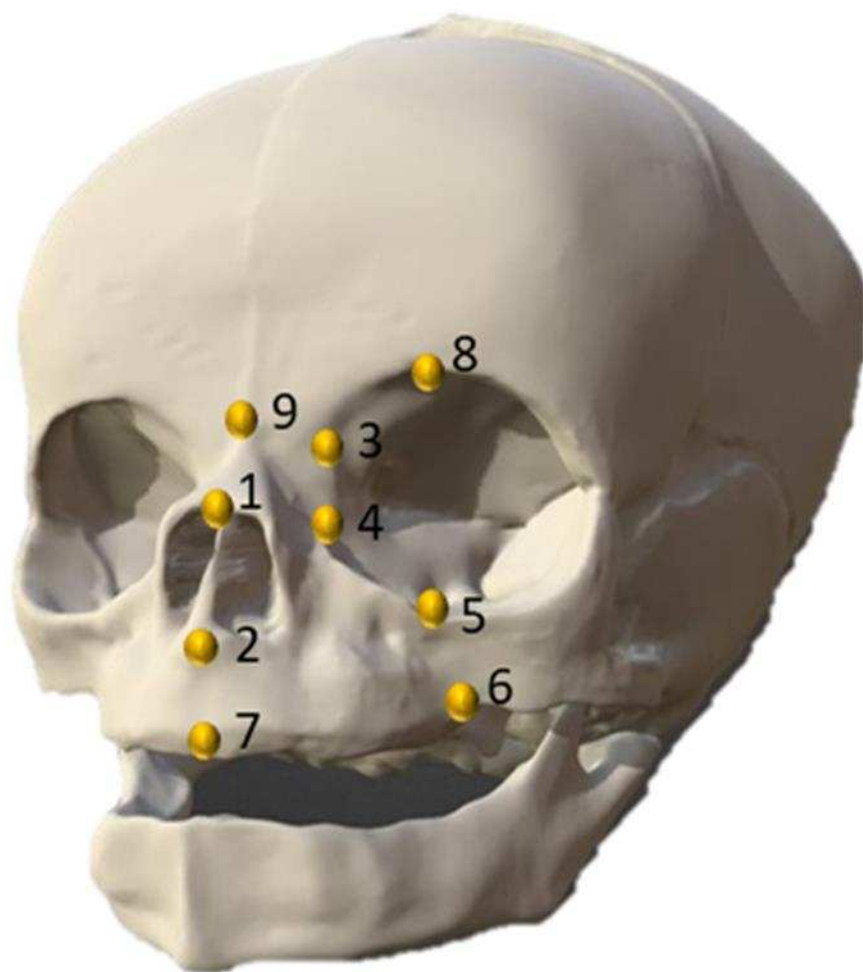
884 Figure 1



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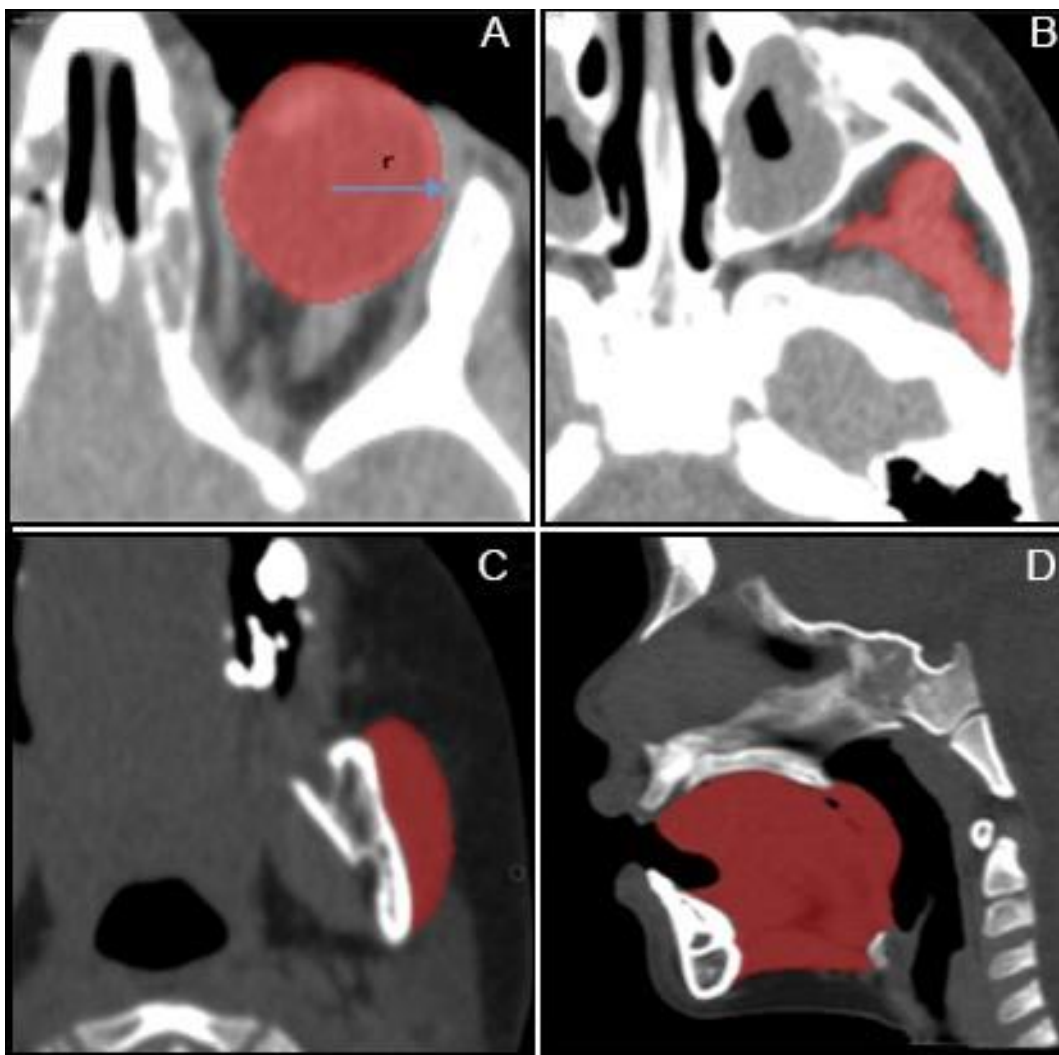
887 Figure 2



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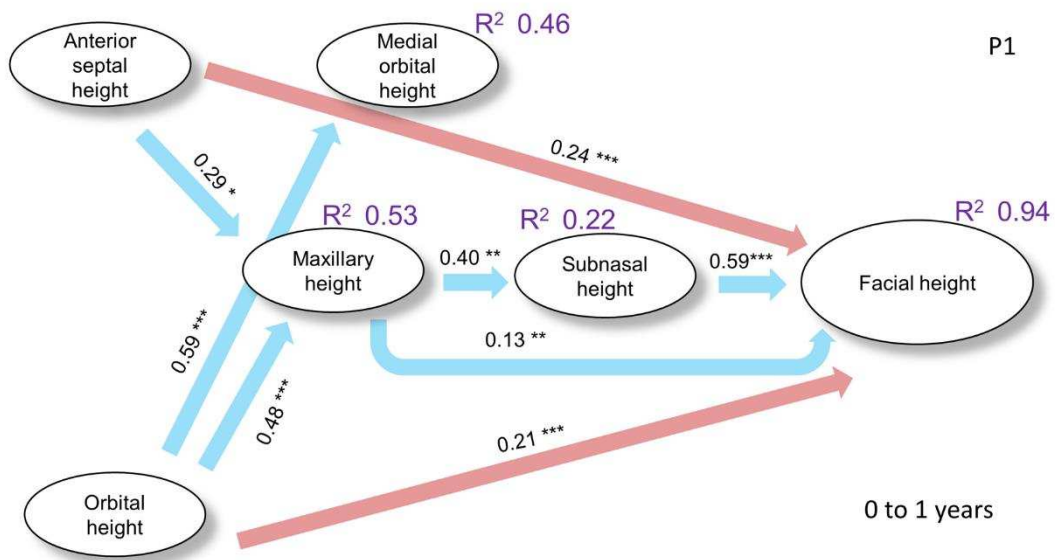
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890 Figure 3



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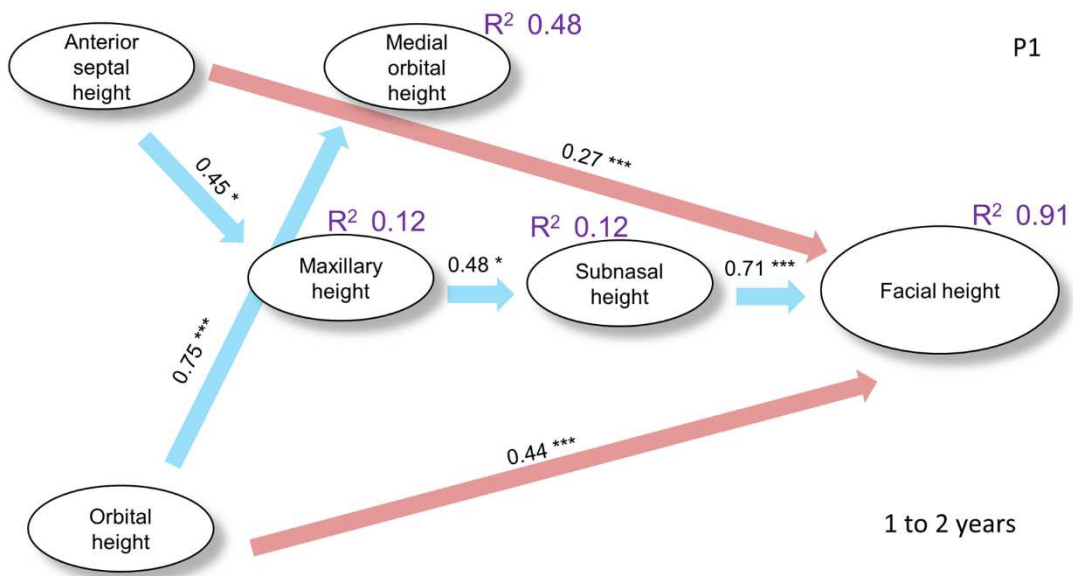


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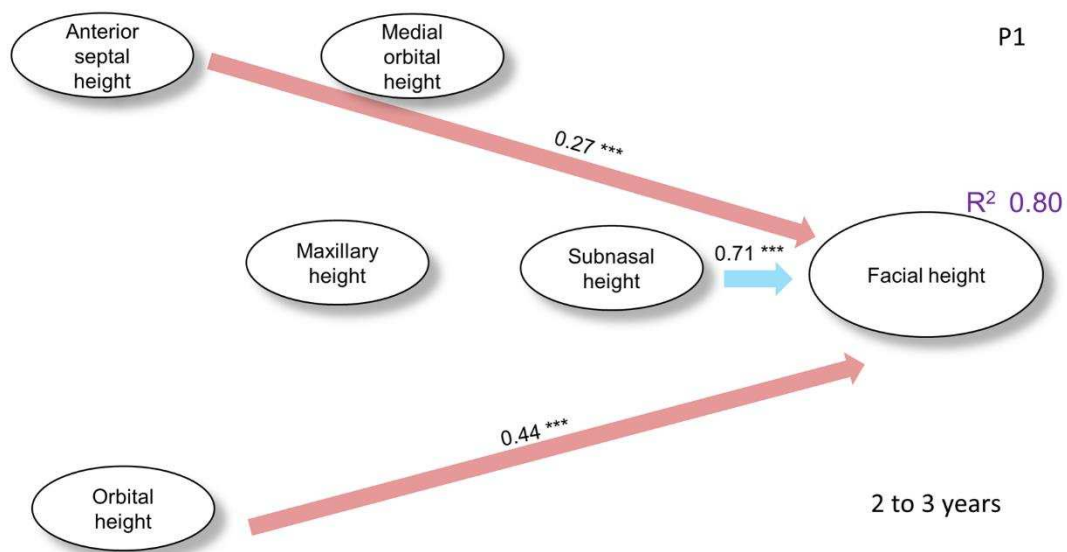
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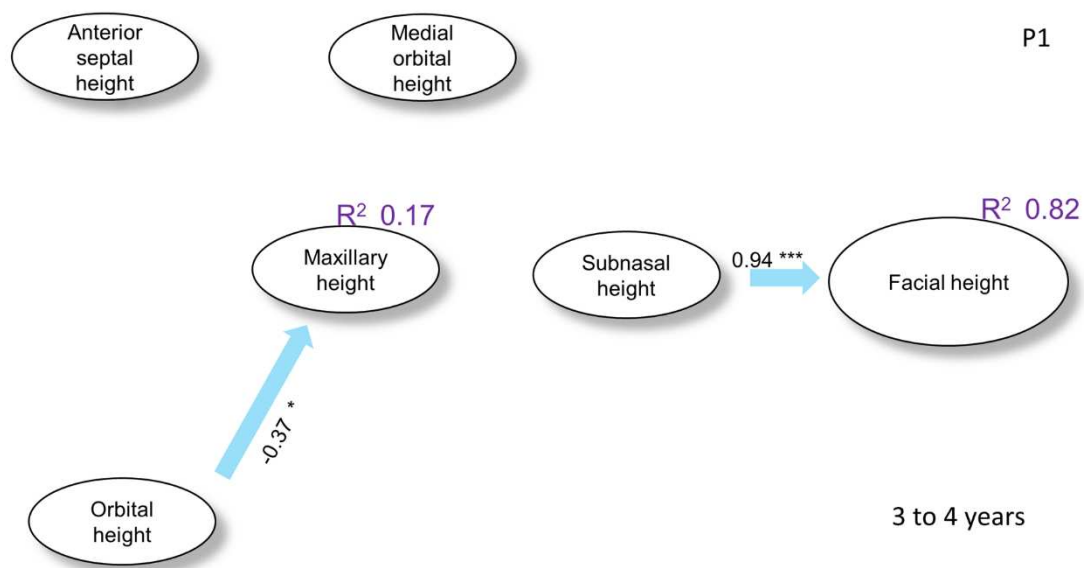
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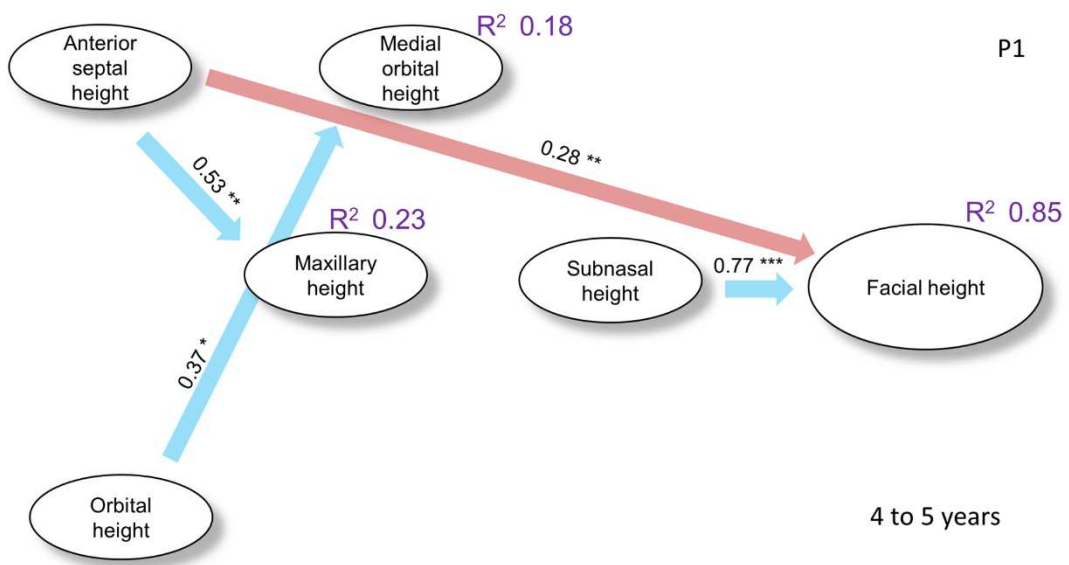
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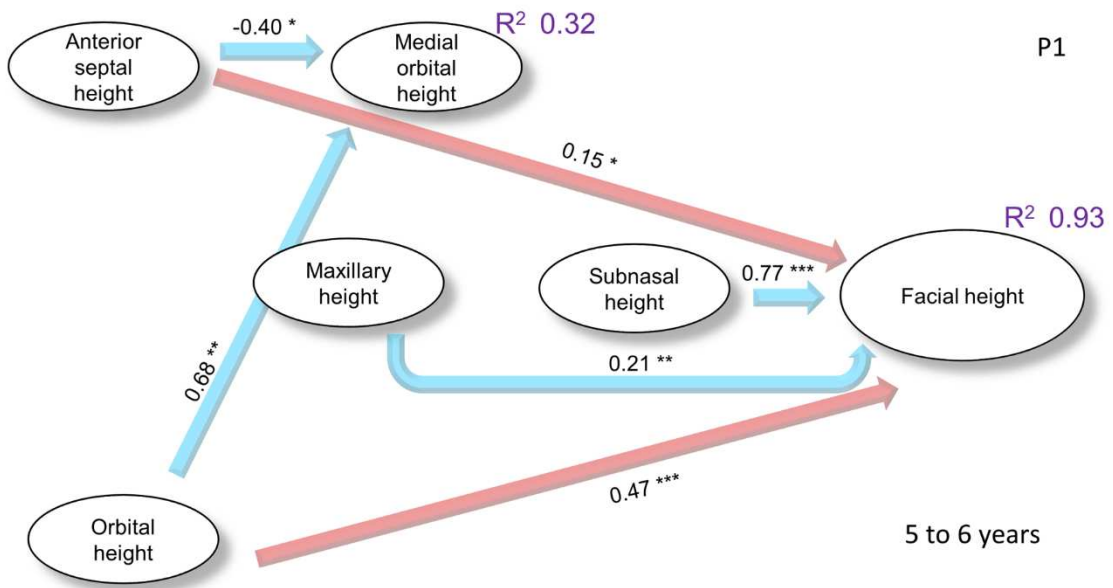
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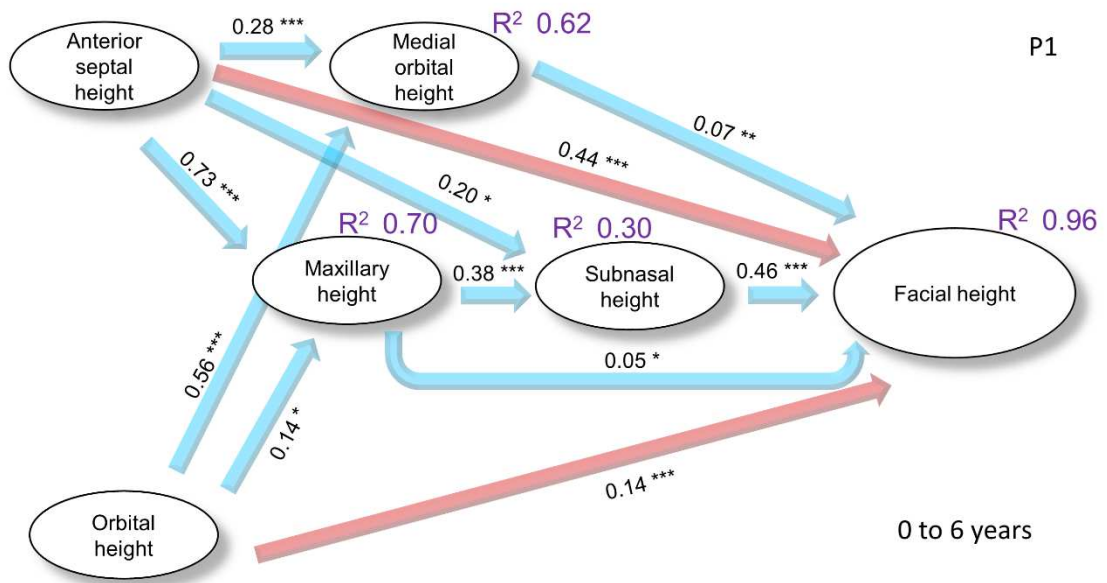
909 Figure 9



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912 Figure 10



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915 Figure 11

