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REVIEW ARTICLES

The role of craniofacial maldevelopment in the modern OSA epidemic: a scoping review

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Objectives: There is increasing recognition that environmental factors affect human craniofacial development and our risk for disease. A scoping review of the literature was performed looking at environmental influences on craniofacial development to better understand this relationship and investigate what further study is needed to determine how this relationship may impact obstructive sleep apnea.

Methods: A comprehensive literature search was performed using the Ovid Medline database from inception to May 2020 with relevance to craniofacial development in 5 clinically oriented variables: diet, secular change, breastfeeding/nonnutritive sucking habits, nasal obstruction/mouth breathing, and masticatory muscle function. The Oxford Centre for Evidence-Based Medicine Levels of Evidence was used to assess studies based on study design.

Results: We initially identified 18,196 articles, of which 260 studies were fully reviewed and 97 articles excluded. The remaining 163 articles were categorized as follows: secular change (n = 16), diet (n = 33), breastfeeding/nonnutritive sucking habits (n = 28), nasal obstruction/mouth breathing (n = 57), and masticatory muscle function (n = 35). Ninety-three percent of included studies reported a significant association between craniofacial morphology and environmental factors. The majority of studies were characterized as low-level-of-evidence studies, with 90% of studies being a level-of-evidence of 4 or 5.

Conclusions: The studies in this review suggest that environmental factors are associated with changes in craniofacial development. However, most studies were heterogeneous and low-level studies, making strong conclusions about these relationships difficult. Future rigorous studies are needed to further our understanding of environmental influences on craniofacial development and obstructive sleep apnea risk.

Keywords: craniofacial development, maxilla, mandible, diet, breastfeeding, nasal obstruction, masticatory muscles

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INTRODUCTION

Obstructive sleep apnea (OSA) is a sleep-related breathing disorder characterized by intermittent reduction or complete cessation of breathing during sleep leading to hypoxemia, hypercapnia, and arousals.[1] Over the past 50 years since OSA was first characterized as a medical pathology, there has been an ever-increasing prevalence of the disease that is now estimated to affect over 25 million Americans and almost 1 billion people worldwide.[2–5] This epidemic has been partially attributed to various factors, including an aging population and weight gain[6]; however, the pathophysiology of OSA is influenced by multiple factors, including sleep dynamics, pulmonary loop gain, neuromuscular activity, and upper airway anatomy and craniofacial anatomy.[1,2,7]

Certain craniofacial features are associated with OSA. Increased anterior facial height and an inferiorly and posteriorly positioned hyoid on cephalometry have been associated with increased OSA risk.[8] Acute anterior cranial base angles, decreased anterior cranial base length, shorter maxillary and mandibular length, and increased posterior rotation of the mandible were also reported to be associated with OSA but with greater variability and heterogeneity among studies.[8] Three-dimensional imaging has been used to compare transverse facial dimensions between individuals with OSA and individuals without OSA showing decreased interdental widths and higher arched palates among individuals with OSA.[9–11] The studies, taken together, suggest that individuals with OSA have an overall lengthening, narrowing, and posterior rotation of their lower face compared with those without OSA. The literature is limited, however, in identifying factors influential to craniofacial development that predispose humans to OSA.

Craniofacial development is influenced by both evolutionary/hereditary and environmental factors. Evolutionary anthropologists have compared humans to our primate ancestors and suggest that aspects of our unique evolution may predispose us to OSA, namely due to enlarged brains and augmented vocal tracts. Increased brain size in mammals has been shown to correlate with more acute cranial base angles.[12,13] In humans, the increased acuity of the cranial base angle that accommodates our larger brains results in decreased facial projection and more downward oriented and posteriorly rotated facial growth. The evolution of the human upper airway is also unique because our larynx descends during infancy, separating the epiglottis from contacting the soft palate.[14,15] All other primates maintain a contact between the epiglottis and soft palate, which separates the airway from the alimentary tract. This separation is thought to allow humans to create more complex speech patterns but has also resulted in the oropharynx, a region where the posterior tongue enters the pharynx.[14,15] It is interesting to note that both a reduced cranial base angle and lower hyoid position (a marker of a more descended larynx) have both been associated with OSA risk.[8]

The evolution of our craniofacial structure has been encoded into our genetics and inherited from generation to generation, but craniofacial development is also influenced by environmental factors. In the last 3 years, both lay press and scientific journals have brought to light the role of environmental factors in human facial development, including diet, breastfeeding, and nasal obstruction/mouth breathing.[16–19] **Figure 1** and **Figure 2** provide an example of how the rapid changes in our environment pre- and post-Industrial Revolution may have influenced our craniofacial morphology. **Figure 3** illustrates the possible putative mechanisms for this evolutionary pathology. As there may be a significant potential to modify the trajectory of craniofacial development in our patients, there may be a correlative potential to modify patient risk for OSA. Studies of environmental factors and facial development in the literature are numerous, ranging from small observation studies to systematic reviews of specific variables, but there has been no work that attempts to synthesize the diversity of studies in one broad overview. Herein, we perform a novel scoping review to organize and analyze the available data regarding the role of environmental factors with respect to specific changes in our craniofacial development. Specifically, has recent civilization led to environmental changes that have influenced our craniofacial development, placing us at increased risk for craniofacially associated pathologies, specifically OSA?

METHODS

Scoping review overview

This scoping review was performed based on the framework described by Arksey and O'Malley[20] and further elaborated by Levac et al[21] and Munn et al.[22] This framework outlines several key goals in conducting a scoping review, as follows:

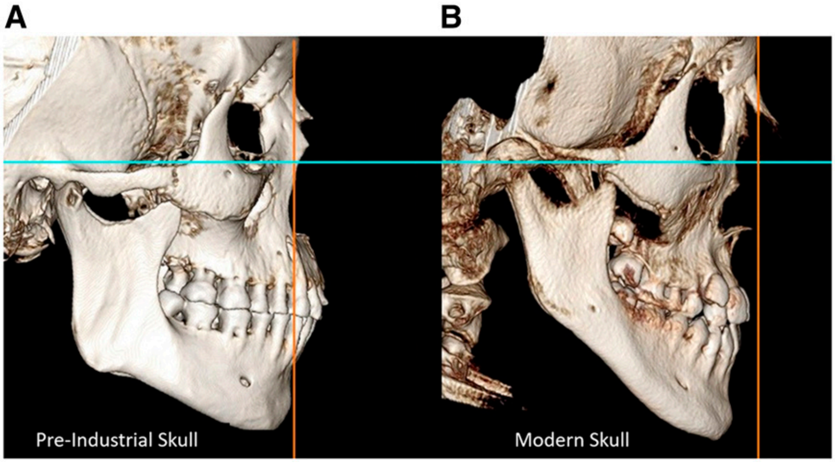
- To identify the types of available evidence in a given field
- To clarify key concepts/definitions in the literature
- To examine how research is conducted on a certain topic or field
- To identify key characteristics or factors related to a concept
- As a precursor to a systematic review
- To identify and analyze knowledge gaps[22]

Following this framework, we devised a search strategy to identify evidence from different environmental factors influencing craniofacial development. We clarify definitions and concepts in the literature regarding craniofacial analysis as well as identify key characteristics in studying craniofacial development. We performed a quality assessment using the Oxford Centre for Evidence-Based Medicine Levels of Evidence to assess the quality and type of research being conducted. Finally, we summarized the data to identify knowledge gaps and provide suggestions for future studies as a precursor to a systematic review.

Search strategy

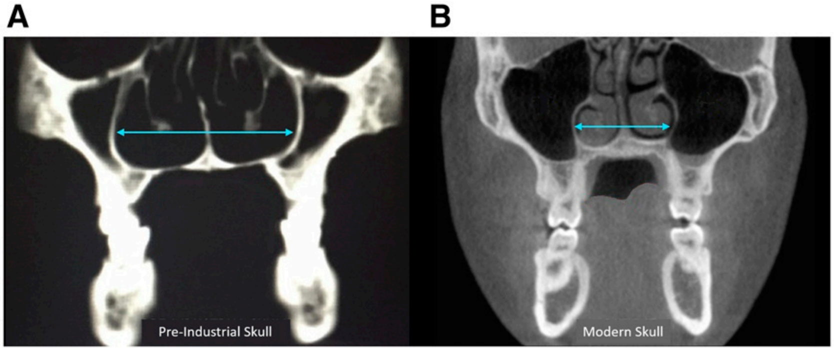
The search strategy was developed by the study authors in collaboration with an experienced medical librarian. A comprehensive search of the literature was performed using the Ovid Medline database from inception to May 2020. Publications were limited to English-language abstracts only. The purpose of the search was to maximally identify articles relevant to craniofacial growth and development pertaining specifically to size and morphology. To identify the maximum number of relevant articles, a broad search strategy was used using the following keywords: craniofacial, mandible, maxilla, or cranial base. These keywords were paired with permutations of the following

Figure 1—Sagittal profiles of 3-dimensional reconstructed CT imaging.



(A) Preindustrial and **(B)** modern human skull with history of nasal obstruction and mouth breathing. Features to note are a lengthening of the face as well as posterior rotation of the mandible in the modern skull that may be attributed to modern environmental influences. CT = computed tomography.

Figure 2—Coronal cross-sectional CT imaging.



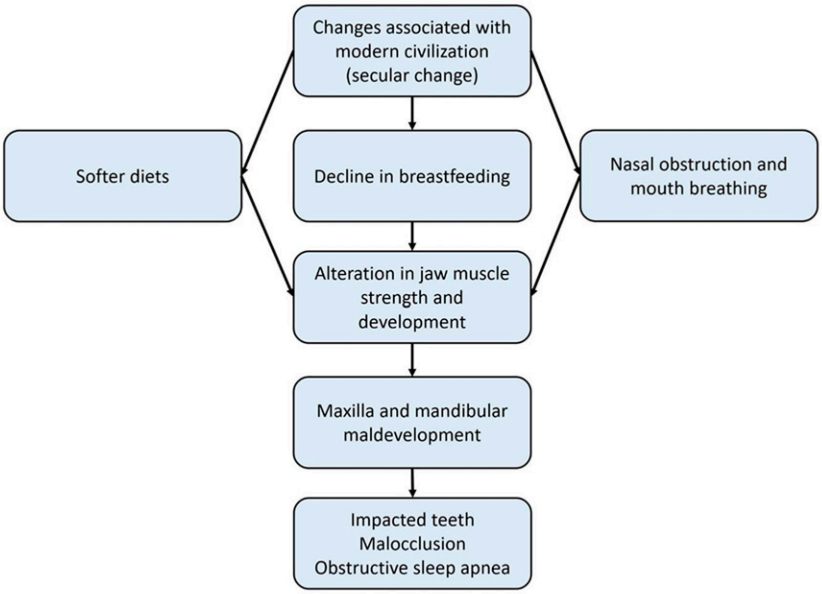
(A) Preindustrial and **(B)** modern human skull showing a narrowing of the bony nasal and oral cavity width in the modern human skull. CT = computed tomography.

adjectives: development, morphology, shape, size, growth, anthropology, evolution, consistency, structure or breadth, width, depth, arch, malocclusion, obstructive sleep apnea, airway, OSA, breastfeeding, and bite. The search was then restricted to remove nonrelevant studies pertaining to embryology, genetic disorders, disease processes, craniofacial surgeries, or molecular and cellular biology. The exclusion terms were as follows: embryo, cleft, nucleic, molecular, inflammation, dysplasia, stroke, carcinoma, cancer, microsomia, craniosynostosis, Pierre Robin, surgery, osteotomy, distraction, receptor, signaling, hedgehog, osseointegrated, ceramic, radiation, treatment, zebrafish, sinus, cyst, transcription, mutation, BMP, injury, therapy, advancement, implant, prosthetic, graft, anomaly, and chromosome.

Study selection process

Given the broad search strategy, it was decided to limit the scope of the studies to specific environmental factors. The following 5 clinically oriented variables were initially agreed upon by consensus among 3 authors (J.L.Y., A.T., and R.C.D.) prior to screening: diet, secular change, breastfeeding, nasal obstruction/mouth breathing, and masticatory muscle function. Experimental animal studies were included as part of the "To examine how research is conducted on a certain topic or field" mission in the scoping review framework. Experimental testing within animals may inform us of potential methods that could be applied for future human research. Animal models were limited to rodent and primate studies and must have used the same animal species as controls. All studies pertaining to maxillary and mandibular

Figure 3—Proposed interaction of environmental influences leading to craniofacial maldevelopment and ultimate pathology.



size and morphology or dental malocclusion were included. Dental malocclusion, defined as the abnormal alignment of the maxillary/mandibular teeth, was included as a marker of craniofacial deficiency. Studies looking at cranial skull dimensions, cranial base dimensions, bone histopathology, bone density, temporomandibular joint function, or dental factors other than malocclusion were excluded. Studies looking at masticatory muscle size and function were included, except for those assessing electromyography as the only variable or outcome.

Screening of the titles and abstracts of the retrieved studies for relevance was performed by 2 reviewers (J.L.Y. and A.T.), and discrepancies were resolved by consensus. Structured abstracts without full publication, case reports, and nonsystematic reviews were excluded at this stage. Two reviewers (J.L.Y. and A.T.) reviewed the remaining articles in their entirety for consistency with the study protocol. Disputes were resolved by a third reviewer (R.C.D.)

Additional search

During the initial screening, it was noted that several studies pertained to craniofacial development and the influences of nonnutritive sucking habits (NNSH), such as bottle-feeding, thumb-sucking, and pacifier use. It was decided by the 3 reviewers (J.L.Y., A.T., and R.C.D) to include NNSH as an additional factor of the "breastfeeding" category and a supplemental search was performed in the Ovid Medline database. The original unrestricted search parameter listed above was then cross-referenced with the following search terms: bottle-feeding, finger, thumb, sucking, pacifier, nonnutritive. The screening of titles and abstracts of these additional articles was performed by 2 reviewers (J.L.Y. and A.T.) following the same criteria outlined in the original search. Duplicates of articles already present in the original search were removed.

Quality assessment

Methodological quality of the included studies was assessed independently by 2 reviewers (J.L.Y. and A.T.). The Oxford Centre for Evidence-Based Medicine Levels of Evidence was used to assess studies based on study design: level 1, systematic review of randomized trials or n-of-1 trials; level 2, randomized trial or observational study with dramatic effect; level 3, nonrandomized controlled cohort/follow-up study; level 4, case series, case-control studies, or historically controlled studies; and level 5, mechanism-based reasoning. All animal studies were considered level 5 studies based on this scale. Data extraction was independently performed by 2 reviewers (J.L.Y. and A.T.) and discrepancies were resolved by consensus. The data extraction form for this scoping review included the following: (1) modifiable variable of interest, (2) study model (human vs animal), (3) study design, (4) level of evidence, (4) study groups, (5) outcome metric, and (6) study outcomes. The data underlying this article will be shared on reasonable request to the corresponding author.

Data pooling

Unlike systematic reviews, the framework of a scoping review excludes meta-analyses or assessing for risk of bias. Therefore, no meta-analyses were performed due to the heterogeneity of the included studies, sample populations, and data. The risk of bias across studies was not assessed.

RESULTS

We identified 18,196 articles in the initial search, with an additional 137 articles identified on the additional search for NNSH (**Figure 4**). After screening of titles and abstracts, 260 studies were fully reviewed and 97 articles were excluded for not meeting criteria on full review. A summary table of excluded fully reviewed articles is available in the supplemental material (**Table S1** in the supplemental material). The remaining 163 articles were categorized into 5 categories: secular change (n = 16), diet (n = 33), breastfeeding/NNSH (n = 28), nasal obstruction/mouth breathing (n = 57), and masticatory muscle function (n = 35). Overall, 152 studies (93%) reviewed reported a significant relationship between craniofacial morphology and environmental factors. See **Table 1** for a summary of articles with positive findings and level of evidence (LoE).

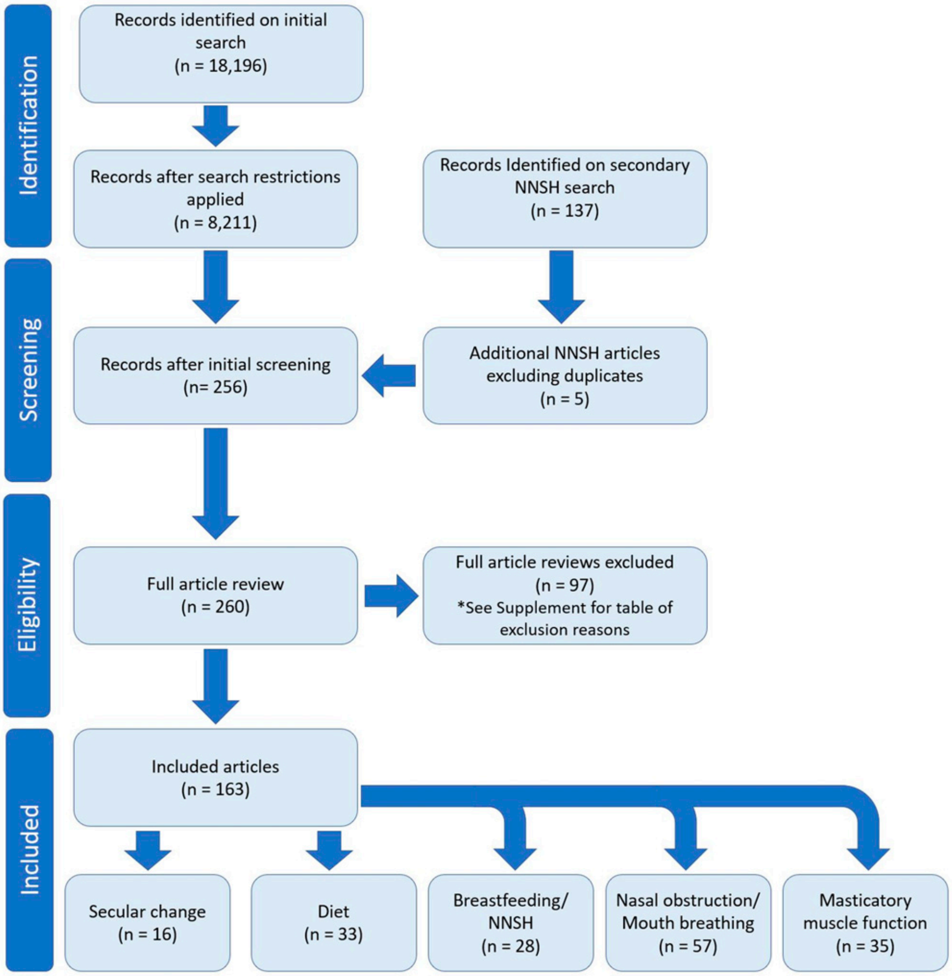
Secular change

Secular change is defined as biological change occurring over decades and generations, primarily thought to be driven by environmental factors. Our review identified 16 articles reporting secular changes to craniofacial dimensions. No animal model studies were identified for this topic. A summary table of articles fully reviewed in this category is available in **Table S2a** in the supplemental material.

Multiple studies have compared ancient human skulls and modern human cohorts showing differences in craniofacial dimensions over time. Festa et al[23] reported a millimeter (mm) reduction in maxillary length in modern Italians compared with a cohort of ancient skulls from the same Italian village (∼200 BC). A comparison of craniofacial dimensions between medieval European skulls (12th–14th century) and modern cohorts showed that modern cohorts had decreased mandibular breadth and height, increased mandibular body length, and increased gonial angle compared with ancient samples in similar geographic locations.[24,25] Kaifu[26] reported a narrowing of the mandible when comparing medieval Japanese skulls with modern contemporaries. Medieval skulls were also noted to have decreased incidence of malocclusion and dental crowding.[27,28] Bosman et al[29] reported on mandibular morphology of samples from 2 Dutch archaeological sites (1400s and 1800s), comparing them with mandibular magnetic resonance images (MRIs) from a modern Dutch sample. Results were mixed, as the older archaeological site and modern Dutch samples had comparably sized mandibles, while both samples had larger mandibles compared with skulls from the more recent archaeological site.

Several studies compared craniofacial dimensions between modern individuals and more recent historical cohorts. Defraia et al[30] compared skulls from 19th-century Italians with a modern Italian cohort, showing that modern samples had greater retrusion of the maxilla and more protrusion of the mandible. Comparisons of mandibles and maxillas from early and late

Figure 4—Flow diagram for study selection.



NNSH = nonnutritive sucking habits.

20th century samples in the United States report narrowing maxillary widths as well as thinner and more posteriorly rotated mandibular bodies.[31–34] Weisensee and Jantz[35] used geometric morphometrics to study Portuguese and U.S. skull collections spanning 150 years, showing an associated increased palatal breadth but decreased bizygomatic breadth over time. Hossain et al[36] compared cephalometric measurements between modern Japanese women with a population sample measured 20 years

Table 1—Summary characteristics of included studies reporting distribution of human/animal studies, whether a positive difference was reported, as well as the LoE.

Modifiable Factor of Interest	% Study Model (n)	Difference Reported (n [%] of studies)	LoE (n)
Secular change	100% Human (16)	Yes: 16 (100%)	4 (16)
Diet	33% Human (11); 67% animal (22)	Yes: 31 (94%); no: 2 (6%)	3a (1); 4 (11); 5 (21)
Breastfeeding and nonnutritive sucking habits	100% Human (28)	Yes: 23 (82%); no: 5 (18%)	2a (1); 3a (3); 4 (24)
Mouth breathing and nasal obstruction	79% Human (45); 21% animal (12)	Yes: 49 (86%); no: 8 (14%)	2a (1); 3a (1); 4 (43); 5 (12)
Muscles of mastication	56% Human (19); 44% animal (16)	Yes: 33 (97%); no: 1 (3%)	4 (19); 5 (15)

Overall, 93% of studies included in this scoping review reported significant differences in craniofacial morphology associated with environmental influences. However, the majority of studies were lower-level evidence, with 90% of all studies being LoE 4 or lower. LoE = level of evidence.

prior, also showing a significant increase in mandibular gonial angle and increased anterior facial height.

Two studies reported that changes in craniofacial dimensions over time may have been linked to specific environmental factors. Little et al[37] compared craniofacial dimensions in 3 samples from a rural Mexican community from 1968–1999. Both head length and bizygomatic breadth were narrower with time, which the authors attributed to changes in dietary consistency in the rural community over that time period. De Souza et al[38] evaluated the incidence of malocclusion among semi-isolated Amazonian tribesmen compared with those of the same ethnic background living in an urbanized society, showing a lower incidence of malocclusion in the former sample. The authors attributed the change from tribal to a more modern society to the observed differences in malocclusion.

Diet

The transition of the human diet from a hard to a soft consistency has been reported as a possible driving force for craniofacial changes. This review identified 33 studies evaluating diet and its influence on craniofacial development. Of these, 22 were in animal models and 11 studies were in humans. A summary table of articles fully reviewed in this category is available in the supplemental material (**Table S2b**).

Diet—animal studies

Experiments using rodents divided them into groups that were fed either a soft/liquid or hard diet. These studies revealed significant changes in maxillary and mandibular morphology between the groups. Craniofacial dimensions in the soft/liquid diet groups were characterized by decreased condylar length, decreased mandibular volume and thickness, decreased mandibular breadth and height, and decreased maxillary width.[39–56] Scheidegger et al[57] performed a systematic review and meta-analysis of diet and craniofacial development in rodent animal models, concluding there is significant evidence to suggest that a soft diet is associated with reduced condylar dimensions. Tuominen et al[58] presented contrasting results reporting that rats fed a soft diet had greater condylar height and length. Beecher et al[59] performed a primate study that compared squirrel monkeys fed either a hard (wild) or soft (laboratory) diet. They observed a decreased maxillary arch width, greater palatal arch height, and increased incidence of dental crowding in monkeys fed a soft diet.

Diet—human studies

Archaeological studies have looked at changes in craniofacial dimensions in ancient civilizations before and after their adoption of agriculture. Overall reductions in mandibular size have been observed as a result of the transition from hunter-gatherer to farming societies.[60] Increased incidence of malocclusion was also associated with this agricultural transition.[61] Studies have compared skulls from tribes existing in concurrent time periods within the geographical regions showing reduced maxillary and mandibular dimensions among tribes that had adopted agriculture vs those that remained hunter-gatherers.[62–66]

Beyond the agricultural revolution, studies have also shown more recent associations of craniofacial changes to evolving diets. Varrela[67,68] reported on differences in craniofacial dimensions between a modern cohort of Finns and preindustrial Finnish skulls dating back to the 16th century. Greater dental wear in the historical skulls was interpreted as a sign of a tougher diet, and those skulls had a decreased gonial angle, greater mandibular ramus height, and anterior placement of the lower portion of the face. Mays[69] also utilized dental wear as a marker of tougher diets, finding smaller gonial and ramus dimensions in mandibles with reduced dental wear among 2 northern European archaeological sites.

In contrast, our review identified 1 study reporting limited influence of dietary consistency on craniofacial dimensions. Eyquem et al[70] compared a cohort of modern South Americans with skulls of different ancient populations of the same region that differed in dietary consistency. Using 3-dimensional morphometric comparisons, the authors concluded that softer dietary consistency did not contribute to an overall decreased craniofacial size. Instead, their findings suggested that softer diets reduced constraints on the growth of the face and mandible, leading to greater variations in size and shape in modern humans compared with ancient populations.

Breastfeeding and NNSH

There were 28 studies in this review comparing changes in craniofacial development related to breastfeeding and NNSH. Ten studies evaluated breastfeeding vs bottle-feeding, 8 studies evaluated NNSH, and 10 studies looked at both breastfeeding and NNSH. Exclusive breastfeeding was defined as obtaining nutrition solely from suckling of the breast while bottle feeding included feeding of both pumped breast milk and infant formula. NNSH included digit sucking and pacifier use. No animal studies were identified in this review. A summary table of articles fully reviewed in this category is available in the supplemental material (**Table S2c**).

Exclusive breastfeeding was associated with decreased incidence of malocclusions, including posterior crossbite, anterior open bite, anterior overjet, and dental crowding.[71–79] Exclusive breastfeeding was also found to influence craniofacial dimensions, with several studies reporting increased maxillary arch width, decreased palatal arch depth, decreased mandibular plane angles, and decreased anterior facial height.[73,80,81] Of the studies assessing duration of breastfeeding, 4 reported that exclusive breastfeeding for 6–12 months or longer was associated with decreased incidence of malocclusion.[71,73,74,77]

Four studies noted no significant differences between breastfeeding duration and incidence of malocclusion.[82–85] Carrascoza et al[82] reported no significant differences in incidence of malocclusion with bottle-feeding. Luz et al,[83] Thomaz et al,[84] and Lopez-Freire et al[85] all reported no significant differences in malocclusion in response to breastfeeding duration.

Four systematic reviews of the literature were performed and are included in this review.[86–89] Abreu et al[86] reported mixed results of studies associating breastfeeding and malocclusion, concluding no significant relationship. Hermont et al[87] also reported that there was not sufficient evidence to confirm an association between breastfeeding and malocclusion, but found exclusive breastfeeding to be associated with a decrease in overall incidence of malocclusion. None of these reviews included a meta-analysis due to heterogeneity of the included articles. Boronat-Catalá et al[88] and Thomaz et al[89] performed systematic reviews with meta-analyses. Boronat-Catalá et al reported an increased risk of posterior crossbite and type II malocclusion among children breastfed less than 6 months; no other forms of malocclusion were associated with a decreased duration of breastfeeding.[88] Thomaz et al reported decreased incidence of posterior crossbite, anterior open bite, and overjet among children exclusively breastfed greater than 6 months.[89]

NNSH were associated with a variety of malocclusions, including CLASS II malocclusion, overjet, posterior crossbite, and anterior open bite.[31,71,77,83,90–92] NNSH were also found to influence craniofacial dimensions, with several studies observing decreased maxillary arch width and increased maxillary arch depth.[31,90,93–96] In studies examining both breastfeeding and NNSH, there was an additive effect of NNSH to worsening malocclusion.[76,77] Zen et al[97] reported the anterior palatal arch increased in both length and transverse dimension with pacifier use, but these measurements were obtained at only 6 months of age. There were no systematic reviews identified studying NNSH and craniofacial development.

Nasal obstruction and mouth breathing

Nasal obstruction and mouth breathing have been reported as potentially influencing craniofacial growth. This review revealed 56 articles related to nasal obstruction or mouth breathing and craniofacial development. Twelve were experimental studies performed in animal models and 44 were human studies. A summary table of articles fully reviewed in this category is available in the supplemental material (**Table S2d**).

Nasal obstruction and mouth breathing—animal studies

Of the animal studies, 7 were performed in rodent animal models. Studies in rats, where nasal obstruction was induced either through placement of nasal plugs or with surgical cautery, showed obstruction was associated with decreased mandibular height and length, decreased bigonial breadth, and decreased nasomaxillary height.[98–100] Placement of bite blocks in rats to prevent mouth closure as a way to simulate mouth breathing was reported to decrease mandibular condyle volume and width,[56,101,102] and was also associated with increased gonial angle, decreased mandibular ramus height, and posterior rotation of the maxilla.[101,103]

Five studies were performed in primates. Monkeys nasally obstructed with plugs had increased anterior facial height, a downward and backward rotation of the mandible, upward and backward growth of the condyle, increased gonial angle, increased mandibular plane angle, and development of anterior open/crossbite when compared with unobstructed controls.[104–106] One primate study used a dental device to force an open-mouth posture showing increased downward and anterior growth of the maxilla vs untreated controls.[107] Another study using a dental block to force an open-mouth posture reported that compensatory changes occurred in the mandible, including increased mandibular length and anterior rotation that attempted to close the physical gap imposed on the mouth.[108]

Nasal obstruction and mouth breathing—human studies

Our review identified 43 human studies that were performed looking at nasal obstruction or mouth breathing and craniofacial development. Many of the studies compared observed nasal obstruction or mouth breathing with craniofacial dimensions in children. Nasal obstruction or mouth breathing was associated with increased anterior facial height, decreased maxillary width, increased maxillary depth, increased mandibular gonial angle, increased mandibular plan angles, backward rotation of the mandible, and lower positioned hyoid bone.[109–128] Studies that quantified nasal obstruction through nasal-resistance measurements reported that increased nasal resistance was associated with increased maxillary–mandibular plane angles, decreased palatal width, and increased facial height.[129,130] Bakor et al[131] compared craniofacial morphology between mouth-breathing, nasal-breathing, and tracheostomy-dependent children. Mouth-breathing children had narrower mandibular and maxillary widths and increased facial height compared with both nasal-breathing and tracheostomy-dependent children, suggesting the open-mouth posture influenced facial growth.[131] Gross et al[114] serially monitored growth rates of children with open-mouth vs closed-mouth posture, finding decreased rates of maxillary arch growth over 3 years among open-mouth-posture children. Mouth breathing was also associated with increased incidence of malocclusions, including anterior open bite, posterior crossbite, increased dental crowding, and increased dental overjet.[78,92,96,110,125]

Specific etiologies of nasal obstruction and mouth breathing included allergic rhinitis, septal deviation, and adenoid hypertrophy. Children with mouth breathing or nasal obstruction attributed to allergic rhinitis showed higher palatal arches, decreased palatal volume, narrower maxillary widths, decreased maxillary length, greater anterior facial height, increased mandibular plane angle, and decreased mandibular length.[132–135] Children with nasal obstruction due to septal deviation were also reported to have similar findings of increased anterior facial height, increased gonial angle, maxillary retrusion, mandibular retrusion, high arched palate, and narrower maxillary width.[136] Finally, nasal obstruction and mouth breathing due to adenoid hypertrophy were associated with increased lower facial heights, steeper mandibular plane angles, and more retrognathic mandibles.[137–139]

Specific to adenoid and/or tonsillar hypertrophy, there have been studies looking at whether surgical excision led to improvement in nasal obstruction/mouth breathing and facial development. Kerr et al[138] and Woodside et al[140] reported that patients with nasal obstruction who received adenoidectomy had increased mandibular growth rate at the gnathion compared with unobstructed controls, suggesting "catch-up" growth after treatment of nasal obstruction. Linder-Aronson et al[137] reported greater transverse mandibular growth rates in participants treated with adenoidectomy, but this finding was only statistically significant in a female subgroup analysis. Mattar et al[141] reported that mouth-breathing children with adenotonsillar hypertrophy showed decreased posterior facial height, more inclined mandibular plane, and increased gonial angle compared with a control group of nasal-breathing children. After adenotonsillectomy, the mouth-breathing group had an increase in posterior facial height and a reduction in gonial angle, but growth did not fully normalize compared with controls. A systematic review by Becking et al[142] looked at 461 patients with adenotonsillar hypertrophy among 16 studies and reported that adenotonsillectomy was associated with increased maxillary arch width, decreased lateral crossbite, and overall more horizontal mandibular growth; however, there was significant heterogeneity between studies, impeding clear conclusion of these relationships.

Eight of the 43 human studies did not associate craniofacial differences with nasal obstruction or mouth breathing. Klein[143] reported no association between mouth breathing and increased facial height. Feres et al[144] reported no differences in cephalometric measurements between children with or without adenoid hypertrophy while Melink et al[90] and Costa et al[145] reported no association between adenoid hypertrophy and posterior crossbite. One systematic review that included 10 studies comparing posterior crossbite incidence with allergic rhinitis also concluded no association between the 2 variables.[146] Kumar et al[147] compared hyoid position among nasal- vs mouth-breathing children, finding no difference in position between groups. Franco et al[148] reported no significant changes in facial height growth patterns between nasal vs mouth breathers when observed for 1 year. Coelho et al[149] reported no differences in incidence of nasal vs mouth breathing in patients with Class II Division 1 malocclusion.

Muscles of mastication

Masticatory muscles act as an external force against the craniofacial bones that allow for movement of the jaw for chewing. It is believed that this traction and countertraction of the muscles and bones can lead to morphological changes in craniofacial development. Thirty-five studies were identified in this review specifically focused on how masticatory function can influence craniofacial development. Fifteen studies were in animal models while 20 were human studies. A summary table of articles fully reviewed in this category is available in the supplemental material (**Table S2e**).

Muscles of mastication—animal studies

Thirteen studies were performed in rat models. Studies induced muscle hypofunction through use of techniques including botulinum toxin (Botox, Allergan, Irvine, CA) injection, surgical denervation/surgical resection, or insertion of a bite device. Muscles of interest included the masseter, temporalis, pterygoid, digastric, and mylohyoid musculature.

Rats that were unilaterally injected with Botox into the masseter muscle, temporalis muscle, or both were found to have decreased mandibular ramus height, decreased mandibular body length, decreased mandibular corpus length, decreased maxillary length, decreased maxillary width, and an asymmetric tilt of the mandibular plane toward the injected side.[150–156] Botox injections into bilateral masseter muscles showed decreased mandibular body length and ramus height, increased facial height, clockwise rotation of the mandible, constricted bicoronoidal width, and constricted bigonial width compared with saline or uninjected controls.[154,157] Rats with induced masticatory hypofunction due to a bite appliance had narrower mandibular alveolar widths compared with unrestricted controls.[158] Unilateral denervation of masseter muscles in rats was reported in 1 study and showed no significant differences in craniofacial morphology when compared with both sham and unoperated control rats.[159]

Cruz et al[160] performed unilateral detachment and repositioning of the medial pterygoid muscle in rats, which was associated with decreased mandibular lengths and angular processes when compared with unoperated and sham-operated controls. Navarro et al[161] performed bilateral resections of masseter, temporalis, or suprahyoid muscles in different groups of rats and compared them with unoperated controls. The results showed that rats with masseter transection developed a downward rotated mandibular plane, while those with temporalis muscle or suprahyoid transection had an upward rotated mandibular plane. Spyropoulos et al[162] resected suprahyoid musculature, including bilateral digastric and mylohyoid muscles, finding decreased mandibular height and length, and an upward rotation of the mandibular plane among resected rats.

Hohl[163] performed surgical transposition of bilateral temporalis and masseter muscles on 5 monkeys with 1 unoperated monkey serving as a control. Cephalometric measurements 2 years after the surgery showed widening of the gonial angle and anterior and superior rotation of the mandibular–maxillary complex. Madeira et al[164] performed unilateral resection of the right masseter muscle on 10 monkeys. They reported asymmetric changes to the mandible including resorption at the mandibular angle and a diminished masseteric fossa on the resected side when compared with the unoperated left side.

Muscles of mastication—human studies

Twenty-two studies comparing human masticatory muscle function and craniofacial development were identified in this review. Muscle function and strength were assessed by a variety of methods, including muscle volume, muscle cross-sectional area (CSA), bite force, and mechanical advantage. Mechanical advantage is defined as the amount of force generated by a muscle for a measured contraction and is an indication of its efficiency in generating force.

Decreased muscle volumes in the masseter and medial pterygoid were associated with increased anterior facial height and decreased facial width.[165,166] Increased masseter muscle thickness measured on ultrasound was associated with a decreased anterior facial height, increased posterior facial height, increased mandibular length, decreased mandibular plane angle, and decreased gonial angle, as well as increased maxillary intermolar width, bizygomatic widths, and increased overall facial width.[167–172] Greater masseter, temporalis, and medial pterygoid muscle CSAs were associated with decreased anterior facial height, increased facial width, increased mandibular length, decreased gonial angle, and decreased mandibular plane angle.[173–175]

Sella-Tunis et al[176] performed a 3-dimensional morphometric analysis of mandibles and compared them with masseter and temporalis CSAs. They reported significant correlation of muscle CSA with specific mandibular morphology. Larger CSA was associated with a wider and more trapezoidal mandibular ramus, larger coronoid, more rectangular body, and more curved basal arch. Those with small muscle CSA had a triangular body, long and narrow ramus, and triangular basal arch.

Several studies also looked at muscle insertions, bite force, and mechanical advantage. Greater insertion angles were associated with decreased mandibular plane angles, increased posterior facial height, and increased gonial angle.[166,177] Greater bite force and mechanical advantage were associated with a greater posterior-to-anterior facial height ratio, decreased anterior facial height, increased mandibular ramus height, decreased gonial angle, increased bizygomatic width, increased intergonial width, and increased incidence of overbite.[172,175,178–183] In 1 study, children treated with a jaw muscle device to improve jaw strength reported significant increases in transverse maxillary and mandibular growth during 3 years of treatment when compared with 1-year observations both before and after completion of the therapy.[184]

DISCUSSION

Animal studies

Several articles in this review used animal models to study the relationship between specific environmental influences and craniofacial changes. Through these experiments, it is suggested that changes in dietary consistency, nasal obstruction, and muscle function led to measurable differences in craniofacial features when compared with control animals. This was apparent in different animal models, including rodent and primate, suggesting these influences may be generalized to all animals. However, as noted earlier, the human craniofacial form is unique among animals, and interpreting the significance of specific changes in craniofacial dimensions of other animal models in the context of human pathology is likely not applicable. Rather, these studies are significant in that they support the notion that environmental factors influence craniofacial development across species. Ultimately, further human studies are needed to better understand the relationship between environmental factors and craniofacial maldevelopment.

Secular change

The results of this section suggest that various ethnicities around the world have experienced a change in craniofacial dimensions over time. The most common patterns reported are narrowing of the maxilla and mandible, lengthening and thinning of the mandibular body, and downward/posterior rotation of the mandible leading to a narrower and longer face. Malocclusion rates have also increased over time. These changes have occurred in relatively short time spans of a few hundred years, with some evidence suggesting significant changes even across a few generations. Environmental changes, such as changes in diet or urbanization, are suggested to have played influential roles in shaping our craniofacial morphology.

Although these studies provide an interesting context for us to observe changes in craniofacial morphology, these historical comparisons of ancient and modern craniofacial shape can only be retrospective and observational. Information regarding historical specimens can only be inferred based on archaeological evidence and we can only theorize over the contributing factors that have led to reported changes. With regard to OSA specifically, it is likely impossible to ascertain a diagnosis in a historical sample population and therefore studies of secular change in relation to an increase in OSA incidence will likely be unfeasible.

Diet

The results of these studies suggest that changes in diet are associated with changes in craniofacial shape. Commonly reported changes describe a reduction in maxillary and mandibular dimensions as well as posterior rotation of the mandible. Softer diets were also associated with increased incidence of malocclusion. However, the current body of literature remains limited with weaknesses in study design, making these conclusions difficult to confirm. All studies were retrospective and observational in nature using historical samples. Changes in consistency of diet could only be inferred based on archaeological context or with indirect evidence such as dental wear. Outcomes of interest were also variable, including malocclusion and mandibular and/or maxillary measurements, making cross-comparison of studies difficult.

Breastfeeding and NNSH

The results of this section suggest an association between breastfeeding duration and changes in craniofacial dimensions as well as incidence of malocclusion. The larger prospective studies and systematic reviews with meta-analyses of the literature suggest that exclusive breastfeeding for greater than 6 months may be associated with a significant reduction in risk of craniofacial maldevelopment, namely in reducing malocclusion. Furthermore, NNSH also appear to be associated with increased incidence of malocclusion, decreased maxillary arch width, and increased maxillary arch depth.

However, this conclusion is by no means definitive as the overall quality of the literature remains poor, with several studies reporting no significant relationship. Most studies included were retrospective case series or cohort studies, and there was significant variability in outcome measures both noted in this review as well as in previous reviews. There was also a variety of different types of malocclusions and craniofacial dimensions being examined. Dental and craniofacial measurements were taken at various ages ranging from 6 months to adolescence. This can confound results if children were at different stages of primary or secondary dentition or if they had different rates of bone growth and maturity. Finally, in some studies, breastfeeding duration and NNSH were reported by parents retrospectively years afterward and could be confounded by recall bias.

Nasal obstruction and mouth breathing

Overall, nasal obstruction and mouth breathing were associated with features that suggest a narrowing and lengthening of the face as well as a backward rotation of the mandible. Incidence of malocclusion was increased in nasally obstructed or mouth-breathing patients. Similar metrics were reported across specific etiologies of nasal obstruction, including allergic rhinitis, septal deviation, and adenoid hypertrophy. There was limited evidence that correction of nasal obstruction could improve craniofacial growth patterns.

All studies regarding nasal obstruction or mouth breathing and craniofacial development were retrospective or low-quality prospective studies. Studies looked at a variety of different metrics, including cephalometric measurements of length, width, or height as well as different types of malocclusion, making it difficult to compare results across studies. The assessment of nasal obstruction and mouth breathing also varied among studies. Some studies observed children in nonclinical settings for open-mouth posturing and few studies used quantitative nasal airflow measurements. However, most studies identified nasal obstruction or mouth breathing through a combination of self-reported clinical examination findings and parental reporting, which may be subject to bias.

Muscles of mastication

The results of the review suggest that masticatory muscle function bears a relationship to craniofacial development. Studies show that smaller muscle size as well as weaker bite were associated with greater lower anterior facial heights, decreased facial width, and posterior rotation of the mandible. Greater insertion angles of masseter and pterygoid muscles against the bones were also associated with flatter mandibular planes. Differences related to muscle orientation may influence how efficient the muscles are in producing bite force, with studies demonstrating that participants with greater mechanical advantage had wider maxillary widths, shorter anterior facial height, and less posterior rotation of the mandible. It was suggested in 1 study that therapy to improve muscle function may alter craniofacial growth in children, but the study had a poor control group, using growth rates in the same children 1 year prior to therapy as a control.

All studies were retrospective or low-level prospective studies. Studies reported on a variety of different maxillary and mandibular cephalometric variables, with significant findings present in some, but not in other, studies. Studies also focused on different muscles of mastication, the most common being the masseter, but also the pterygoids and suprahyoid musculature. The methods to assess muscle function were also varied, making comparisons between studies difficult and overall conclusions hard to confirm.

Future directions

The purpose of this scoping review was to identify studies that explore the relationship between environmental factors and craniofacial morphology. Studies across all 5 topics of interest in our review provide support for the idea that environmental factors can influence craniofacial growth among humans as well as in animal models. However, when focused on the details of specific craniofacial measurements, the evidence becomes less clear. There was a lack of high LoE studies across all topics, with 90% of studies reviewed being LoE 4 or 5. Assessments of environmental factors like breastfeeding or mouth breathing were in general subjective, relying on patient or parent reporting, which could result in recall bias. Studies reported on a variety of craniofacial dimensions, making cross-comparison difficult. In addition, differences in specific craniofacial dimensions were sometimes significant in some studies but not in others.

Future studies on environmental influences and craniofacial development are needed to address the gaps and weaknesses of the current literature. A study design flow diagram outlining recommendations for standardizing future studies is presented in **Figure 5**. Standardized craniofacial measurements, including both transverse and sagittal points, can provide objective measurements for comparison between study groups and different studies. Angular cephalometric measurements of the maxillomandibular complex should also be recorded, as a posterior rotation of the mandible and mandibular plane was a common change reported in this review. The hyoid bone position should also be incorporated into craniofacial analysis as it is influenced by craniofacial development and may affect OSA risk. Given that lateral cephalograms only provide information in the sagittal position, alternative modalities such as computed tomography or magnetic resonance imaging may be suitable to obtain 3-dimensional imaging of the head and face for analysis. Although malocclusion may be a marker of craniofacial deficiency noted in this review, it is difficult to standardize across different malocclusion types and can be influenced by orthodontic care and should be avoided. Ideally, craniofacial measurements should be acquired after 6 years of age when greater than 80% of craniofacial growth has occurred.[185,186]

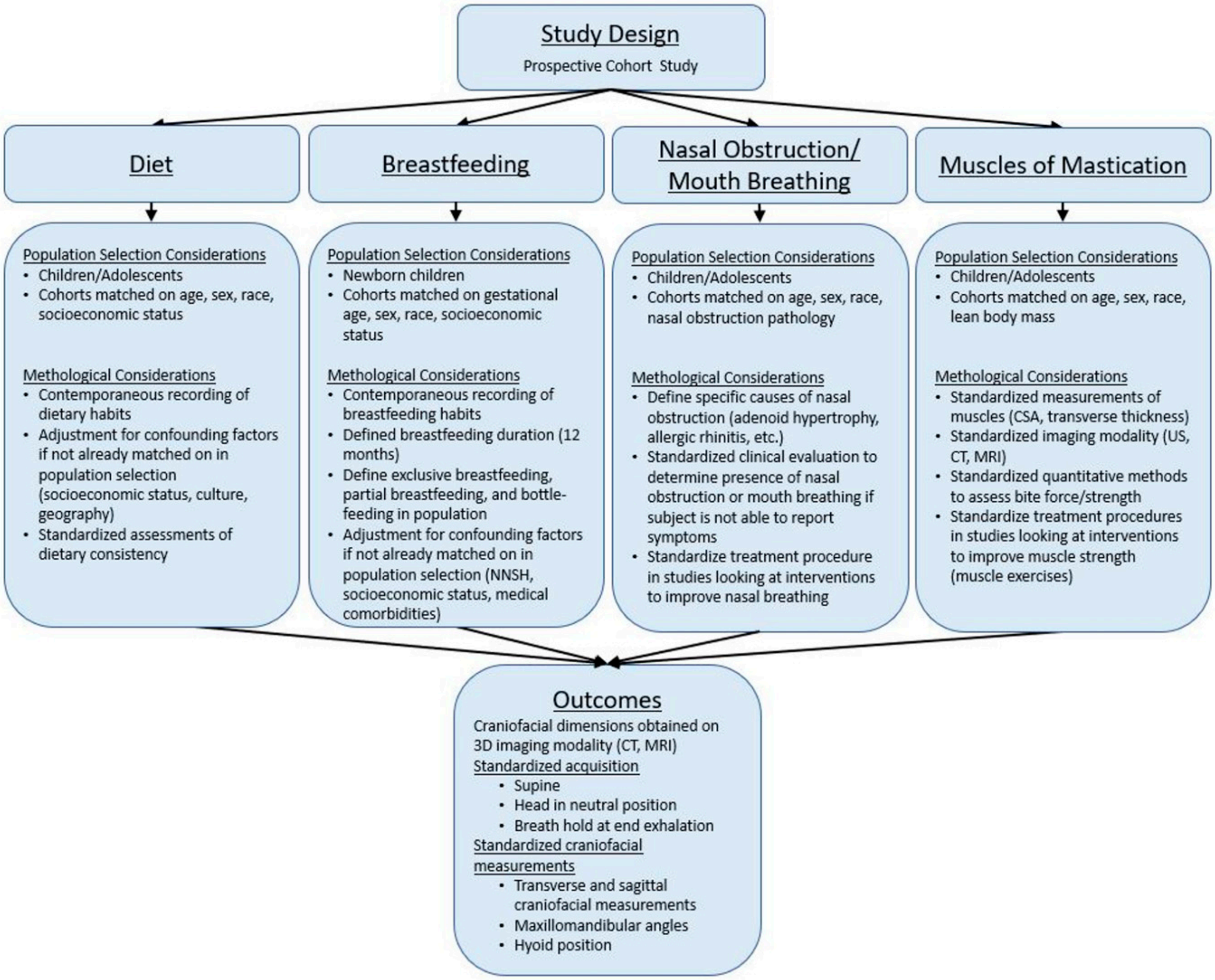
Reporting of environmental factors of interest also needs to be standardized and rigorous. Patient-reported factors such as breastfeeding, dietary habits, or mouth breathing should be determined contemporaneous with the time period of investigation to control for potential recall bias years later. Given that multiple environmental factors can influence craniofacial development, researchers need to be aware of these influences and should try to control for them, if possible, when studying a specific primary factor of interest. Although this review did not elaborate on genetic/hereditary factors, it is important to consider these factors when determining the study population. Unfortunately, experimental human studies may be difficult to execute as craniofacial development occurs over many years in childhood, with ethical challenges in restricting children's breastfeeding, diet, or nasal-breathing options. Large-scale prospective observational studies designed to control for confounding influences may offer a viable alternative method to study the relationships between certain environmental influences, craniofacial development, and ultimate OSA risk.

Strengths and limitations

Our study had several strengths. The scoping review was designed following a previously described framework. Inclusion of animal models and specifying 5 different environmental variables allowed us to broadly explore the evidence in the field, a primary goal of the review. Finally, we used the Oxford Centre for Evidence-Based Medicine Levels of Evidence to assess for quality of the research in the field.

There were several limitations to the study. We did not include multiple databases or a review of the gray literature, which may have limited our results and created selection bias. However, given the large number of articles reviewed from the single database, there was enough literature for us to accomplish the goals of the scoping review in identifying key concepts and current knowledge gaps. An assessment of bias was also not assessed among the studies reviewed. Bias assessment is not part of the scoping review framework but should be considered in future systematic

Figure 5—Study design considerations in evaluation of environmental influences and craniofacial development.



CSA = cross-sectional area, CT = computed tomography, MRI = magnetic resonance imaging, NNSH = nonnutritive sucking habits, US = ultrasound.

reviews. Finally, our recommendations for future studies include using a standardized craniofacial analysis; however, given the variety of measurements in the literature reviewed, a specific algorithm for craniofacial analysis is beyond the scope of this review but should be determined in future studies.

CONCLUSIONS

Craniofacial development is influenced by both genetic and environmental factors. Our understanding of modifiable environmental factors that influence craniofacial growth may be critical in reducing our risk for diseases related to craniofacial maldevelopment like OSA. Factors including diet, breastfeeding, nasal breathing, and masticatory muscle function are associated with changes in human craniofacial morphology. Commonly reported findings in the literature are an overall lengthening and narrowing of the face with a posterior rotation of the maxillomandibular complex in relation to changes in our environment. Of note, these features are also described as being risk factors for OSA. However, the strength of these relationships remains unclear as most studies in this review were heterogeneous, low-level studies, making it difficult to draw strong conclusions about specific craniofacial changes related to environmental influences. Future, rigorous prospective studies will allow us to better understand the complex relationship between environmental influences on craniofacial development and OSA risk.

ABBREVIATIONS

CSA, cross-sectional area
CT, computed tomography
LoE, level of evidence
MRI, magnetic resonance imaging
NNHS, nonnutritive sucking habits
OSA, obstructive sleep apnea
US, ultrasound

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