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Quantification of Mandibular Sexual Dimorphism during Adolescence

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Abstract

The present study investigates how sexual dimorphism in the human mandible develops in 3D during adolescence. A cross-sectional sample of mandibular meshes of 268 males and 386 females, aged between 8.5 and 19.5 years of age, were derived from cone beam computed tomography and were analyzed using geometric morphometric methods. Growth trajectories of the mandible in males and females were modeled separately using a recently developed non-linear kernel regression framework. Growth rate and direction at a dense array of points all over the mandibular surface were visualized within each group and compared between groups. We found that mandibular sexual dimorphism already exists at nine years of age, but this is mostly in size not in shape. The differential growth rate and duration between the sexes during pubertal growth largely explained the adult sexual dimorphism: growth direction in both males and females is similar but the male mandible changed more quickly and over a longer period than the female mandible, where the growth rate peaked and declined earlier. This results in increasing dimorphism in form which is evident in both size and shape. The development of dimorphic features, concentrating in the chin and ramus, were further visualized. The dense morphometric approach provides detailed quantitative assessment of the development of sexual dimorphism of the mandible in 3D.

Keywords: mandible, sexual dimorphism, ontogeny, geometric morphometrics, CBCT

Introduction

The mandible is the largest bone of the human face and continuously adapts to functional demands during growth. Although dynamic mandibular changes from childhood to adulthood have been documented, how and when each region develops in three dimensions is not fully understood. Dimorphism of the adult human mandible has been documented in diverse populations (Hu et al. 2006; Kharoshah et al. 2010; Sharma et al. 2016). However, the development of sexual dimorphism of the adult mandible has received little attention.

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Traditional anthropometry, using calipers or rulers, can be performed directly on dried mandible specimens. The morphological change of the mandible is measured and compared between different individuals at different stages of development (Popa et al. 2009). However, using anthropometric apparatus, exact measurements of the morphological changes of the bone are difficult to obtain. When performed on living subjects, the measuring instruments must be placed on the soft tissues overlying the bony landmarks, reducing the accuracy of measurements (van der Haven et al. 1997). The bone remodeling processes of deposition and resorption have been evaluated in histological studies (Enlow & Harris, 1964) but such studies are limited by the availability of cadavers and do not allow repeated measurement. Radiographic cephalometry has permitted the study of mandibular growth in living children (Björk 1963; Björk 1968). Although the mandible has been measured extensively and reported using cephalometrics, three problems remain: (1) the 2D radiograph is adversely affected by projection distortion and positioning of the subject, making it hard to standardize the images and compare results between different studies (Moyers & Bookstein 1979); (2) commonly used 2D lateral cephalometrics emphasize changes in the sagittal and vertical dimensions, changes in the transverse dimension are missing; (3) the mandible has always been represented by sparse landmarks. The morphological changes during growth and development has been oversimplified as incremental changes in linear distances or angles. Arguably these do not accurately represent the changes in the full 3D structure.

Clinicians have entered the next phase of diagnostic evaluation and treatment planning using 3D imaging. Among them, Cone beam computed tomography (CBCT) provides an effective, rapid scan of the head that depicts undistorted craniofacial structures giving a lower radiation dose than conventional CT. In recent years, new methodologies using computational approaches for evaluating craniofacial structures have been developed to augment conventional cephalometry (Wei et al. 2011; Franchi et al. 2001). Geometric morphometrics – the statistical analysis of shape and form, abandons traditional linear, angular, or volumetric variables and provides methods of evaluating the entire 3D structure (Mitteroecker & Gunz, 2009). However, little information is available in the literature about the morphological changes of the mandible in 3D, especially how sex differences of the mandible emerge during adolescence. An in-depth understanding of how

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sexual dimorphism arises during ontogeny is likely to lead to better understanding of the functional and developmental influences that underpin variation. Further, such understanding opens up new possibilities for practical applications such as evaluation of craniofacial abnormalities and determining age and sex of the found remains of juveniles.

Using a large cross-sectional database of pre-orthodontic treatment CBCT images, we model the growth trajectories of human mandibles in males and females separately, using a recently developed non-linear modelling framework (Matthews et al. 2018). We examine the rate and direction of change within each group and compare the growth trajectories to examine how sexual dimorphism in the mandible develops during adolescence.

Methods

Image data

The CBCT images of untreated adolescent patients were retrospectively sourced from an orthodontic clinic in Melbourne, Australia, where images had previously been obtained for clinical indications. Ethics approval for this study was obtained from the University of Melbourne Human Research Ethics Committee (HREC ID: 1647544.1). The CBCT scans were anonymized except for information about sex and age. All images were taken using an i-Cat Flx machine (Imaging Sciences International, PA, USA) with a standardized protocol. While it was not possible to definitively determine ethnicity, the patient population was predominantly European. Corresponding facial images were reviewed and patients of non-Caucasian appearance were excluded, as were patients with defined craniofacial abnormalities. CBCTs were screened for evidence of previous trauma or multiple missing teeth and detected cases excluded.

The remaining images were then statistically screened for outliers to remove extreme individuals. This was achieved by adapting a standard procedure for multivariate outlier detection. A particular patient was determined to be an outlier and removed from the analysis if its Mahalanobis distance exceeds a threshold distance corresponding to a p-value of 0.01 (Brereton, 2015). The computation of the Mahalanobis distance used an age appropriate estimate of the

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covariance calculated separately for each participant. This was defined by a weighted principal components analysis, retaining PCs that explain 98 percent of the variance (Matthews, 2018). The participant was excluded from the calculation of the covariance. In total, 268 males and 386 females, ranging from 8.5 to 19.5 years of age were included. The age distribution of the sample is plotted in Figure 1.

Automatic mandible segmentation from CBCT images

The mandible was automatically segmented from each CBCT image of the head using previous validated approach (Fan et al. 2018). The outer surface of the mandible was tessellated with the standard marching cubes technique in MATLAB software (https://au.mathworks.com/help/matlab/ref/isosurface.html). Each mandible was then represented by a surface mesh composed of a dense cloud of points linked to define the surface of the mandible.

Template mapping and mandible registration

Existing spatially-dense morphometric techniques were used to register the mandibles (Claes et al. 2012a). Essentially, a generic mandibular template, represented by 17,415 quasi-landmarks, was warped into the shape of each mandible. After template mapping, each quasi-landmark occupies the same position on a given mandible as on all the other mandibles. In other words, each quasi-landmark is a single measurement in a specific anatomical location of the mandible, making spatially dense measurements consistent across all mandibles. The mapping was conducted with an open source implementation available at https://github.com/TheWebMonks/meshmonk. All the mandibles were made symmetrical by averaging the original mandible and its own mirror version, so that only the symmetrical component of shape variation was analyzed. All the mandibles were translated and rotated into a common frame of reference using Generalized Procrustes Analysis (GPA) with robust Procrustes superimposition (Claes et al. 2012b). Those quasi-landmarks indicating teeth were cut off so that only the non-dental component of the mandible was investigated.

Modelling the morphological change of the mandible as a function of age

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To model change in the mandible we follow the basic principle of the non-linear, non-parametric Nadaraya-Watson kernel regression (Watson 1964; Nadaraya 1965), as adapted for high-dimensional multivariate shape or form data by Hutton et al. (2003) and Matthews et al. (2018). The goal is to estimate the expected shape or form of the mandible at each age as well as the expected rate and direction of change at each point on the mandible. Briefly, for any given target age, a weighted linear partial least-squares regression (PLSR) of quasi-landmark co-ordinates onto age was fitted. The weights emphasized those cases closest in age to the target age and de-emphasized those further away. As these weightings change depending on the target age, the predicted mandible and predicted the growth rate can change non-linearly. This PLSR model is used to predict the expected shape or form of the mandible at the target age. The regression coefficients also provide information about the typical growth direction and rate of change at each point on the mandible. Specifically, they comprise coefficients on each quasi landmark co-ordinate, estimating the typical amount of change per year in each direction at each point. The weights declined from the target age according to a Gaussian function. The standard deviation of this Gaussian is the only tunable parameter of the model. This was optimized using a repeated grid-search (Krstajic et al. 2014). We model growth trajectories separately for males and females but use the same standard deviation for both.

Specifically, we measured the size of the mandible as the mean distance of each point on the mandible from its centroid and compared growth trajectories in size of males and females. Total form changes were visualized along the surface normals of each expected mandible at 9 year of age and in the vertical, transverse and sagittal dimensions using color maps. The growth direction and growth rate of the mandibles were compared between males and females.

We analyze growth rate and direction in terms of form (size and shape together) as this is closest to the biological reality. For these analyses, mandibles were not scaled to a common size. We also further investigate sexual dimorphism in shape by scaling each mandible to unit centroid size during GPA and re-fitting the kernel regression models. This was done because the shape of the mandible could be useful for sexing fossilized crania.

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Results

Mandibular size

Figure 2 demonstrates the change in mandibular size as a function of age. The two lines represent the expected size of mandibles with the 95% confidence intervals for both males and females. In general, the size of the mandible was larger in males than in females at all ages studied. The size difference became greater as the size of the mandible increased more rapidly in males than in females. The rate of mandibular size change slowed at approximately 14 years in females but continued to change at a faster rate until it plateaued at 17 years in males.

Total form changes

Figure 3 shows the estimated form changes between 9 and 19 years. The mandibular body became elongated, indicated by the chin projecting anteriorly and the ramus projecting posteriorly. The condyles elongated predominantly posteriorly and superiorly. The ramus height increased vertically, and the two sides of the ramus diverged outward to increase inter-ramus distance. The total change, plotted as colormaps, show the pattern of growth across the mandible. The morphological changes occur at similar regions but with different magnitude between males and females. The total amount of change in males was much larger than in females. For example, color red indicates more than 10 mm expected outward change at the chin and the condyles in males from 9 years to 19 years, but only approximately half the amount of change in females over the same period. The overall amount of change was larger in the sagittal and vertical dimensions than in the transverse dimension.

Growth rate and direction in form

The velocity of the annual form changes for males and females, as well as the difference in growth rate between the sexes, are plotted on the expected mandibles at some selected ages (Figure 4). The rate of change for males and females averaged over all points on the mandible are plotted with 95% confidence intervals in Figure 5. In general, the direction of mandibular growth was similar for both males and females. The growth rate was similar at 9-10 years for both sexes.. Active growth occurred at the condyles and the chin, and, to a lesser degree on the ramus and

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the mandibular body. The growth rate became slower from age 9 and visually plateaued by 16 years of age in females. Males accelerated from age 9 to 14. The condyles and the chin continued to change even at 18 years in males.

Sexual dimorphism in shape

The shape differences between expected mandibles are visualized using colormaps in the first row in Figure 6. P values at each age were calculated by comparing the observed Procrustes distance between the male and female expected mandibles to an empirically estimated sampling distribution. This sampling distribution was estimated by permuting the group labels and refitting the regression models and calculating the Procrustes distance between mandibles 10,000 times. Exaggerated mandibles were produced by adding twice the difference between the expected male and female mandibles onto the expected mandibles at each age. These are plotted in the second and third rows. Sexual dimorphism in shape is not statistically significant until around age 11 ($P<0.05$). The exaggerated figures showed that females were characterized by a more obtuse gonial angle and a narrower chin than in males. These two traits became more distinct from 9 to 19 year of age.

Discussion

In this study, we use a large sample of human mandibles to model the non-linear growth trajectories of size, shape and form, and measure sex differences in growth rate and direction during adolescence in 3D. We find that mandibular sexual dimorphism already exists at nine years of age, but this is mostly in size. We did not find significant dimorphism in shape at 9 years, but this could reflect a lack of statistical power. Significant dimorphism was evident by 11 years and increased through adolescence. Growth direction in both males and females is similar but is faster, peaks later, and occurs over a longer period in males than in females. This results in increasing dimorphism in form which is evident in both size and shape.

The growth of the craniofacial complex is governed by a combination of predetermined genetic blueprint and epigenetic factors such as mechanical forces and function (Carlson 2005). The mandible has movable articulations with the basicranium and continuously adapts to changes in

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both the maxilla and the dentition during growth. The morphological changes of the mandible have been frequently simplified by measuring only certain linear parameters, such as the mandibular length (distance between Condylion and Gnathion) (Mitani & Sato, 1992; Baccetti et al. 2005), bigonial breadth (the distance between two gonia) or bicondylar breadth (the straight distance between the most lateral points on the two condyles) (Vinay & Gowri, 2013). The orthodontic cephalometric literature has been preoccupied with the vertical and sagittal relationships, but the actual changes involve every region of the mandible and are composed of diverse three-dimensional growth vectors (Moyers & Bookstein, 1979). We confirm in three dimensions that the condyle shows active morphological changes, elongating predominantly posteriorly and superiorly along with the lengthening of the ramus. The mandibular body also elongates so as to permit the dental arc to accommodate more permanent teeth. The chin protrudes distinctively over time. These processes contribute to the known vertical and sagittal changes in the mandible. The changes in the transverse dimension are more subtle. It is well-established that the ossification of the mandibular symphysis occurs shortly after birth so after that time, changes in mandibular width would be expected to occur only by surface apposition or resorption. Nonetheless, in our analysis the left and right rami mandibular body diverge laterally, but by less than 4mm. These transverse changes may be constrained because the middle cranial fossa and its neural contents have stopped growing in early childhood and the bi-condylar width is fixed thereafter (Enlow & Hans, 2008).

We found sex differences in the overall size of the mandible. The mandibles of males are significantly larger than those of females over the whole of the study period. This trait has been documented by anthropologists and has been used for sex determination in forensic practice and for medico-legal purposes (Sikka & Jain, 2016; Sharma et al. 2016). Our study further shows how the size difference of the mandible between males and females gradually develops. At age 9, the mandibular size is generally larger in males than in females. The males and females show similar rates of change in size from 9 to 12 years. Thereafter the size increment slows down gradually in females but not in males until 17 years old. The overall greater mandibular size in males may relate to the greater masticatory forces to which the male mandible is subject. On average, females produce weaker muscle forces during mastication, resulting in smoother surfaces of

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muscle attachments and smaller sized mandibles, whereas males have larger mandibles and produce stronger muscle forces (Vodanović et al. 2006; Velemínská et al. 2012).

Our study quantifies the annual change at a dense array of points over the mandible and visualizes the differential growth between males and females during adolescence. Growth in both male and female mandibles is rapid at the condyles and the chin, and to a lesser degree in the body of the ramus. Peak adolescent growth velocity is later in males than in females, which agrees with the finding in previous 2D studies (Nanda 1955; Buschang et al. 1989). It is the continuation of this growth pattern in males which results in the differences in form between male and female mandibles. This confirms that sexual dimorphism in the craniofacial structures is mainly the result of a differential growth rate after puberty and during adolescence (Ursi et al. 1993; Rosas & Bastir 2002).

A strength of the current study is the sophisticated modelling technique. Some previous studies of soft and hard tissue growth from cross-sectional data use the first principal component (PC) as the growth trajectory (Hammond et al. 2004; Hammond et al. 2012; Suttie et al. 2013; Ibrahim et al. 2016). The first PC is the direction of greatest variability in the sample. Where the sample is of heterogeneous ages this often correlates strongly with age, but there is no guarantee that it is the dimension of variation that is most strongly correlated with age. Furthermore, it is limited in that it assumes growth proceeds along the same growth vectors throughout development (i.e. that growth is linear). On the contrary, the modeling approach used in this study allows growth vectors to change, depending on the age. Another strength is the use of color-maps to illustrate these growth vectors. This differs from the standard approach in geometric morphometrics, which is to plot growth patterns abstractly as lines in the subspace spanned by two or three principal components. In such a subspace inferences about differences between growth trajectories cannot really be made since the impression can change radically dependent on the choice of subspace (Mitteroecker et al. 2005).

The analysis of the morphological changes and the sex differences of the mandible has important implications for clinicians. When planning orthodontic treatment, the general intention is to

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target the active growing sites and take advantage of accelerated or intense growth periods. Our study is consistent with previous findings that the greatest morphological changes during growth occur in the condyles (Nanda, 1955; Buschang et al., 1988) and therefore orthopedic forces should be applied to the condyles so as to encourage or restrict the mandibular growth (Hägg & Taranger 1982). (Deguchi et al. 2002). Our study also confirms the empirical practice of initiating orthodontic treatment earlier in females and delaying orthognathic surgery till after 16 years in females and after 18 in males when growth has plateaued (Weaver et al. 1998).

Determination of sex from an unknown human mandible is useful in forensic and anthropology field. Even though the mandible carries more information about a child's age than other bones, determining the gender of an isolated mandible remains a problem of shape. Franklin et al. suggests that it is difficult to use the subadult mandible for sex determination. It is not manifest at an appreciable level until after pubertal modifications have taken place (Franklin et al. 2007). Coquerelle et al. found that there is significant mandibular shape difference between males and females at birth. They found that this dimorphism diminishes so that there is no difference between male and female average shapes between age 4 of years and ~14 years. (Coquerelle et al. 2011). Our study is consistent with their findings of no statistically significant difference in the mandibular shape from 9 to 10 years of age, however, both of these findings should be treated cautiously since sample sizes at these ages were small in both studies. With a larger sample size, we have been able to identify a sex difference in shape by age 11. The dimorphic features extend and become more obvious during adolescence.

Our study further shows how the dimorphic features develop comprehensively in 3D. The chin is one of the most distinctive anatomical traits of modern humans. We found that adult males end up with more protruded, broader and almost square chins while adult females are characterized as narrower and more rounded. This agrees with the descriptions of Thayer et al. (Thayer & Dobson, 2010) and Coquerelle et al. (2011). The mandibular angle is more prominent in males than in females and this trait is preserved from pre-teen to post-teen. The mandibular angle is acted on by the masseter muscle, and differential biomechanical forces may explain this sex difference. It should be possible, using the data from this study to automate sex prediction from

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an image of an isolated mandible using dense morphometric techniques.

The use of modern imaging technologies provides detail of bone anatomy without the need to dissect or compromise the integrity of skeletal material (Franklin et al. 2016). This is an especially valuable tool for investigating of the morphological changes in bone. Although growth related changes are ideally investigated longitudinally, to the best of our knowledge, only four studies have investigated longitudinal changes of the mandible in 3D. Three of these studies were limited by very small sample sizes (Bro-Nielsen et al. 1997; Andresen et al. 1998; Andresen et al. 2000). They also applied restrictive, biologically implausible mathematical forms to growth, assuming it follows either a linear or polynomial trajectory. Krarup et. al evaluated mandibular growth and tooth eruption on 10 children with Apert syndrome without commenting on mandibular form changes or sexual dimorphism (Krarup et al. 2005). Furthermore despite contemporary understanding that the mandible is unaffected in individuals with Apert Syndrome (Kreiborg et al. 1999), it has yet to be ascertained that the syndromic group is characterized as the same growth trajectory as otherwise unaffected individuals. As there will always be difficulty obtaining sufficient numbers of longitudinal CBCTs of otherwise normal individuals due to ethical limitations, we used cross-sectional images collected prior to orthodontic treatment. We also applied a flexible, non-linear modelling technique that does not assume any particular form to the growth trajectory (Matthews et al. 2018). To the best of our knowledge, only Coquerelle et al. employed piecewise linear regressions to approximate a non-linear growth trajectory and to estimate expected mandibles from birth to 20 years of age (Coquerelle et al. 2011). This is conceptually quite similar to our method, however, they relied on projection of each growth trajectory into the subspace spanned by the first three principal components to investigate differences in rate of change and growth direction between the sexes which is limited for the reasons described earlier. A limitation of our study is that it evaluates the mandibular changes indexing by chronological age only. As there is considerable variation in the age at which children reach puberty, chronological age may not reflect developmental stage sufficiently and accurately, particularly for adolescents (Baccetti et al. 2005). Additional biological measurements, such as skeletal age or ossification stages, could potentially be added to the model in the future. Also, this is a clinical cohort which may include more orthodontic skeletal class II and III individuals

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than the general population. A cohort of 'normal' individuals would be preferable for such a study, but CT/CBCT imaging of such a cohort would be difficult to justify.

Conclusions

Sexual dimorphism in the mandible results from the initial pre-teen difference and growth rate difference between males and females during pubertal growth trajectories. Mandibular sexual dimorphism already exists at nine years of age, but this is mostly in size not in shape. Growth direction in both males and females is similar but is faster, peaks later, and occurs over a longer period in males than in females. This results in increasing dimorphism in form which is evident in both size and shape. The dense morphometric approach provides detailed quantitative assessment in understanding the developmental mandibular sexual dimorphism in 3D.

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Conflict of Interest

None

Author contributions

Y.F. contributed to the design of the work, performed all the analysis under the supervision of H.M. and wrote the first draft of the manuscript. H.M. implemented the kernel regression model and played an important role in interpreting the results. N.K., R.H. and A.P. contributed to constructive discussion and revised the manuscript critically for important intellectual content. P.S. and P.C. revised the manuscript. All authors have read and approved the final manuscript. Our dear colleague John Clement, who's vision was instrumental in initiating this body of work tragically died while the manuscript was in preparation. He is greatly missed.

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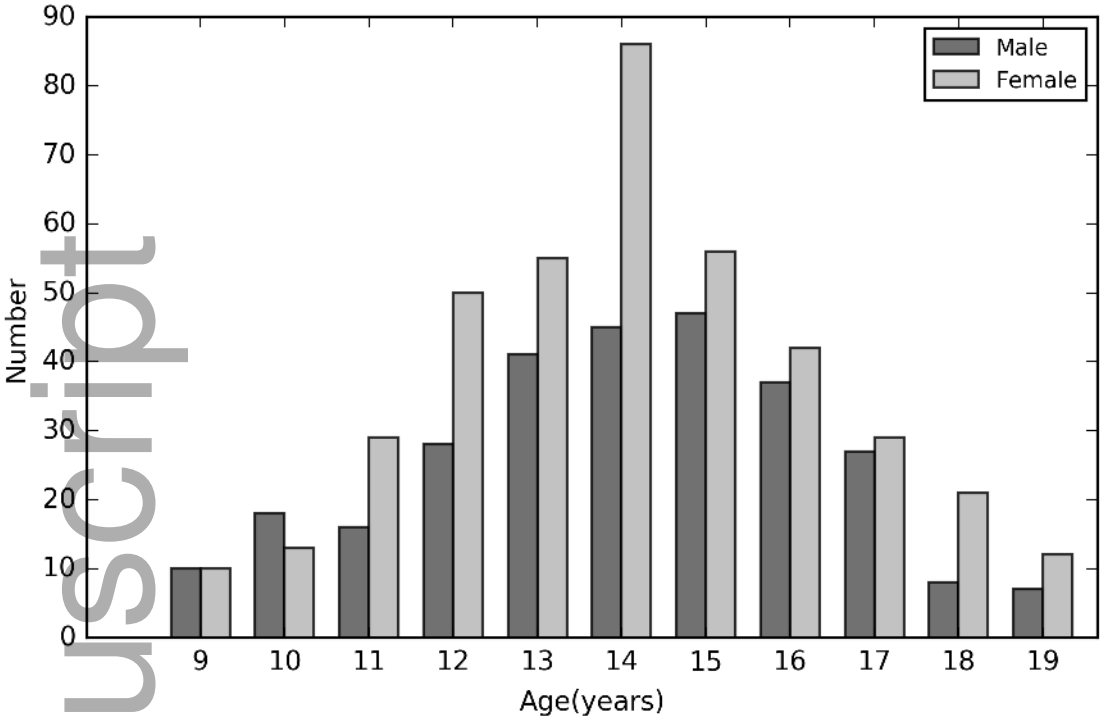
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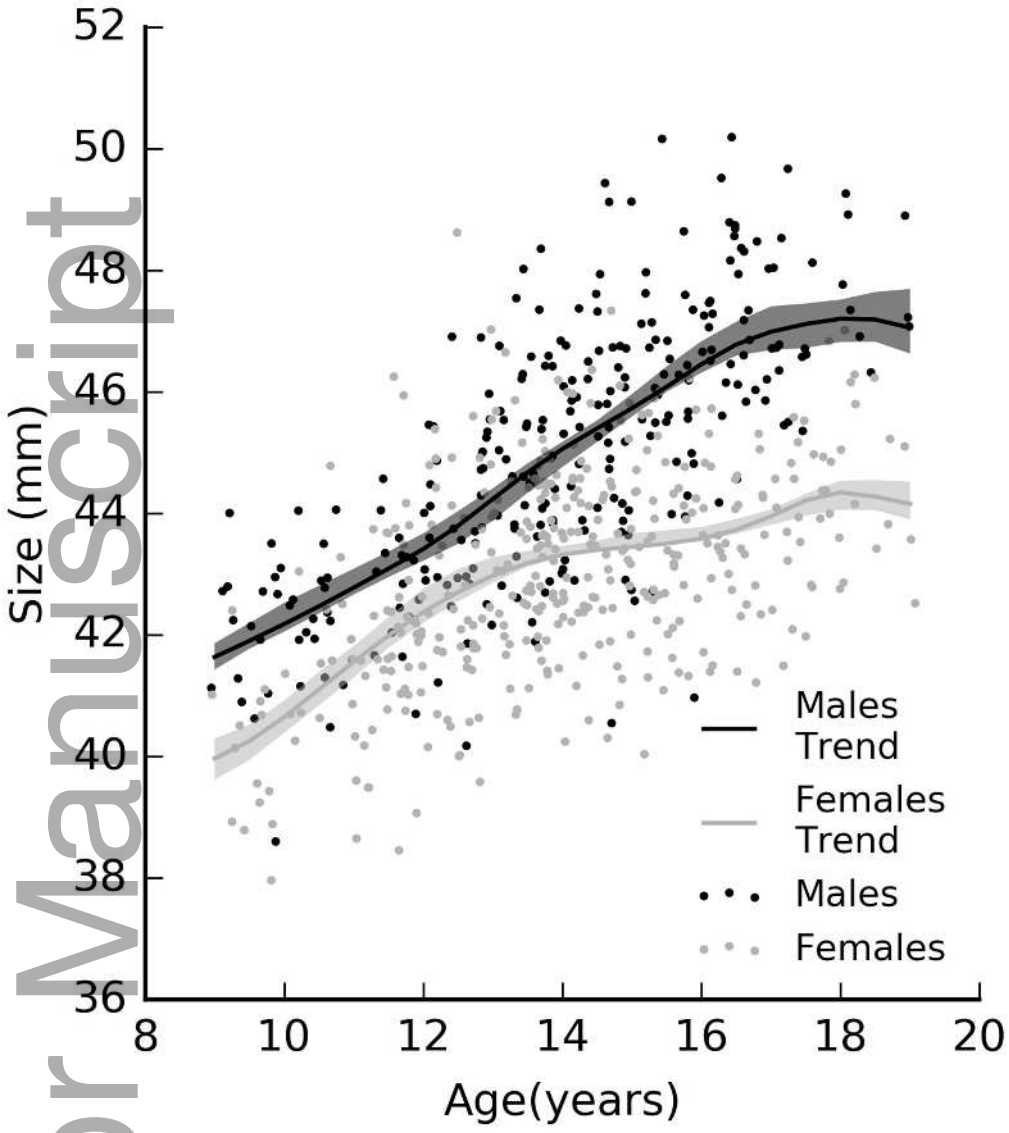


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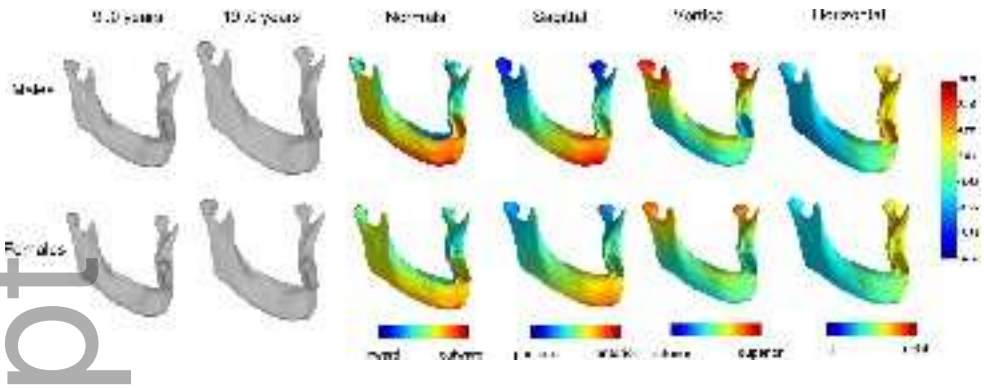
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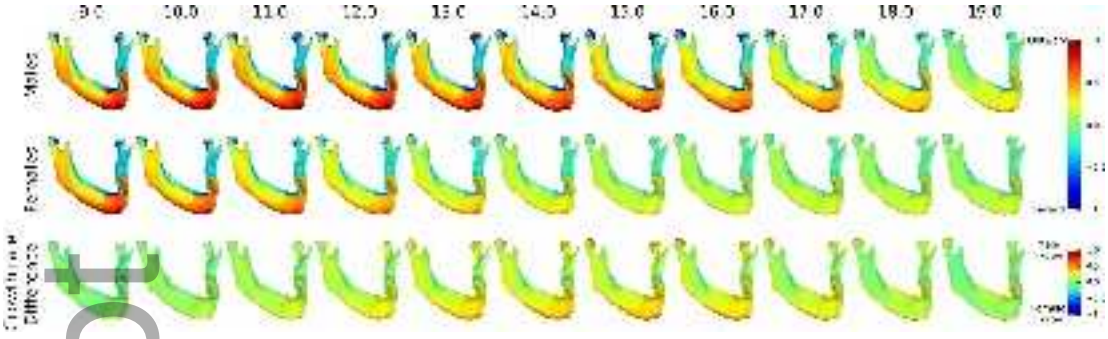
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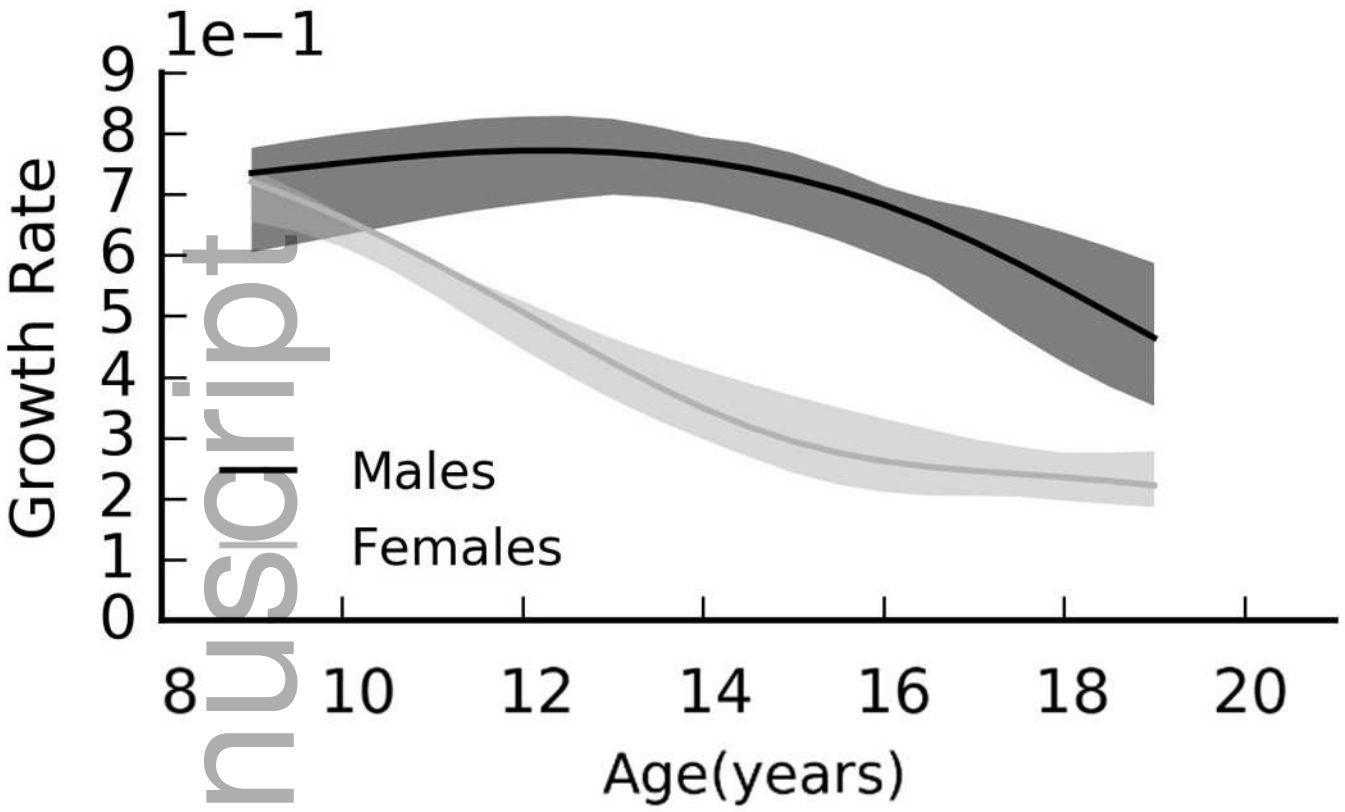
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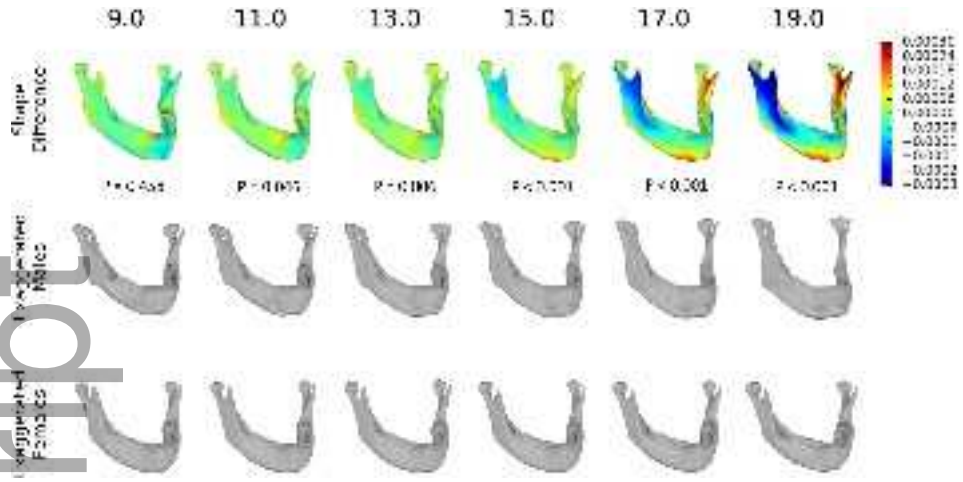
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