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Lower face asymmetry as a marker for developmental instability

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Abstract

Objectives: Fluctuating asymmetries in the craniofacial skeleton have been shown to be predictive for mortality from degenerative diseases. We investigate whether lower face asymmetries are a potential marker for the developmental origins of health and disease.

Methods: The lower face of a representative sample of 6654 12- to 17-year old United States (US) adolescents (1966-1970, National Health Examination Survey III) was classified as asymmetric when the mandibular teeth occluded prognathically (forward) or retrognathically (backward) on one side of the face only. It was investigated whether these lower face asymmetries were directional (preferentially to the left or the right) or fluctuating (random left-right distribution) in the US population.

Results: Lower face asymmetries affected 1 in 4 of the US adolescents. Unilateral retrognathic dental occlusions were fluctuating asymmetries, had a US prevalence of 17.0% (95% confidence interval: 15.5-18.4) and were associated with race/ethnicity ($P < .0001$), not with handedness ($P < .7607$). Unilateral prognathic dental occlusions were directional asymmetries ($P < .0001$), had a US prevalence of 7.6% (95% confidence interval: 6.4-8.7) and were associated with large household size ($P < .001$) and handedness ($P < .0223$). Lower face asymmetries were not associated with distinct heritable traits such as color blindness.

Conclusions: The findings suggest that lower face asymmetries are a marker for environmental stress and cerebral lateralization during early development.

1 | INTRODUCTION

Developmental stress during early life has been associated with fluctuating and directional asymmetries in the craniofacial skeleton. Fluctuating asymmetries (FA) are randomly distributed deviations that occur equally likely on the left or the right side of the face (Waddington, 1957). FAs have been documented for dental cusp traits (Khraisat et al., 2013), calcium content of teeth (Siegel & Mooney, 1987), mesio-distal or bucco-lingual tooth sizes (Khalaf, Elcock, Smith, & Brook, 2005), and mandibular condyle shape (Costa, 1986). FAs have been suggested to be the result of early-life stress such as protein deprivation, weaning trauma, heavy metal exposure, obesity and smoking (Corruccini, Handler, Mutaw, & Lange, 1982; Doyle & Johnston, 1977; Doyle, Kelley, & Siegel, 1977; Graham, Roe, & West, 1993; Harris & Nweeia, 1980; Kieser, 1992; Kieser, Groeneveld, & Da Silva, 1997; Kohn & Bennett, 1986; Mooney, Siegel, & Gest, 1985; Siegel & Doyle, 1975). Fluctuating asymmetries in the craniofacial skeleton have been interpreted within the framework of the developmental origins of health and disease, and identified as predictive of an increased mortality risk due to degenerative diseases (Weisensee, 2013).

Directional asymmetries (DA) are deviations from bilateral symmetry that occur preferentially on the left or the right side of the face (Waddington, 1957). Craniofacial DA have been widely documented (Vig & Hewitt, 1975) and related to cerebral asymmetries associated with handedness (Foundas, Leonard, & Heilman, 1995) In particular, right handedness has been associated with a higher ethmoid roof on the left side as identified on computed tomography scans (Kizilkaya et al., 2006) and larger areas on the left side of the face as identified on radiographs (Keles, Diyarbakirli, Tan, & Tan, 1997), photographs (Özener, Pelin, Kürkçüoğlu, Ertuğrul, & Zağyapan, 2011), and craniofacial tomography (Dane, Ersöz, Gümüstekin, Polat, & Dastan, 2004; Dane et al., 2002). DAs

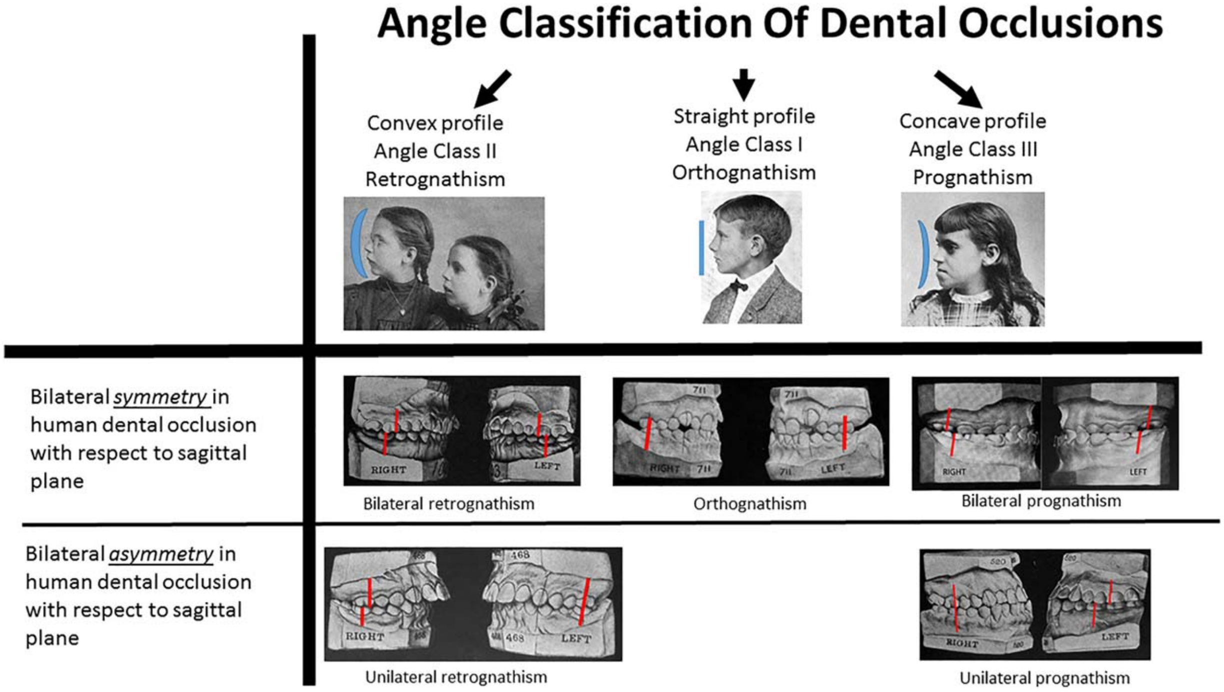

FIGURE 1 Edward Angle's classification of lower face variability based on dental occlusions with pictures from his 1907 textbook

have also been documented for mandibular landmarks and tooth sizes in response to in utero stresses such as twinning and maternal alcoholism (Heikkinen, Harila, Ollikkala, & Alvesalo, 2016; Klingenberg et al., 2010).

The asymmetries in craniofacial parameters can theoretically be expected to lead to, or to be reflected in, lower face asymmetries in the dental occlusion (Garn, Lewis, & Kerewsky, 1966; Topkara & Sari, 2012). Asymmetric tooth mineralization may lead to asymmetric dental caries distributions (Hujoel, Lamont, DeRouen, Davis, & Leroux, 1994; Vanobbergen et al., 2007) and consequent asymmetric arch lengths (Angle, 1907). Asymmetric tooth impactions, tooth agenesis and discrepancies can similarly lead to asymmetric arch lengths (Garn et al., 1966; Topkara & Sari, 2012). These dental and arch length asymmetries may contribute to asymmetries in dental occlusion (Figure 1).

It is a general biological hypothesis that development stress can lead to fluctuating asymmetries; random deviations from bilateral symmetry in a sagittal plane (Palmer & Strobeck, 1986). Our aim was to identify whether this general hypothesis applies to lower face asymmetries of the dental occlusion. To this purpose, we investigated whether occlusal asymmetries in the sagittal plane are fluctuating or directional, and to what extent these asymmetries are associated with socio-demographic and phenotypic characteristics. These evaluations were performed in the largest US survey with information on lower face variability.

2 | MATERIALS AND METHODS

The National Health Examination Survey (NHES) III was a probability sample of the US civilian, non-institutionalized population (1966–1970). Dental examinations were performed by seven dentists in 12- to 17-year-old adolescents [National Center for Health Statistics (U.S.), 1969]. The original race descriptors of "white," "black," and "other" have been replaced by European-American, African-American, and Asian-American. Lower income level was defined as those families reporting an annual income of less than the mode in the US population, which was less than $7000 a year (1966 income—unadjusted for inflation).

Lower face asymmetries: Angle's occlusal class I, II, III relationships were diagnosed independently on the right and the left side of the face. Angle's Class I, II, and III relationships are schematically represented in Figure 1 by the relative position of vertical lines on the maxillary and mandibular first molars. The top (cranial) vertical line bisects the mesiobuccal cusp of the maxillary first molar (|). The bottom (caudal) vertical line is the mid buccal grove on the mandibular first molar (|). These two vertical lines define the Angle occlusion classes I, II, and III. A straight line (|) reflects an orthognathic or Angle Class I occlusion. A forward staggered line on the right side (┌┘) and a backward staggered line on the left side (└┐) describe a retrognathic or Angle Class II occlusion. And, a backward staggered line on the right side (└┐) and a forward staggered line on the left side (┌┘) describe a prognathic or Angle Class III occlusion. The Angle Class II or III occlusal relationships were furthermore graded as moderate (up to a cusp-to-cusp deviation or (┌┘ or └┐)) or severe (beyond a cusp-to-cusp deviation or (┌──┘ or └──┐)).

Based on the original Angle classification (Angle, 1907), lower face symmetry was defined as a bilateral Angle Class I occlusion which is typically associated with a straight profile (left and right sides are ┃ and ┃, respectively), a bilateral Angle Class II (retrognathic) relationship (right and left side are respectively ┌┘ and └┐) and a bilateral Angle Class III (prognathic) relationship (right and left side are respectively └┐ and ┌┘). Angle referred to bilaterally prognathic or retrognathic occlusal relationships as Divisions.

Lower faced asymmetries, the focus of this report, were defined as Angle Class II (e.g., right side ┌┘) or an Angle Class III occlusion (e.g., right side └┐) on one side of the occlusal arch, and an Angle Class I occlusion (┃) on the other side. Angle referred to unilaterally prognathic or retrognathic occlusal relationships as Subdivisions.

The Angle mixed occlusions (a Class II on one side and a Class III on the other side) are not reported here due to their low prevalence ($n = 80$ or 1.1% of US population in NHES III). Following Angle's interpretation, we considered that adolescents with varying degrees of severity of bilateral Class II or Class III relationships on both sides (e.g., (┌──┘ on one side and └┐ on the other side) expressed bilateral symmetry.

Statistical analyses took into account the multistage, stratified, probability sample using the weights (H3ED0042), the strata (H3ED0023), and the clusters (H3ED0025) (SAS proc SurveyFreq, proc SurveyMeans, and proc Survey Logistic).

Aim I: Statistical assessment of fluctuating versus directional dental occlusal asymmetries: Randomness was evaluated by testing the null hypothesis that a unilateral prognathic or retrognathic occlusal relationship had the same odds for occurring on the right or left side of the face. A logistic regression model was selected to test this hypothesis. Failure to reject the null hypothesis led to a conclusion of FA. Rejection of this null hypothesis led to a conclusion of DA. The effect of ancestry and gender was evaluated by means of stratification. The following confounders were evaluated for their impact on the conclusions of FA or DA: past orthodontic care, past trauma, the number of decayed, missing, or filled teeth (DMFT), problems during pregnancy, and a parent assessment whether something was wrong at birth. Summary statistics on these potential confounders are provided in Table 1. The parent reports of "problems during pregnancy or delivery" and "something wrong at birth" were used as surrogate for potential forceps delivery and resulting occlusal asymmetries (Pirttiniemi, Gron, Alvesalo, Heikkinen, & Osborne, 1994). In addition, we tested the Geschwind-Galaburda hypothesis that left-handedness is randomly determined and more likely to be associated with symmetry in anatomical characteristics (Geschwind & Galaburda, 1985). The handedness as diagnosed by physicians was classified as left-handed versus right-handed or ambidextrous.

Aim II: The socio-demographic and phenotypic characteristics of adolescents with lower face asymmetry were compared to (i) adolescents with the corresponding bilateral symmetric prognathic or retrognathic malocclusions, and (ii) adolescents with bilateral symmetric orthognathic occlusions (Angle Class I). The age-dependent prevalence of occlusal asymmetries was evaluated by regressing prevalence on age, using the inverse of the squared standard error as weights. The significance of difference between regression slopes was assessed by means of an interaction term.

Aim III: Using logistic regression, dental occlusal asymmetry was related to commonly reported appearance-related occlusal characteristics: dental crowding (crooked teeth), overbite, overjet, and posterior crossbite. These occlusal characteristics were labeled here as appearance-related because they are defined in laymen dictionaries to describe the appearance of a person. In contrast, popular dictionaries do not have a laymen's term for the bilateral (a)symmetry of dental occlusions because the diagnosis of occlusal symmetry requires an intra-oral exam.

Prevalence of phenotypic characteristics were standardized for age (14.5 years old), ancestry (European-American, African-American, and Asian-American equally weighted), and sex (male and female equally weighted). To reduce the likelihood for spurious association, a Bonferroni correction for 10 comparisons ($P < .005$) was presented separately in the tables.

Summary survey statistics: The sample size in NHES III US was 6768 adolescents aged 12 to 17 years. The Angle classification of dental occlusions was missing for 114 individuals or 1.8% of the US adolescents (95% confidence intervals: 1.2%–2.4%). The number of individuals with an occlusal examination was thus 6654 (6768 − 114 = 6654). The socio-demographic characteristics of this study sample are described in Table 2. Eighty-six percent of the US sample with orthodontic examinations was European-American (95% CI, 82.4%–89.7%), 13.4% African-American (95% CI, 9.8%-17.0%), and 0.5% Asian-American (95% CI, 0.3%–0.7%). Males represented 50.5% of the sample (95% confidence interval: 49.5-51.5). The weighted mean age of the studied population was 14.9 years (95% CI 14.8–14.9). Forty-one percent of the population (including those with missing income information) reported having a total annual family income of less than the mode ($7000) (95% CI 36.3–45.7).

3 | RESULTS

Fluctuating versus directional lower face asymmetries (Table 3): Adolescents with a unilateral retrognathic occlusion (Angle Class II on right or left side, Angle Class I on the other side) had a fluctuating dental occlusal asymmetry (a failure to reject test for directional asymmetry: $P < .55$). Stratification for race/ethnicity and gender showed consistent results. Adjustment for potential traumatic events (broken

TABLE 1 Lower face variability and prevalence of past orthodontic care, trauma, and dental decay among 6654 US adolescents 12 to 17 years old in the National Health Examination Survey (1966–1970)

Lower Face Variability[a]	Orthognathic Class I	Retrognathic Class II		Prognathic Class III	
	Symmetric	Bilateral Symmetric	Unilateral Asymmetric	Bilateral Symmetric	Unilateral Asymmetric
Anything wrong at birth (missing 41)	220 6.1% (0.5)	51 5.4% (0.7)	69 6.3% (1.0)	22 5.8% (1.3)	32 5.9% (0.7)
Birth Injury (missing 3902)	3 0.2% (0.1)	5 1.3% (0.5)	1 0.2% (0.2)	1 0.6% (0.6)	2 1.2% (0.8)
History of orthodontic care (missing 40)	313[b] 9.4%[c] (0.6)[d]	115 13.0% (1.7)	102 9.3% (0.9)	40 9.8% (2.2)	36 7.1% (1.7)
History of bone fractures (missing 41)	625 17.7% (0.7)	178 18.0% (1.5)	177 15.5% (1.0)	71 17.2% (2.4)	84 15.4% (1.9)
History of accidents or injuries (missing 38)	423 12.1% (0.9)	113 11.6% (0.7)	137 13.2% (1.3)	59 13.7% (1.7)	65 11.9% (1.1)
History of Hospitalization for accidents (missing 36)	211 6.1% (0.5)	56 6.1% (0.7)	68 6.7% (0.7)	29 6.2% (1.4)	33 6.1% (0.9)
DMF[e]	6.0 (0.3)	6.3 (0.3)	6.4 (0.3)	6.3 (0.4)	6.2 (0.5)

[a]Eighty individuals with a mixed occlusion are not presented in this table.
[b]Sample size.
[c]Proportion of US population (adjusted for sampling design).
[d]Standard error of percent.
[e]Mean number of decayed, missing, and filled teeth.

bones, acute injuries, hospitalizations for injuries), a history of past orthodontic care, or past caries experience did not alter this lack of an association ($P < .59$, $P < .37$, $P < .93$, respectively). Neither did adjustment for problems during pregnancy or delivery or the observation that anything was wrong at birth change this lack of an association ($P < .25$ and $P < .58$, respectively). This conclusion remained accurate regardless of whether moderate or severe Class II unilateral relationships were evaluated ($P < .91$ and $P < .26$, respectively).

Adolescents with a unilateral prognathic occlusion (Angle Class III on right or left side, Angle Class I on the other side) had directional occlusal asymmetries (a rejection of the test for directional asymmetry: $P < .001$). Stratification for ancestry and gender showed consistent effects for gender but not for ancestry. The directionality was limited to adolescents with European-American ancestry. Adjustment for potential traumatic events (either broken bones, acute injuries, or hospitalizations for injuries), past orthodontic care, past caries experience, or problems during pregnancy did not alter the significance of this association ($P < .02$, $P < .001$, and $P < .04$, respectively). Neither did adjustment for "problems during pregnancy or delivery" or the observation that "anything was wrong at birth" change the significance of the association ($P < .002$ and $P < .0009$, respectively). This directionality was driven by a preponderance of moderate Angle Class III occlusal relationships on the left side of the occlusal arch ($P < .001$). There was no directionality in the left-right distribution of severe unilateral prognathic occlusions ($P < .95$). The Geschwind-Galaburda hypothesis of an increased prevalence of occlusal symmetry among left-handers was rejected ($P < .79$).

Asymmetry and handedness: For every 2 adolescents with unilateral prognathic dental occlusions occurring on

TABLE 2 Lower face variability and socio-demographics among 6654 US adolescents 12 to 17 years old in the National Health Examination Survey (1966–1970)

Angle Classification Symmetry	Orthognathic Class I Symmetric	Retrognathic Class II Division subdivision Symmetric	Retrognathic Class II Division subdivision Asymmetric	Prognathic Class III Division subdivision Symmetric	Prognathic Class III Division subdivision Asymmetric
Sample size[a]	3542[b] 53.6%[c] (1.0)[d]	978 14.5% (0.7)	1107 17.0% (0.7)	420 6.3% (0.5)	527 7.6% (0.6)
Sex					
Male	1835 50.3% (0.8)	521 50.9% (1.6)	574 50.1% (1.2)	224 51.6% (2.2)	277 50.4% (2.5)
Female	1707 49.7% (0.8)	457 49.1% (1.6)	533 49.9% (1.2)	196 48.4% (2.2)	250 49.6% (2.5)
Ancestry					
European-Am.	2914 83.9% (2.0)	911 94.0%**[g] (1.0)	994 90.3%** (2.0)	336 82.2% (3.2)	409 79.9% (3.4)
African-Am.	611 15.7% (2.0)	63 5.5%** (0.9)	111 9.5%** (2.0)	78 16.4% (3.0)	114 19.3% (3.3)
Asian-Am.	17 0.5% (0.1)	4 0.5% (0.3)	2 0.2% (0.2)	6 1.4% 0.5)	4 0.8% (0.4)
Income					
< mode	1527 41.5% (2.7)	341 34.6% (2.3)	439 38.3% (2.8)	200 45.7%* (3.5)	275 52.5%** (3.4)
> mode	2015 58.5% (2.7)	637 65.4% (2.3)	668 61.7% (2.8)	220 54.3% (3.5)	252 47.5% (3.4)
Household size	5.7[e] (0.1)[f]	5.7 (0.1)	5.6 (0.1)	5.6 (0.1)	6.2* (0.2)

[a]Eighty individuals with a mixed occlusion are not presented in this table.
[b]Sample size.
[c]Proportion of US population (adjusted for sampling design).
[d]Standard error of percent.
[e]Mean.
[f]Standard error of mean.
**Significance $P < .0005$; * significance $P < .05$ (Angle Class I comparison group).

the right side of the face, there were approximately 3 adolescents with a unilateral prognathic occlusion occurring on the left side of the face. The relationship between handedness and unilateral prognathic dental occlusion was complex. Overall, left-handers were less likely to have a unilateral prognathic dental occlusion. However, among those with a unilateral prognathic dental occlusion, left-handers were significantly more likely to have a unilateral prognathic dental occlusion on the left side of their face (crude odds ratio, 2.12; 95% confidence interval:1.12-4.00). There was no such association between handedness and the side of the unilateral retrognathic dental occlusion. Left-handers were not more likely to have a unilateral retrognathic dental occlusion on the left side of their face (crude odds ratio: 0.93; 95% confidence interval: 0.59-1.48; p-value: 0.7607).

TABLE 3 Prevalence and sidedness of lower face asymmetries in the adolescent U.S. population

Deviation from Bilateral symmetry	Severity of asymmetry	Laterality[a]	Prevalence (%)	95% confidence intervals		Directional Asymmetry[b]
Unilateral retrognathic (Class II Subdivision)	moderate	Left	6.7	6.1	7.3	0.91
		Right	6.8	5.9	7.7	
	severe	Left	1.6	1.1	2.1	0.26
		Right	1.8	1.4	2.3	
	Combined (mod.+sev.)	Left	8.3	7.7	9.0	0.55
		Right	8.6	7.6	9.6	
Unilateral prognathic (Class III Subdivision)	moderate	Left	3.8	3.1	4.5	<0.0001
		Right	2.6	2.0	3.2	
	severe	Left	0.6	0.4	0.8	0.94
		Right	0.6	0.4	0.8	
	Combined (mod.+sev.)	Left	4.4	3.8	5.0	<0.0001
		Right	3.2	2.5	3.8	

[a]Left means that the Angle class II/III was on the left side of the face, the Angle class I on the right side of the face. Conversely, right means that the Angle class II/III was on the right side, the Angle class I on the left side of the face.
[b]*P*-value for asymmetry in the left-right prevalence.

Asymmetry and socio-demographic factors: Unilateral retrognathic occlusions (Table 2) were associated with race/ethnicity ($P < .0001$), not with age ($P < .10$) (Table 4). This is in contrast to adolescents with bilateral retrognathic occlusions whose prevalence decreased with increasing age ($P < .005$) (Table 4). These age-specific prevalences of unilateral versus bilateral retrognathic occlusions differed significantly ($P < .02$).

Unilateral prognathic occlusions were associated with lower family income ($P < .0001$) and a large household size ($P < .0001$) (Table 2). Inclusion of both household size and poverty suggested that household size was the primary driver of this association. The prevalence of adolescents with unilateral prognathic dental occlusions did not change with age ($P < .41$) (Table 5). This is in contrast to adolescents with bilateral prognathic occlusions whose prevalence increased with increasing age ($P < .05$) (Table 4). These age-specific prevalence statistics of unilateral versus bilateral prognathic occlusions differed significantly ($P < .05$).

Asymmetry and anthropometric characteristics (Tables 4 and 5): Adolescents with lower face asymmetries (prognathic or retrognathic) and Angle Class I occlusions were similar with respect to ectomorphy, mesomorphy, endomorphy, adiposity, and phenotypic genetic markers. In contrast, adolescents with symmetric prognathic, retrognathic, and orthognathic dental occlusions differed with respect to ectomorphy, mesomorphy, endomorphy, adiposity, and phenotypic genetic markers (Tables 4 and 5).

Lower face asymmetry and appearance-related occlusal characteristics (Tables 4 and 5): Adolescents with a unilateral prognathic or retrognathic occlusion and adolescents with the bilateral orthognathic symmetry (Angle Class I occlusion) were dissimilar with respect to appearance-related occlusal characteristics. Adolescents with the unilateral and bilateral retrognathic occlusions had an increased prevalence of overjets of 6+ mm ($P < .0001$), deepbites of 6+ mm ($P < .0001$), and buccal crossbites ($P < .0001$) compared to adolescents with bilateral orthognathic symmetry. Adolescents with unilateral and bilateral prognathic dental occlusions (Table 3) were characterized by a higher prevalence of openbites ($P < .0001$), anterior crossbites ($P < .0001$), and posterior crossbites ($P < .0001$) compared to adolescents with bilateral orthognathic symmetry. With the exception of dental crowding, adolescents with a bilateral prognathic or

TABLE 4 Phenotypic and appearance-related occlusal characteristics of US adolescents with unilateral retrognathic (Class II) occlusions when compared to symmetric occlusions (12 to 17 year olds)

	Asymmetric	Symmetric	
	Unilateral Retrognathic	Bilateral Retrognathic	Bilateral Orthognathic
Phenotypic characteristics[a]			
Birthweight	3.3 (0.0)	3.2 (0.0)*[c]	3.3 (0.0)
Prevalence change with age	−0.5 (0.2)	−2.0 (0.3)*	−0.3 (0.1)
Body-Mass-Index	20.5 (0.3)	20.0 (0.3)**[d]	20.6 (0.3)
Ectomorphy	3.1 (0.1)	3.3 (0.2)**	3.0 (0.1)
Endomorphy	3.6 (0.2)	3.3 (0.1)**	3.6 (0.2)
Mesomorphy	3.9 (0.1)	3.7 (0.1)**	4.0 (0.1)
Waist-to-Height-ratio	41.6 (0.4)	40.8 (0.4)**	41.7 (0.4)
Color Blindness	1.8 (0.4)	3.0 (0.8)**	1.8 (0.4)
Rhesus EE phenotype	76.1 (1.8)	79.8 (1.6)*	75.5 (1.4)
Appearance-related occlusal characteristics[b]			
Dental crowding score	4.6 (0.1)**	4.9 (0.3)**	3.8 (0.1)
Overjet (6 mm or more)	22.0% (1.8)**	46.4% (2.7)**	8.1% (0.8)
Deepbite (6 mm or more)	6.4% (0.8)**	9.0% (1.5)**	3.1% (0.3)
Left buccal crossbite	4.2% (0.9)**	7.5% (1.1)**	2.0% (0.3)
Bilateral buccal crossbite	0.6% (0.3)*	1.7% (0.4)**	0.2% (0.1)

[a]Phenotypic characteristics for a representative sample of 12–17-year-old US adolescents with sex and ancestry equally weighted and with the reference age for estimation set at 14.5.
[b]Adolescents with a mixed occlusion ($n = 80$) and Asians ($n = 33$) excluded due to instability of estimates for appearance-related occlusal characteristics.
[c]*Statistically significant difference ($P < .05$) with Angle Class I as comparison group.
[d]**Statistically significant difference ($P < .005$) with Angle Class I as comparison group.

retrognathic dental occlusions had a significantly higher prevalence of the listed appearance-related occlusal characteristics than adolescents with a unilateral prognathic or retrognathic dental occlusion.

4 | DISCUSSION

Our findings suggest that dental markers for lower face asymmetries are common, affecting one fourth of US adolescents. Seventy percent of those affected, or 17% of the US population, have a unilateral retrognathic dental occlusion which was fluctuating and associated with race/ethnicity. The remaining 30% of those affected, or 8% of the US population, have a unilateral prognathic dental occlusion which was directional and related to handedness and family size. Lower face asymmetries developed before adolescence as their prevalence in the US population was invariable after the age of 12. The development of lower face asymmetries was not associated with phenotypic traits with high heritability estimates. These findings are consistent with the hypothesis that environmental stressors and cerebral lateralization contributes to the dental markers of lower face asymmetries.

Asymmetric lower face variability shows no associations to phenotypic characteristics with moderate to high heritability estimates. Adolescents with a prominent lower jaw on both sides of their face (symmetric) have an increased muscularity, increased adiposity, and increased skeletal robustness. In contrast, adolescents with a prominent lower jaw on just one side of their face do not share these phenotypic characteristics. Similarly, adolescents whom have a receding lower jaw on both sides of their face (symmetric) have a decreased muscularity, decreased adiposity, increased skeletal slenderness and traits such as colorblindness. In contrast, adolescents with a receding jaw on just one side of their face do not have these phenotypic characteristics. These distinct patterns of associations suggest that prognathism and retrognathism, when symmetric, are inherited characteristics.

TABLE 5 Phenotypic and appearance-related occlusal characteristics of US adolescents with unilateral prognathic (Class III) occlusions when compared to symmetric occlusions (12 to 17 year olds)

	Asymmetric	Symmetric	
	Unilateral Prognathic	Bilateral Prognathic	Bilateral Orthognathic
Phenotypic Characteristics[a]			
Birthweight	3.3 (0.0)	3.3 (0.1)	3.3 (0.0)
Prevalence change with age	−0.4 (0.4)	0.8 (0.3)*[c]	−0.3 (0.1)
Body-Mass-Index	20.6 (0.3)	21.3 (0.4)*	20.6 (0.3)
Endomorphy	3.6 (0.2)	3.9 (0.2)*	3.6 (0.2)
Ectomorphy	3.0 (0.1)	2.8 (0.1)*	3.0 (0.1)
Mesomorphy	3.9 (0.1)	4.2 (0.1)*	4.0 (0.1)
Waist-to-Height-ratio	41.8 (0.4)	42.8 (0.5)**[d]	41.7 (0.4)
Appearance-related occlusal characteristics[b]			
Dental crowding score	4.4 (0.2)*	4.8 (0.3)**	3.8 (0.1)
Openbite (0 mm or more)	11.6% (2.2)**	30.2% (3.2)**	5.9% (0.7)
Ant. cross/edge-to-edge bite	6.8% (1.8)**	21.9% (3.0)**	1.0% (0.3)
Crossbite of at least one tooth	19.0% (1.6)**	30.8% (2.5)**	14.2% (0.8)
Right lingual crossbite	9.5% (1.7)*	20.1% (2.3)**	6.4% (0.7)
Left lingual crossbite	10.1% (1.1)**	19.9% (1.8)**	6.5% (0.6)
Bilateral lingual crossbite	3.8% (1.1)*	11.9% (1.7)**	2.0% (0.4)

[a]Phenotypic characteristics for a representative sample of 12–17-year-old US adolescents with sex and ancestry equally weighted and with the reference age for estimation set at 14.5.
[b]Adolescents with a mixed occlusion ($n = 80$) and Asians ($n = 33$) excluded due to instability of estimates for appearance-related occlusal characteristics.
[c]* Statistically significant difference ($P < .05$) with Angle Class I as comparison group.
[d]** Statistically significant difference ($P < .005$) with Angle Class I as comparison group.

Prognathism and retrognathism, when asymmetric, are acquired characteristics.

Symmetric lower face variability is uniquely related to growth characteristics of the lower jaw. Adolescents with a prominent lower jaw on both sides of their face (symmetric) continue to have pronounced lower jaw growth grow during adolescence. In contrast, adolescents with a prominent jaw on just one side of their face do not exhibit such pronounced lower jaw growth. Similarly, adolescents whom have a receding lower jaw on both sides of their face (symmetric) have pronounced lower jaw growth during their adolescence (as reflected by the decreasing prevalence of this type of lower face variability with increasing age). In contrast, adolescents with a receding jaw on just one side of their face do not exhibit such pronounced lower jaw growth during their adolescence. The extent of lower jaw growth during adolescence thus depends significantly on the symmetry of the lower face. These findings from our cross-sectional study and inference from prevalence data on growth are consistent with a longitudinal growth study which reported that occlusal asymmetries do not improve or worsen with growth (Veli, Yuksel, & Uysal, 2014). Growth patterns are largely an inherited characteristic therefore suggesting once again that that prognathism and retrognathism, when symmetric, are inherited characteristic and that lower jaw asymmetries are acquired characteristics.

The fluctuating nature of retrognathic asymmetries suggests an etiology of developmental instability. The influence of early life experience on chronic disease in adulthood, particularly with regard to critical periods of pre- and post-natal development has become increasingly accepted (Hales & Barker, 2013; Wells, 2012) This model suggests that systemic disruption by stress during early life may result in increased risk for chronic disease through physiologic, structural, metabolic, immunologic and epigenetic pathways

(Bateson, 2001; Bateson et al., 2004; Hales & Barker, 2013). Unilateral retrognathic occlusions may serve as early-life markers caused by such physiologic stressors (Gluckman & Hanson, 2005). Such a hypothesis is consistent with the hypothesis of asymmetric craniofacial relationships being a predictor for a susceptibility for degenerative diseases in adulthood (Hales & Barker, 2013; Weisensee, 2013).

It is noteworthy that hemifacial microsomia and unilateral retrognathic occlusion, two conditions with a smaller mandible on one side of the face, both exhibit fluctuating asymmetry (Xu et al., 2015). Hemifacial macrosomia occurs in the 4th week of pregnancy and has a wide spectrum of clinical severity ranging from mild to severe (Kan, Doyle, & de Chalain, 2002; Vento, LaBrie, & Mulliken, 1991). Possibly, a fraction of the unilateral retrognathic occlusions are low-grade forms of hemifacial microsomia shaped by common environmental stressors early in pregnancy. Evidence on deviations from bilateral symmetry in the permanent teeth sizes (which mineralize after birth) suggests that postnatal factors, separate from prenatal factors, may also play a role in the genesis of unilateral retrognathic dental occlusions.

Our study does not find an association between low birth weight and lower face asymmetries. This finding is inconsistent with the Barker hypothesis that low birthweight is a marker for environmental in utero stress and a subsequent adverse life course (Barker, Winter, Osmond, Margetts, & Simmonds, 1989). On the contrary, our findings suggested that low birth weight is typical for adolescents with a bilateral (symmetric) retrognathic lower jaw and the range of associated phenotypic characteristics (Hujoel, Bollen, Yuen, & Hujoel, 2016). In the early 20th century such somatotypes were described as ectomorphs and many studies have suggested they have an increased susceptibility to infectious diseases (Hujoel et al., 2016). Thus, our findings imply that low birth weight can be a marker for a distinct life course because of hereditary factors, and that fluctuating deviations in the lower face may be a more specific measure of environmental stress in early life.

The directional nature of unilateral prognathic occlusions and their association with handedness suggests cerebral lateralization as an etiology. DAs in the facial skeleton have been extensively documented and start shaping in utero with handedness and asymmetries detected as early as in the 10th week of gestation (Corballis, 2014). Unilateral prognathic occlusions may reflect an inability of early craniofacial growth to accommodate unequal development of the cerebral hemispheres. Our findings suggest such unilateral directionality is independent of sex but limited to adolescents with European-American ancestry. The potential role of environmental stress such as increased levels of testosterone (Chura et al., 2010) as a cause of rare and severe unilateral prognathic occlusions, which could not be confirmed as directional asymmetries, cannot be excluded given the association with family size and poverty. Possibly, these socio-demographic variables are markers for some form of environmental stress. The association of DAs with poverty suggests they may be predictive of the chronic diseases that are associated with low socio-economic class (Agardh, Allebeck, Hallqvist, Moradi, & Sidorchuk, 2011; van Loon, Brug, Goldbohm, van den Brandt, & Burg, 1995). The role of fetal testosterone levels has been discussed earlier in terms of asymmetric development (Geschwind & Galaburda, 1985; Heikkinen et al., 2016)

Our findings suggest that the common practice of classifying dental malocclusions on appearance-related occlusal characteristics such as dental crowding regardless of the underlying asymmetry is problematic within the context of etiology. Adolescents with a bilateral or a unilateral prognathic jaw may share the appearance-related characteristics of an underbite. Similarly, adolescents with a bilateral or a unilateral retrognathic lower jaw may share the appearance-related characteristics of an overbite. These similar dental appearance characteristics may belie distinct inherited versus acquired etiologies.

The practice of largely ignoring lower face asymmetry became prevalent toward the end of the 20th century. The last US national survey to measure bilateral symmetry in dental occlusions ended in 1973 (National Center for Health Statistics, 1972). National surveys in Brazil and the UK similarly ignored the diagnosis of bilateral symmetry (Roncalli, Cortes, & Peres, 2012; Todd et al., 1975). A survey of orthodontic textbooks shows that most defined prognathic occlusions ignoring the presence of sagittal symmetry (Graber, Vanarsdall, & Vig, 2005; Huang et al., 2011; Moyers et al., 1989; Proffit, 2013).

We speculate that ignoring lower face asymmetry is in part responsible for the current controversy over whether human malocclusions are inherited or acquired. Medical explorers, bio-archeologists, and anthropologists have provided evidence that appearance-related occlusal characteristics are acquired characteristics, markers of civilization which appear with nutrition transitions (Cleave & Campbell, 1966; Corruccini, 1999; Pinhasi, Eshed, & von Cramon-Taubadel, 2015; Price, 1945) or other environmental stressors (Wang et al., 2003). It is on this basis that asthma and poor vision have been suggested to be associated with malocclusions (Faria, de Oliveira, Santos, Santoro, & Fernandes, 2006; Hegde, Shetty, & Kar, 2015; Monaco et al., 2013; von Hertzen, 2002). Geneticists, in contrast, have provided evidence that facial characteristics and appearance-related occlusal characteristics including prognathism and retrognathism are largely inherited (Frazier-Bowers, Rincon-Rodriguez, Zhou, Alexander, & Lange, 2009; Mossey, 1999; Polderman et al., 2015; Xue, Wong, & Rabie, 2010). We provide evidence in this study that the almost exclusive focus on appearance-related occlusal characteristics may be the cause of this controversy. Darwin's comment that deviations from bilateral symmetry may be key to disentangle genetic from environmental causes may need to be considered when exploring the etiology of lower face variability. (Palmer & Strobeck, 1986).

There is limited evidence to suggest that asymmetry in the occlusal relationships is correlated with both subjective and objective measures of facial symmetry (Ostwald et al., 2015). This may be relevant as a large body of literature has related facial symmetry to attractiveness and thus genetic selection pressures, intelligence, and health-related characteristics such as the number of respiratory infections (Little, Jones, & DeBruine, 2011; Pound et al., 2014). In contrast, we are aware of only one study investigating the biological significance of asymmetries in dental occlusion (Heikkinen, Poikela, Gron, & Alvesalo, 2004). Our findings are in agreement with this study; there is no increased occlusal symmetry among left-handed adolescents as would be predicted by brain laterality being random in a subset of individuals and being more likely to be associated with bilateral symmetry (Annett, 1981; Geschwind & Galaburda, 1985). Further work on the interaction between occlusal and facial asymmetry may link two largely independent research fields.

The study strengths included the representative large sample of the US, the standardized examination protocol executed by dentists, the very low prevalence of unexplained missing data on occlusal (a)symmetries and the low prevalence of orthodontic care. The data from the birth records and parents' questionnaires allowed us to rule out the explanation that directional or fluctuating asymmetries were the result of extra-somatic factors such as trauma, disease, or birth injuries. Weaknesses of this study were the issue of multiple comparisons, the absence of a continuous measure of asymmetry (Palmer & Strobeck, 1986), lack of power and specificity to investigate the role of forceps during delivery as a cause of asymmetries (Pirttiniemi et al., 1994). The lack of 3-dimensional radiography to investigate the role of skeletal and dental components such as bimaxillary protrusion and brachycephaly further limited our evaluations of lower face asymmetry. Such assessments may be feasible for small-scale studies (Minich et al., 2013) but not for large-scale epidemiological investigations where simplicity and ethics prevent radiographic examinations. The small number of Asian-Americans was a weakness in the explorations on the role of race/ethnicity in the bilateral symmetry of malocclusions.

We conclude that developmental stress and cerebral lateralization may play a role in the development of lower face asymmetry. Healthy People 2020 has adopted a life-course perspective of health and disease, and reported a need to identify biomonitoring tools for intercepting adverse life courses that are set in early life. Asymmetries in craniofacial landmarks have already been commonly advocated as useful tools to measure developmental instability. Our findings suggest that occlusal asymmetries may provide an additional non-invasive and simple biomonitoring tool.

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AUTHOR CONTRIBUTIONS

PH analyzed the data and drafted the manuscript. EM and AMB edited the manuscript for intellectual content, provided content expertise, and provided critical comments on the manuscript.

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