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The Facial Morphology in Down Syndrome: A 3D Comparison of Patients with and without Obstructive Sleep Apnea

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Abstract

Obstructive sleep apnea (OSA) occurs at a high prevalence in patients with Down syndrome (DS). A polysomnogram, which is often cumbersome and challenging, remains the gold standard method of diagnosing OSA. OSA in patients with DS is often attributed to skeletal and soft-tissue structural alterations that are characteristic of the DS phenotype; as such, we hypothesized that assessing anthropometric facial measurements may be predictive of OSA in patients with DS. We used the 3dMDface stereophotography system to capture and create 3D facial images, and we subsequently identified facial landmarks using a single, experienced investigator and utilizing proprietary software to calculate inter-landmark distances and angles. We compared our findings with similar data for neurotypically developing participants. We further compared the findings in participants with DS with and without OSA. Participants with DS had maxillomandibular hypoplasia with smaller ear, nose, and eye measurements compared to neurotypically developing peers. We found no statistically significant differences in 3D photogrammetric measurements between participants with DS with or without OSA.

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Keywords

Down syndrome; Trisomy 21; Obstructive sleep apnea; polysomnography; 3D imaging; anthropometry

INTRODUCTION

Down syndrome (DS) is the most common chromosome condition in humans. Patients with DS have distinctive facial features. Some of the facial characteristics reported in the literature include almond-shaped palpebral fissures, epicanthical folds, reduced orbital width and height, smaller interorbital distances, midfacial hypoplasia, missing or small nasal bones, mandibular prognathism and ear dysmorphology [Fink et al. 1975; Frostad et al. 1971; O'Riordan and Walker 1978; Starbuck et al. 2011]. Obstructive sleep apnea (OSA) is particularly prevalent in patients with DS, with prevalence estimates ranging from 30–60% [Levanon et al. 1999; Shott et al. 2006; Stebbens et al. 1991]. This has been attributed to the skeletal and soft-tissue structural alterations that are characteristic of the DS phenotype, predisposing patients with this condition to sleep disordered breathing and airway obstruction. These specific alterations include adenotonsillar hyperplasia, midfacial and mandibular hypoplasia, hypotonia, macroglossia, choanal atresia, an acute cranial base angle, and small upper airways [de Miguel-Diez et al. 2003; Goffinski et al. 2015; Ng et al. 2006].

Given the relationship of these structural alterations and sleep-disordered breathing, we hypothesized that inter-landmark distance and angular measurements in the craniofacial anatomy of patients with DS might be predictive of OSA in DS. Due to the high incidence of sleep-disordered breathing in this population, the American Academy of Pediatrics currently recommends that all children with DS have a baseline polysomnogram by age four, and again if symptoms occur later in life [Bull 2011]. Although polysomnography is the gold standard for diagnosing OSA, this test is often costly, uncomfortable, and inconvenient for families, and as such has motivated research aiming to establish alternative, less cumbersome methods of reliably predicting OSA [Skotko et al. 2017].

The earliest assessments of facial morphology used simple visual examination (i.e., anthroposcopy). More recently, facial morphology was assessed by manual anthropometry using calipers [Jayaratne et al. 2014a]; however, the technique was inconvenient and cumbersome for both patients and the operator. The current standard for characterizing facial morphology is 3-dimensional digital anthropometry using non-contact surface imaging systems [Ferrario et al. 2004a; Ferrario et al. 2005; Sforza et al. 2005; Starbuck et al. 2011].

The aims of our research were (1) to characterize facial morphology of patients with DS using 3D digital anthropometry, (2) to compare facial anthropometric characteristics of patients with DS versus published norms, and (3) to compare facial anthropometric characteristics of patients with DS between those with versus without OSA for predicting OSA status in patients with DS.

MATERIALS AND METHODS

Subjects

The sample used for this study consisted of patients with DS recruited from Boston Children's Hospital. This study was approved by the Institutional Review Board of the Boston Children's Hospital (Protocol No.: 10-03-0092), and written informed consent/assent was obtained from the research participants and/or their parents. Patients with a history of adenotonsillectomy, adenoidectomy, tonsillectomy, a sleep study within the past 6 months, or being treated for OSA with continuous positive airway pressure were excluded.

Imaging Technique

The 3dMDface stereophotography system (3dMD, Atlanta, GA, USA) was used for capturing the 3D facial images. The system consists of 6 paired, synchronized cameras (4 grayscale and 2 color) positioned at specific angulations. The 6 images acquired simultaneously are then merged using a complex triangulation algorithm to generate a lifelike 3D photograph of the face (see Figure 1). This imaging system has been validated for accuracy and reliability [Aldridge et al. 2005; Weinberg et al. 2006].

The subjects were imaged while they were sitting on a chair at a set distance from the cameras. When needed, younger children sat on the lap of their caregiver.

Image Analysis

An anthropometric analysis scheme developed for qualifying facial norms [Jayaratne et al. 2013a; Jayaratne et al. 2013b; Jayaratne et al. 2014b; Jayaratne et al. 2014c] was used with suitable modifications to suit the current project. Landmarks were identified by a single investigator (YSNJ) with significant experience in digital craniofacial anthropometry. Interlandmark distances and angles were calculated in SAS (SAS Institute, Cary, NC, USA). The anthropometric landmarks and measurements used and demographic information collected for the analysis are specified in Table I & II respectively.

Assessment of OSA Status

An overnight polysomnogram was performed at the Boston Children's Hospital Sleep Laboratory. Each polysomnogram was evaluated by a single clinician (DR) using the standardized criteria proposed by the American Academy of Sleep Medicine [Berry et al. 2015]. The main outcome measure was the apnea-hypopnea index (AHI), which represents the total hypopneas and apneas per hour. OSA was defined as an AHI greater than 1 per hour.

Normative Data

Data for neurotypically developing subjects was obtained with permission from the FaceBase database (www.facebase.org). This database contains age- and gender-specific anthropometric landmark coordinate data (x,y,z) obtained from 2,545 individuals of European-Caucasian ancestry between 3–40 years. The Facebase data were collected using the same 3dMD imaging systems used in our current study.

Statistical Analysis

Demographic characteristics were summarized and compared between participants who did versus did not complete 3D photogrammetry by Fisher's exact test and t-test. Age-specific means and standard deviation were estimated from the FaceBase data separately by sex for each metric using a generalized additive model for location and scale [Stasinopoulos et al. 2007]. Both means and standard deviations were fit using penalized beta splines [Sabri et al. 2005]. Data for each metric from participants with DS were transformed to z-scores by subtracting the appropriate age- and sex-specific mean and dividing by the appropriate age- and sex-specific standard deviation. Z-scores were tested for a difference of the mean from zero for each metric using one-sample t-tests. Two-sided p-values were adjusted for multiple comparisons by a step-down Bonferroni adjustment [Heisterberg et al. 1979]. Each metric was compared among participants with DS between those with vs. without OSA on its original scale and as a z-score by two-sample t-tests with step-down Bonferroni-adjusted two-sided p-values. Adjusted p-values less than 0.05 were considered significant. In a separate analysis, we had previously applied an ensemble machine learning algorithm, the Logic Learning Machine (LLM) by from the Rulex 3.1 suite (www.rulex-inc.com), to predict three levels of OSA severity [Skotko et al., 2017].

RESULTS

A total of 98 subjects had 3D facial photography with the 3dMD face imaging system. However, since 3D norms from Facebase were available only for Caucasian subjects, the analysis here was confined to our 63 Caucasian participants. The anthropometric measurements of the participants are presented in Table III.

Comparison with normative data

A majority of 3D linear anthropometric measurements in patients with DS were lower than age- and gender-matched norms. These included facial depth measurements indicating a maxillomandibular hypoplasia accompanied by smaller ear, nose, and eye measurements. Only alar slope angle and subnasal protrusion angle were significantly larger than matched norms. However, the lower face height, chin height, labial fissure length, and upper vermilion height of patients with DS did not differ from their neurotypical counterparts.

Comparison between participants with DS with vs. without OSA

No statistically significant differences in 3D photogrammetric measurements were noted between participants with DS with versus without OSA after adjusting for multiple comparisons. Z-scores can be found on Table IV. The LLM analysis did not identify rules based on 3D photogrammetric measurements that improved prediction of OSA severity based on cross-validated positive and negative predictive values.

DISCUSSION

Although the high prevalence of OSA among patients with DS is attributed to altered facial morphological in this population, our findings suggest that variation in these morphological features do not distinguish individuals with OSA. While a few previous studies [Ferrario et

al. 2004a; Ferrario et al. 2005; Sforza et al. 2005; Starbuck et al. 2011] in the literature have assessed the morphological features in patients with DS using 3D imaging, the current study is the first to assess the association between these anthropometrics and sleep-disordered breathing and OSA.

Our study was focused on the external soft tissue morphology of patients with DS. However, several other factors including central apnea and issues related to internal soft tissues including reduced muscle tonicity, narrowing of the upper airway, a relatively large tongue, adeno-tonsillar hypertrophy and poor coordination of airway movements may contribute the high incidence of OSA in patients with DS [Fung et al. 2012; Shott 2006]. Therefore, our inability to find any statistically significant differences in facial anthropometric measurements between patients with DS with versus without OSA may be more related to internal soft tissue variations, rather than facial morphology alone.

Nevertheless, the clinical impact of our negative findings provides caution for clinicians—who may intuitively consider facial morphology in patients with DS in the context of OSA—against relying on these instincts and instead consider other factors when evaluating for sleep-disordered breathing. Furthermore, our reported anthropometric measurements and descriptions add to the growing body of literature conveying anthropometric measurements in patients with DS by employing 3D imaging techniques.

Although craniofacial morphology of patients with DS have been compared to corresponding measurements in neurotypically developing controls since the 1960s [Shapiro et al. 1967], the advent of 3D imaging technology has allowed us to assess facial landmarks and anthropometric measurements with far greater precision. Our findings regarding overall facial anthropometric characteristics of DS are in agreement with previous research on this topic. More recent studies using 3D assessments have demonstrated that people with DS have a reduced overall facial size when compared to matched controls [Ferrario et al. 2005; Sforza et al. 2005]. This is consistent with our findings of mostly decreased linear anthropometric measurements. Ferrario et al. [Ferrario et al. 2004b] used an electromechanical digitizer to obtain the 3D anthropometric landmark coordinates from 28 white Italian subjects with DS. They found that the skull base and the mandible were narrower with shorter and shallow facial thirds (upper, middle, and lower face) than neurotypically developing subjects. They also noted that participants with DS had smaller ears. Sforza et al. [Sforza et al. 2011] evaluated the nasolabial morphology in 64 North Sudanese participants with DS using a hand-held laser scanner. Similar to our results, they found that the vertical and anteroposterior nasal dimensions plus the mouth and philtrum width of participants with DS were reduced than the reference group. However, the horizontal nasal dimensions (alar base width, inferior widths of the nostrils) and vermilion height were increased, indicating some racial differences in the Sudanese group compared to our Caucasian sample.

Our study is limited by the restriction of ethnicity, in that only Caucasian individuals were available as published healthy controls. Further analysis of different races and ethnicities and a broader age range may have yielded different characteristics and measurements, ultimately expanding our knowledge of the DS phenotype and how we understand craniofacial

morphology and development. Kruszka et al. demonstrated that there are morphologic (geometric) differences between various ethnicities among people with DS [Kruszka et al. 2017]. As such, making a distinction between phenotype and ethnicity may be of further value. Although all participants in the study identified their race as white, a subset of these participants identified their ethnicity as Latino. However, with only 6 Latino participants in our sample, we had little power to evaluate whether facial morphometry differed between the two ethnic groups. There is also a lack of published norms for individuals of Hispanic/Latino ethnicity; as such, we could not determine whether any observed differences associated with ethnicity were due to DS or just to the ethnicity, independent of DS.

Other limitations include the practical limitations to applying 3D imaging technology, particularly when it involves individuals with intellectual disability. Such limitations have been described in the literature and encompass maintaining a neutral facial expression while being photographed, minimizing interference of artifacts and unwanted motion, and ensuring adequate surface coverage for targeted facial regions, all of which may impede the clinical and research applications of 3D imaging technology [Heike et al. 2010]. Moreover, using an ensemble method derived from logic regression, Ruxel's Logic Learning Machine, we did not identify features predictive of OSA. Future research could incorporate other advanced analyses methods such as support vector mechanisms, neural networks, and C5.0 decision trees [Hammond et al. 2004]. This may have limited the scope of our study. Using similar technology, further studies can expand to assess how different craniofacial morphological characteristics may pertain to different conditions that are of increased prevalence in patients with DS.

CONCLUSION

Compared to age- and gender-matched norms, patients with DS have maxillomandibular hypoplasia with smaller ear, nose, and eye measurements. While soft-tissue and craniofacial structural alterations in individuals with DS are thought to be the root cause of the increased susceptibility and prevalence of OSA in this population, anthropometric analysis of different craniofacial landmarks and measurements demonstrated that OSA cannot be correlated with the presence, absence, or degree of any of these structural alterations within this population. These findings reinforce that clinical decision-making, as it pertains to polysomnography and OSA, should be informed by other factors, and not on the perceived degree of dysmorphology or craniofacial measurements.

Acknowledgments

Conflict of Interest

Dr. Skotko occasionally consults on the topic of Down syndrome through Gerson Lehrman Group. He receives remuneration from Down syndrome non-profit organizations for speaking engagements and associated travel expenses. Dr. Skotko receives annual royalties from Woodbine House, Inc., for the publication of his book, *Fasten Your Seatbelt: A Crash Course on Down Syndrome for Brothers and Sisters*. Within the past two years, he has received research funding from F. Hoffmann-La Roche, Inc. and Transition Therapeutics to conduct clinical trials on study drugs for people with Down syndrome. Dr. Skotko is occasionally asked to serve as an expert witness for legal cases where Down syndrome is discussed. He serves in a non-paid capacity on the Honorary Board of Directors for the Massachusetts Down Syndrome Congress, the Board of Directors for the Band of Angels Foundation, and the Professional Advisory Committee for the National Center for Prenatal and Postnatal Down Syndrome Resources. Dr. Skotko has a sister with Down syndrome.

Dr. Macklin serves on Data and Safety Monitoring Boards for Acorda Therapeutics and Shire Human Genetic Therapies and he receives research grant support from Acorda Therapeutics, Adolph Coors Foundation, ALS Association, Autism Speaks, Michael J. Fox Foundation, FDA, HRSA, NIH, and PCORI.

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a)

b)

Figure 1.

Some of the anthropometric landmarks and measurements used for 3D image analysis. a) Frontal view b) Profile view (al - alare, ch - cheilion, cp- cervical point, en – endocanthion, ex - exocanthion, g – glabella, gn - gnathion, n - nasion, pg – pogonion, prn – pronasale, sl – sublabiale, sn - subnasale, t - trigion)

Table I**Anthropometric landmarks used for analyzing 3D Photographs**

Landmark Name	Landmark Label	Definition
Glabella	g	The most prominent midline between eyebrows
Nasion	n	The midpoint on the soft-tissue contour of the base of the nasal root
Tragion	t	The most superior aspect of the tragus where it abuts the face
otobasion inferius	obi	The point of attachment of the ear lobe to the cheek
Pronasale	prn	The most protruded point of the nasal tip
Subnasale	sn	The midpoint of the angle at the columella base where the lower border of the nasal septum and the surface of the upper lip meet
Sublabiale	sl	The midpoint of the labiomental sulcus
Pogonion	pg	The most anterior midpoint of the chin
Gnathion	gn	The lowest median landmark on the lower border of the mandible
Cervicle Point	cp	The junction of the submental, the submandibular regions and the neck in the midline
Exocanthion	ex	The soft tissue point located at the outer commissure of each eye fissure
Endocanthion	en	The soft tissue point located at the inner commissure of each eye fissure
Alare	al	The most lateral point on each alar contour
Columella apex	c'	The most anterior, or the highest point on the columella crest at the apex of the nostril
Columella midpoint	cm	The midpoint on the columella crest that transects the lines connecting apices of the nares
Alar curvature point	ac	The most lateral point in the curved baseline of each ala indicating the facial insertion of the nasal wing-base
Labiale superius	ls	The midpoint of the vermilion line of the upper lip
Crista philtri	cph	The point at each raised margin of the philtrum just above the vermilion line
Stomion superius	sto_s	The lowest point of the midline of the upper lip
Stomion inferius	sto_i	The highest point of the midline of the lower lip
Labiale inferius	li	The midpoint of the lower vermilion line
Cheilion	ch	The point located at each labial commissure

Table II

Demographic Information of participants with DS used for the analysis

Variable		% (N)
Gender	Male	55.6% (35)
	Female	44.4% (28)
Race	White	100.0% (63)
Ethnicity	Not Hispanic/Latino	90.5% (57)
	Hispanic/Latino	9.5% (6)
OSA status	No OSA	55.8% (29)
	OSA	44.2% (23)
	[missing]	(11)
Age	years	7.49±4.86 (range: 3.1–24.4)

Table III

Facial anthropometric measurements of patients with DS

Region	Metric	N	Mean Z-score	SD	Range			95% CI		Nom. p-val	Adj. p-val
					Min	Max	Lower	Upper			
Face	Morphological Face Height (N-Gn)	60	-1.839	1.249	-4.256	0.817	-2.162	-1.516	<.001	<.001	<.001
	Upper Face Height-I (N-Sto_s)	61	-3.145	1.025	-5.391	-0.053	-3.408	-2.883	<.001	<.001	<.001
	Upper Face Height-II (N-Sn)	63	-3.102	1.098	-5.318	0.937	-3.379	-2.825	<.001	<.001	<.001
	Lower Face Height-I (Sto_i-Gn)	57	-0.454	1.340	-3.580	2.890	-0.809	-0.098	0.013	0.080	0.080
	Lower Face Height-II (Sn-Gn)	60	0.078	1.408	-2.828	3.300	-0.286	0.442	0.669	1.000	1.000
	Skull Base Width (T-T)	54	-1.310	1.005	-3.196	0.970	-1.585	-1.036	<.001	<.001	<.001
	Chin Height (SI-Gn)	59	0.417	1.645	-2.553	5.318	-0.011	0.846	0.056	0.277	0.277
	Right Upper Facial third Depth (N-T_R)	54	-2.340	0.940	-4.725	-0.152	-2.597	-2.084	<.001	<.001	<.001
	Left Upper Facial third Depth(N-T_L)	54	-2.182	0.942	-4.991	-0.471	-2.439	-1.925	<.001	<.001	<.001
	Right Orbito-tragial Depth (Ex_R-T_R)	54	-1.450	1.831	-12.17	1.849	-1.950	-0.950	<.001	<.001	<.001
	Left Orbito-tragial Depth (Ex_L-T_L)	54	-1.203	1.310	-7.502	1.280	-1.561	-0.846	<.001	<.001	<.001
	Right Labio-tragial Depth (Ch_R-T_R)	54	-1.673	1.127	-4.840	0.689	-1.981	-1.366	<.001	<.001	<.001
	Left Labio-tragial Depth (Ch_L-T_L)	54	-1.441	1.054	-3.837	0.558	-1.729	-1.153	<.001	<.001	<.001
	Right Maxillary Depth (Sn-T_R)	54	-1.986	1.026	-4.436	0.833	-2.266	-1.706	<.001	<.001	<.001
Eyes	Left Maxillary Depth (Sn-T_L)	54	-1.842	1.051	-4.851	0.517	-2.129	-1.555	<.001	<.001	<.001
	Right Mandibular Depth (Gn-T_R)	54	-1.295	0.898	-3.422	0.251	-1.540	-1.050	<.001	<.001	<.001
	Left Mandibular Depth (Gn-T_L)	54	-1.335	0.962	-3.352	0.821	-1.597	-1.072	<.001	<.001	<.001
	Sn-N-SI Angle	62	-0.001	1.400	-3.709	2.858	-0.356	0.355	0.997	1.000	1.000
	Intercanthal Width (En-En)	63	0.947	0.974	-0.889	3.083	0.702	1.192	<.001	<.001	<.001
	Biocular Width (Ex-Ex)	63	-0.759	0.996	-2.736	1.481	-1.009	-0.508	<.001	<.001	<.001
	Right Eye Fissure Length	63	-1.410	0.910	-3.751	0.833	-1.639	-1.181	<.001	<.001	<.001
	Left Eye Fissure Length	63	-1.433	0.988	-3.560	0.756	-1.682	-1.184	<.001	<.001	<.001
	Morphological Nose Width (Al-Al)	63	-1.143	1.046	-4.042	1.698	-1.407	-0.880	<.001	<.001	<.001
	Anatomical Nose Width (Ac-Ac)	63	-1.490	1.205	-4.394	2.383	-1.793	-1.186	<.001	<.001	<.001
Nose	Nasal Tip Protrusion (Sn-Pmn)	63	-1.090	0.997	-3.585	1.200	-1.341	-0.839	<.001	<.001	<.001
	Nose Height (N-Sn)	63	-3.102	1.098	-5.318	0.937	-3.379	-2.825	<.001	<.001	<.001

Region	Metric	N	Mean Z-score	SD	Range				95% CI		Nom. p-val	Adj. p-val
					Min	Max	Lower	Upper				
Lips and Mouth	Nasal Bridge Length (N-Pm)	63	-3.403	1.173	-5.764	0.326	-3.698	-3.107	<.001	<.001	<.001	<.001
	Right Alar Length (Pm-Ac_R)	63	-1.719	1.159	-5.140	1.177	-2.011	-1.427	<.001	<.001	<.001	<.001
	Left Alar Length (Pm-Ac_L)	63	-2.367	0.994	-5.026	-0.296	-2.617	-2.116	<.001	<.001	<.001	<.001
	Alar Slope Angle (Al-Pm-Al)	63	0.834	1.362	-2.796	3.650	0.491	1.177	<.001	<.001	<.001	<.001
	Subnasal Protrusion Angle (Ac-Sn-Ac)	63	1.758	1.041	-0.370	4.707	1.496	2.020	<.001	<.001	<.001	<.001
	Labial Fissure Length (Ch-Ch)	62	-0.167	1.199	-2.474	4.489	-0.472	0.137	0.276	0.828		
	Philtrum Width (Cph-Cph)	37	-0.869	1.033	-2.583	1.196	-1.214	-0.525	<.001	<.001	<.001	<.001
	Upper Lip Length (Sn-Sto_s)	61	-1.191	1.007	-4.033	2.029	-1.449	-0.933	<.001	<.001	<.001	<.001
	Cutaneous Upper Lip Length (Sn-Ls)	62	-1.141	0.978	-3.182	1.981	-1.390	-0.893	<.001	<.001	<.001	<.001
	Upper Vermilion Height (Ls-Sto_s)	60	-0.283	1.121	-2.778	2.521	-0.572	0.007	0.055	0.277		
Ears	Lower Vermilion Height (Sto_i-Li)	59	-0.760	0.695	-2.975	0.656	-0.941	-0.579	<.001	<.001	<.001	<.001
	Cutaneous Lower Lip Length (Li-SI)	60	-0.644	0.895	-2.920	1.137	-0.875	-0.413	<.001	<.001	<.001	<.001
	Lower Lip Length (Sto_i-SI)	60	-1.317	0.863	-3.327	1.256	-1.540	-1.094	<.001	<.001	<.001	<.001
	Right T-SI Depth (SI-T_R)	53	-1.264	1.041	-4.001	1.465	-1.551	-0.977	<.001	<.001	<.001	<.001
	Left T-SI Depth(SI-T_L)	53	-1.182	1.041	-3.976	1.012	-1.469	-0.896	<.001	<.001	<.001	<.001

Table IV

Z-score Comparisons of anthropometric measurements of patients with DS with and without OSA

Variable	OSA Status		Nom P-val	Adj P-val
	No OSA M±SD (range)	OSA M±SD (range)		
Morphological Face Height (N-Gn)	-1.93±1.40 (-4.23,0.82)	-1.59±0.94 (-3.14,0.68)	0.328	1.000
Upper Face Height-I (N-Sto_s)	-3.20±1.02 (-4.95,-1.45)	-2.86±0.91 (-4.44,-0.05)	0.223	1.000
Upper Face Height-II (N-Sn)	-3.28±1.02 (-5.14,-1.58)	-2.73±1.11 (-4.83,0.94)	0.073	1.000
Lower Face Height-I (Sto_i-Gn)	-0.65±1.35 (-3.58,2.89)	-0.12±1.47 (-2.73,2.62)	0.212	1.000
Lower Face Height-II (Sn-Gn)	0.09±1.50 (-2.45,3.03)	0.13±1.11 (-1.45,2.40)	0.914	1.000
Skull Base Width (T-T)	-1.42±1.11 (-3.20,0.71)	-1.20±0.89 (-2.77,0.33)	0.467	1.000
Chin Height (SI-Gn)	0.31±1.55 (-2.39,4.79)	0.68±1.92 (-2.55,5.32)	0.461	1.000
Right Upper Facial third Depth (N-T_R)	-2.44±0.80 (-3.57,-0.91)	-2.25±1.00 (-4.73,-0.39)	0.478	1.000
Left Upper Facial third Depth (N-T_L)	-2.30±0.82 (-3.65,-0.59)	-2.07±1.05 (-4.99,-0.70)	0.416	1.000
Right Orbito-tragial Depth (Ex_R-T_R)	-1.18±1.13 (-3.32,0.68)	-1.44±0.80 (-2.83,0.28)	0.379	1.000
Left Orbito-tragial Depth (Ex_L-T_L)	-1.05±0.88 (-3.24,0.53)	-1.15±0.93 (-3.06,0.32)	0.701	1.000
Right Labio-tragial Depth (Ch_R-T_R)	-1.69±0.94 (-3.52,-0.10)	-1.65±1.19 (-4.08,0.67)	0.896	1.000
Left Labio-tragial Depth (Ch_L-T_L)	-1.38±0.89 (-2.58,0.54)	-1.50±1.22 (-3.84,0.56)	0.699	1.000
Right Maxillary Depth (Sn-T_R)	-2.15±0.93 (-3.44,-0.06)	-1.83±1.03 (-4.44,-0.05)	0.265	1.000
Left Maxillary Depth (Sn-T_L)	-1.96±0.94 (-3.82,0.14)	-1.79±1.14 (-4.85,-0.21)	0.589	1.000
Right Mandibular Depth (Gn-T_R)	-1.49±0.87 (-2.83,0.17)	-1.13±0.95 (-3.42,0.05)	0.185	1.000
Left Mandibular Depth (Gn-T_L)	-1.50±1.03 (-3.34,0.82)	-1.33±0.94 (-3.35,0.22)	0.557	1.000
Sn-N-SI Angle	-0.01±1.41 (-3.50,2.58)	-0.05±1.16 (-2.88,1.84)	0.914	1.000
Intercanthal Width (En-En)	0.99±0.96 (-0.63,3.08)	0.97±1.10 (-0.85,3.07)	0.940	1.000
Biocular Width (Ex-Ex)	-0.82±0.96 (-2.69,0.95)	-0.65±1.03 (-2.74,1.48)	0.542	1.000
Right Eye Fissure Length	-1.57±0.89 (-3.75,-0.03)	-1.13±0.89 (-2.23,0.83)	0.082	1.000
Left Eye Fissure Length	-1.45±0.89 (-3.17,0.42)	-1.53±1.02 (-2.81,0.76)	0.753	1.000
Morphological Nose Width (Al-Al)	-1.29±1.02 (-4.04,0.90)	-1.09±1.15 (-2.67,1.70)	0.519	1.000
Anatomical Nose Width (Ac-Ac)	-1.68±0.79 (-3.27,-0.11)	-1.59±1.37 (-4.39,1.23)	0.771	1.000
Nasal Tip Protrusion (Sn-Prn)	-1.15±0.93 (-3.58,1.14)	-1.10±0.87 (-2.55,0.16)	0.864	1.000
Nose Height (N-Sn)	-3.28±1.02 (-5.14,-1.58)	-2.73±1.11 (-4.83,0.94)	0.073	1.000
Nasal Bridge Length (N-Prn)	-3.56±1.21 (-5.76,-1.17)	-3.03±1.17 (-5.23,0.33)	0.120	1.000
Right Alar Length (Prn-Ac_R)	-1.70±0.82 (-3.23,-0.18)	-1.85±1.24 (-5.14,0.81)	0.613	1.000
Left Alar Length (Prn-Ac_L)	-2.39±0.95 (-4.03,-0.30)	-2.45±0.98 (-5.03,-0.81)	0.835	1.000
Alar Slope Angle (Al-Prn-Al)	0.59±1.14 (-1.32,3.21)	1.03±1.42 (-2.80,3.65)	0.217	1.000
Subnasal Protrusion Angle (Ac-Sn-Ac)	1.69±0.86 (-0.13,2.92)	1.63±1.18 (-0.37,4.71)	0.820	1.000
Labial Fissure Length (Ch-Ch)	-0.45±0.73 (-1.94,1.75)	-0.00±1.23 (-2.47,2.37)	0.111	1.000
Philtrum Width (Cph-Cph)	-0.75±1.11 (-2.58,1.14)	-0.75±0.99 (-2.47,1.20)	0.992	1.000
Upper Lip Length (Sn-Sto_s)	-1.02±0.87 (-2.02,2.03)	-1.28±0.99 (-3.59,0.50)	0.315	1.000
Cutaneous Upper Lip Length (Sn-Ls)	-0.82±0.93 (-2.28,1.98)	-1.37±0.71 (-2.48,0.01)	0.026	1.000
Upper Vermilion Height (Ls-Sto_s)	-0.34±1.17 (-2.78,2.52)	-0.20±1.07 (-1.71,2.04)	0.665	1.000
Lower Vermilion Height (Sto_i-Li)	-0.76±0.76 (-2.97,0.66)	-0.79±0.62 (-2.19,0.42)	0.890	1.000

OSA Status					
Variable	No OSA M±SD (range)	OSA M±SD (range)	Nom P-val	Adj P-val	
Cutaneous Lower Lip Length (Li-SI)	-0.89±0.81 (-2.77,0.65)	-0.45±1.02 (-2.92,1.14)	0.101	1.000	
Lower Lip Length (Sto_i-SI)	-1.53±0.82 (-3.33,-0.09)	-1.15±0.98 (-2.59,1.26)	0.140	1.000	
Right T-SI Depth (SI-T_R)	-1.38±0.96 (-3.29,0.53)	-1.15±1.06 (-4.00,0.47)	0.445	1.000	
Left T-SI Depth (SI-T_L)	-1.28±1.04 (-3.33,0.66)	-1.22±1.07 (-3.98,0.11)	0.851	1.000	