



ORIGINAL ARTICLE

Differences in three-dimensional upper airway anatomy between Asian and European patients with obstructive sleep apnea

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Abstract

Study Objectives: This study evaluated differences in upper airway, soft tissues and craniofacial structures between Asians from China and Europeans from Iceland with OSA using three-dimensional magnetic resonance imaging (MRI).

Methods: Airway sizes, soft tissue volumes, and craniofacial dimensions were compared between Icelandic ($N = 108$) and Chinese ($N = 57$) patients with oxygen desaturation index (ODI) ≥ 10 events/h matched for age, gender, and ODI. Mixed effects models adjusting for height or BMI and residual differences in age and ODI were utilized.

Results: In our matched sample, compared to Icelandic OSA patients, Chinese patients had smaller BMI ($p < 0.0001$) and neck circumference ($p = 0.011$). In covariate adjusted analyses, Chinese showed smaller retropalatal airway size ($p \leq 0.002$), and smaller combined soft tissues, tongue, fat pads, and pterygoid (all $p \leq 0.0001$), but male Chinese demonstrated a larger soft palate volume ($p \leq 0.001$). For craniofacial dimensions, Chinese demonstrated bigger ANB angle ($p \leq 0.0196$), differently shaped mandibles, including shorter corpus length ($p < 0.0001$) but longer ramus length ($p < 0.0001$), and a wider ($p < 0.0001$) and shallower ($p \leq 0.0001$) maxilla.

Conclusions: Compared to Icelandic patients of similar age, gender and ODI, Chinese patients had smaller retropalatal airway and combined soft tissue, but bigger soft palate volume (in males), and differently shaped mandible and maxilla with more bony restrictions. Results support an ethnic difference in upper airway anatomy related to OSA, which may inform targeted therapies.

Statement of Significance

This study used three-dimensional magnetic resonance imaging to compare upper airway anatomic risk factors for obstructive sleep apnea between Asians from China and Europeans from Iceland with similar age, gender, and disease severity. The results indicate that Icelandic patients have larger combined soft tissue volume, while Chinese patients have larger soft palate volume (in males), as well as smaller retropalatal airway areas and more restricted mandibular and maxillary bone structures. These results confirm and extend evidence of ethnic differences in the upper airway anatomy related to obstructive sleep apnea, and may help to inform targeted treatment approaches.

Key words: obstructive sleep apnea; ethnicity; upper airway structure; three-dimensional magnetic resonance imaging

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Introduction

Obstructive sleep apnea (OSA) is a common sleep disorder characterized by repeated episodes of airway collapse during sleep. Obesity, enlarged upper airway soft tissues, craniofacial abnormalities and their interactions play key roles in anatomical risk for OSA [1–3]. Using three-dimensional magnetic resonance imaging (MRI), upper airway soft tissue volumes have been shown to be larger in patients with OSA [1, 4], which may reduce airway caliber, increasing the propensity for airway collapse during sleep. In addition, alterations in the craniofacial skeleton have been implicated as risk factors for OSA. Previous cephalometric studies showed that individuals with OSA have smaller, retroposed mandibles (retrognathia), an inferiorly positioned hyoid bone, narrow posterior airway spaces, and retroposition of the maxilla [5–7]. Based on three-dimensional MRI, studies found that smaller mandibular length and depth in men and greater hyoid-to-nasion and suprmentale-to-hyoid distances in both men and women were associated with increased risk of OSA [7].

Ethnicity influences OSA risk factors. Although Chinese patients are less obese than Caucasians, the prevalence of OSA is similar in the two populations [8]. A study using two-dimensional cephalometry concluded that Chinese patients had more craniofacial bony restriction and Caucasians were more obese when matched on the apnea-hypopnea index (AHI) [9]. This suggests distinct, ethnic-specific OSA etiologies in the two groups.

Through three-dimensional MRI, quantitative comparisons of upper airway anatomy can be performed [1, 7]. However, there are a limited number of interethnic studies simultaneously evaluating airway, soft tissues, and craniofacial structures in OSA patients. Thus, the present study examined differences in upper airway anatomy between Asian patients with OSA from China and European patients with OSA from Iceland with the same age, gender, and OSA severity. We hypothesized that Chinese would have smaller airway sizes, smaller soft tissue volumes and greater craniofacial restriction compared to Icelandic patients. Our findings elucidate the distinct anatomic factors between OSA patients in the two ethnic groups and provide further understanding of possible ethnic-specific pathogenesis and treatment of OSA.

Methods

See [Supplementary material](#) for details.

Study subjects

Analyses were performed in Icelandic and Chinese patients from clinical sleep centers in each country with data on age, gender, BMI and oxygen desaturation index (ODI). All subjects studied had ODI ≥ 10 events/h. The Institutional Review Boards at Landspítali University Hospital, Iceland, and Shanxi Tongcoal General Hospital, China, approved the project. Written informed consent was obtained from all participants.

Icelandic patients were from the Icelandic Sleep Apnea Cohort (ISAC); described elsewhere [10–12]. A total of 616 Icelandic patients with ODI ≥ 10 events/h and available phenotype data were eligible for inclusion. Chinese patients with symptoms suggestive of OSA were recruited from the sleep center in Shanxi Tongcoal General Hospital, China. A total of 103

Chinese patients were recruited, of whom 72 had an ODI ≥ 10 events/h and available phenotype data for inclusion.

Sleep studies

All patients from Iceland were diagnosed with a portable monitor, as previously described [10–12]. Scoring was started 30 min into the recording and ended 5 min before the study recording was completed to avoid issues related to potential periods of wakefulness. In Chinese patients, in-laboratory polysomnography (PSG) was performed according to the recommendation of the American Academy of Sleep Medicine [13]. To obtain an equivalent ODI to that from portable monitoring in Iceland, ODI from the PSG was recalculated as the number of oxygen desaturations at least 4% per hour of total analysis time, defined using the same approach as on portable monitors in Iceland (e.g. starting 30 min after lights-off and ending 5 min before lights-on).

Magnetic resonance imaging

Three-dimensional upper airway MRI was performed in both samples using the same protocol, as described previously [1, 7, 14, 15]. MRI analysis to quantify upper airway (Figure S1), volumetric (Figure S2), and craniofacial (Figures S3–S9) measurements was performed at the University of Pennsylvania, as previously described [1, 7, 14, 15].

Statistical analysis

To control for covariate differences, Icelandic and Chinese patients were matched with respect to age (± 2 years), gender, and ODI (± 5 events/h) using SAS 9.4 (SAS Institute, Cary, NC) [16, 17]. Given the larger pool of Icelandic patients, to increase statistical power we allowed up to a 2:1 Icelandic:Chinese patient matching; Chinese patients with only 1 available match in Iceland were retained as 1:1 matched pairs (see details on statistical power and precision in *Online Supplement*). Continuous and categorical data were compared between Icelandic and Chinese participants using linear or logistic mixed models, respectively, controlling for matched set as a random effect. Primary analyses were adjusted for residual differences in age and ODI after matching, and height. To evaluate the effect of obesity, the secondary analyses were adjusted for age, ODI, and BMI. To control for multiple MRI measurements being compared, while recognizing that different relationships can be expected for specific groups of MRI parameters, we defined sub-domains of airway, soft tissue and craniofacial measures and utilize domain-specific Bonferroni corrections, as in prior studies [15, 18]. To evaluate the influence of gender on ethnic differences, we tested for a gender-by-ethnicity interaction; any interaction with $p < 0.10$ was considered suggestive and differences between Icelandic and Chinese patients were then assessed separately within males and females.

Results

Patient demographics

One-hundred sixty-five patients with OSA (108 Icelandic, 57 Chinese) were included in the age, gender, and ODI matched analysis set (51 Icelandic:Chinese pairs matched 2:1 and 6 pairs matched 1:1). Given matching, there were no differences in age ($p = 0.941$), gender

($p = 0.989$) or ODI ($p = 0.684$) between Icelandic and Chinese patients (Table 1); participants were on average middle-aged with moderate to severe OSA and a majority were male. Icelandic patients were more obese than Chinese based on BMI ($p < 0.0001$) and neck circumference ($p = 0.011$), taller ($p < 0.0001$), and heavier ($p < 0.0001$).

Upper airway caliber

Comparisons of upper airway caliber between Icelandic and Chinese patients are presented in Table 2 (adjusted) and Supplementary Table S1 (unadjusted). Adjusting for age, ODI, and height, Chinese patients had significantly smaller total airway volume ($p = 0.008$) and cross-sectional area ($p = 0.012$), and smaller retropalatal (RP) airway (volume [$p < 0.0001$], mean [$p < 0.0001$] and minimum [$p = 0.002$] cross-sectional area, minimum anteroposterior [AP] distance [$p = 0.0004$], and minimum lateral distance [$p < 0.0001$]). There were no differences in the size of the retroglossal (RG) airway (Table 2). Adjusting for BMI instead of height, Chinese patients had significantly smaller total airway sizes (all $p < 0.0001$), smaller RP airway sizes for all measures (all $p < 0.002$), and smaller RG airway volume ($p = 0.0004$). Thus, data indicate robust differences in airway size, with a smaller retropalatal airway and total airway volume in Chinese (Figure 1).

Upper airway soft tissues

Analyses comparing soft tissue volumes between Chinese and Icelandic patients are shown in Table 3 (adjusted) and Supplementary Table S2 (unadjusted). Adjusting for age, ODI, and height, Icelandic patients had larger combined soft tissue ($p < 0.0001$), tongues (all $p < 0.0001$), fat pad ($p < 0.0001$), and pterygoid ($p = 0.0003$) volumes. However, Chinese patients demonstrated larger soft palate volume ($p = 0.0001$). There were no significant differences in lateral wall volumes between the two ethnic groups. Results were similar controlling for BMI instead of height, except the soft palate difference was non-significant; this may be due to effect modification by gender (described below). Overall, results indicate soft tissue anatomic differences between the two racial groups, with enlargement of tongue, fat pads, and pterygoid volumes in Icelandic patients (Figure 2).

Craniofacial dimensions

We compared craniofacial dimensions between the two ethnic groups, including adjusted (Table 4) and unadjusted (Supplementary Tables S3) analyses of craniofacial angles,

mandibular measurements, maxillary measurements, hyoid distances, craniofacial heights, and craniofacial volume and areas.

Craniofacial angles

Adjusting for age, ODI, and height (Table 4), Chinese patients had a significantly bigger ANB angle (Subspinale–Nasion–Supramentale; $p = 0.001$) and nominally smaller ACB:HP (anterior cranial base and horizontal plane; $p = 0.031$) compared to Icelandic patients (Supplementary Figure S10). Adjusting for BMI instead of height, the differences in ANB angle became nominal ($p = 0.020$), and Chinese showed significantly larger saddle angle ($p = 0.002$) than Icelandic patients. Results imply Chinese patients have a more retrognathic mandible in reference to the maxilla, but Icelandic patients have a normal anteroposterior relationship between the maxilla and mandible.

Mandibular measurements

Chinese and Icelandic patients had differently shaped mandibles (Figure 3). Adjusting for age, ODI and either height or BMI (Table 5), we found significant differences in mandibular lengths (all $p \leq 0.0001$) and widths (all $p < 0.0001$). The difference in divergence was nominal ($p \leq 0.016$). Chinese patients showed similar mandibular depth, larger mandibular ramus and total lengths, greater mandibular widths, but smaller mandibular corpus length compared to Icelandic patients.

Maxillary measurements

Similarly, we observed differently shaped maxilla between Chinese and Icelandic patients (Supplementary Figure S11). Adjusting for age, ODI, and either height or BMI (Table 6), Chinese demonstrated a wider maxilla (all $p < 0.0001$) with shallower maxillary unit depth ($p \leq 0.0001$) and larger maxillary divergence ($p \leq 0.011$).

Hyoid distances

Adjusting for age, ODI, and height (Table 7), Chinese had significantly longer hyoid-to-C3 ($p = 0.006$) and hyoid-to-sella ($p < 0.0001$) distances, and shorter retropogonion-to-C3 distance ($p < 0.0001$) than Icelandic patients. Adjusting for BMI instead of height, only the difference in retropogonion-to-C3 distance remained significant ($p = 0.008$); the larger hyoid-to-C3 distance in Chinese became nominal ($p = 0.035$). Thus, results suggest ethnic associations in hyoid-related measures may be driven by differences in obesity between the two ethnic groups.

Table 1. Patient demographics matched for age, sex, and ODI

Measure*	Icelandic	Chinese	<i>p</i>
N†	108	57	—
Age (years)	50.85 ± 8.77	50.35 ± 8.83	0.9406
Male, N (%)	84 (77.78)	44 (77.19)	0.9888
Height (cm)	177.1 ± 8.62	168.5 ± 6.65	<0.0001
Weight (kg)	103.0 ± 17.09	78.29 ± 10.28	<0.0001
BMI (kg/m ²)	32.81 ± 4.83	27.71 ± 3.50	<0.0001
Neck circumference (cm)	42.48 ± 3.84	41.18 ± 2.87	0.0107
ODI (events/h)	37.45 ± 18.87	38.13 ± 20.02	0.6840

AHI, apnea–hypopnea index, BMI, body mass index, ODI, oxygen desaturation index. *Estimates presented as mean ± SD for continuous variables or N (percent) for categorical;

†N = 51 2:1 Icelandic: Chinese matched sets and N = 6 1:1 matched pairs. Significant *p*-values in bold.

Table 2. Adjusted comparison of upper airway caliber between Icelandic and Chinese patients matched for age, gender, and ODI

Domain	Variable	Model 1: age, ODI, height Adjusted mean (95% CI)		p	Model 2: age, ODI, BMI Adjusted mean (95% CI)		p
		Icelandic	Chinese		Icelandic	Chinese	
Total Airway [†]	Length (mm)	72.83 (71.64, 74.02)	71.48 (69.76, 73.19)	0.2306	74.56 (72.97, 76.16)	67.99 (65.90, 70.08)	<0.0001
	Volume (mm ³)	13384 (12526, 14242)	11315 (10082, 12549)	0.0075	14177 (13238, 15116)	9655 (8374, 10937)	<0.0001
	Cross-sectional area (mm ²)	182.3 (171.1, 193.4)	157.1 (141.1, 173.1)	0.0120	189.4 (177.9, 200.8)	142.5 (126.5, 158.5)	<0.0001
RP airway [†]	Volume (mm ³)	5057 (4667, 5447)	3391 (2843, 3939)	<0.0001	5337 (4925, 5749)	2839 (2277, 3401)	<0.0001
	Min. cross-sectional area (mm ²)	64.49 (58.36, 70.61)	46.32 (37.55, 55.10)	0.0018	67.39 (61.29, 73.49)	40.87 (32.14, 49.60)	<0.0001
	Mean cross-sectional area (mm ²)	141.3 (132.0, 150.6)	90.61 (77.23, 104.0)	<0.0001	147.4 (137.9, 157.0)	78.59 (65.07, 92.10)	<0.0001
	Min. AP distance (mm)	6.77 (6.38, 7.17)	5.54 (4.99, 6.08)	0.0004	6.72 (6.32, 7.11)	5.64 (5.10, 6.18)	0.0017
	Min. lateral distance (mm)	13.76 (12.77, 14.75)	8.86 (7.49, 10.22)	<0.0001	14.35 (13.39, 15.32)	7.77 (6.45, 9.08)	<0.0001
RG Airway [†]	Volume (mm ³)	8314 (7698, 8930)	7917 (7009, 8825)	0.4934	8834 (8168, 9500)	6803 (5864, 7742)	0.0004
	Min. cross-sectional area (mm ²)	136.3 (123.3, 149.2)	136.2 (117.9, 154.5)	0.9962	140.4 (127.4, 153.5)	128.4 (110.1, 146.6)	0.3083
	Mean cross-sectional area (mm ²)	219.5 (202.8, 236.3)	237.1 (212.7, 261.4)	0.2521	226.8 (209.7, 244.0)	221.9 (197.5, 246.3)	0.7441
	Min. AP distance (mm)	11.59 (10.77, 12.40)	10.27 (9.14, 11.40)	0.0722	11.47 (10.66, 12.27)	10.48 (9.37, 11.59)	0.1679
	Min. lateral distance (mm)	18.23 (16.83, 19.63)	18.37 (16.41, 20.32)	0.9154	18.43 (17.04, 19.82)	17.99 (16.07, 19.92)	0.7268

Significant *p*-values are given in bold.

AP, anteroposterior, BMI, body mass index, CI, confidence interval, ODI, oxygen desaturation index, RG, retroglottal, RP, retropalatal.

[†]Bonferroni corrected significance level: $p < 0.0167$ (equals 0.05/3).

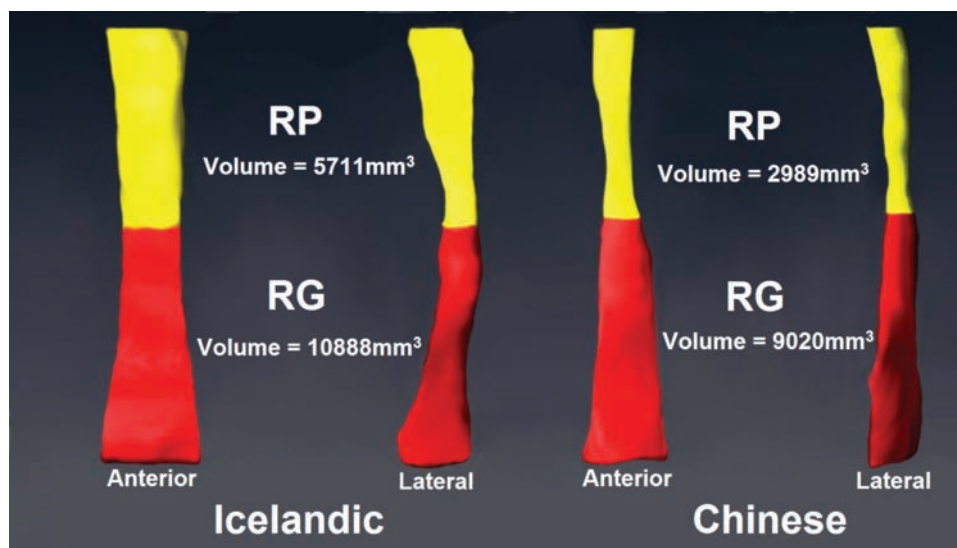


Figure 1. Three-dimensional reconstruction of the upper airway (anterior and lateral views), separated into retropalatal (RP, yellow) and retroglottal (RG, red) regions in representative age, gender, and ODI matched Icelandic and Chinese patients. The Icelandic patient (left), was a 63.5 years-old male with a BMI of 33.0 kg/m² and ODI of 59.4 events/h. The Chinese patient (right), was a 65.0 years-old male with BMI of 25.5 kg/m² and ODI of 57.9 events/h. As observed in our analyses, the Chinese patient has a smaller airway than the Icelandic patient in the RP region, but not the RG region.

[†]Bonferroni corrected significance level: $p < 0.01$ (equals 0.05/5).

Craniofacial heights

Adjusting for age, ODI, and height (Table 8), Chinese generally had larger upper ($p = 0.001$) and anterior ($p = 0.001$) facial height than Icelandic patients. All differences were non-significant when adjusting for BMI instead of height, suggesting obesity may play a role in accounting for these differences.

Craniofacial volume and areas

When adjusting for age, ODI, and height (Table 9), Chinese showed bigger oropharyngeal area ($p = 0.006$) than Icelandic patients, and a nominally larger naso-oropharyngeal area ($p = 0.034$). Adjusting for BMI instead of height, these differences

became nonsignificant; however, a nominal difference was seen in nasopharyngeal area ($p = 0.014$). Thus, there is suggestive, but inconsistent evidence of differences in naso-oropharyngeal areas. Interestingly, while differently shaped mandibles were observed, the overall intramandibular volume was not significantly different between Chinese and Icelandic patients adjusting for age, ODI, and either height ($p = 0.225$) or BMI ($p = 0.065$).

Gender-specific ethnic differences

To assess whether stratification by gender was required to accurately capture ethnic differences, we tested for gender-by-ethnicity interactions for all measurements; suggestive

Table 3. Adjusted comparisons of soft tissue volumes between Icelandic and Chinese patients matched for age, gender, and ODI

Domain	Variable	Model 1: age, ODI, height Adjusted mean (95% CI)		P	Model 2: age, ODI, BMI Adjusted mean (95% CI)		P
		Icelandic	Chinese		Icelandic	Chinese	
Total volumes*	Combined soft tissue (mm ³)	202871 (198010, 207733)	184037 (177128, 190947)	<0.0001	203682 (197796, 209569)	180454 (172970, 187939)	<0.0001
	Tongue (mm ³)	132661 (129488, 135835)	116183(111650, 120715)	<0.0001	132929 (129306, 136553)	114702 (109950, 119453)	<0.0001
	Soft palate (mm ³)	9810 (9297, 10323)	11652 (10920, 12383)	0.0001	10224 (9630, 10817)	10797 (10020, 11574)	0.2079
	Lateral walls (mm ³)	28103 (26801, 29406)	29481 (27605, 31358)	0.2429	28723 (27293, 30153)	28083 (26085, 30081)	0.6024
	Fat pads (mm ³)	8629 (8175, 9082)	6352 (5681, 7022)	<0.0001	8541 (8089, 8994)	6522 (5863, 7181)	<0.0001
	Epiglottis (mm ³)	1461 (1343, 1580)	1436 (1261, 1612)	0.8214	1491 (1367, 1615)	1369 (1191, 1548)	0.2711
	Pterygoid (mm ³)	22275 (21257, 23294)	19218 (17812, 20624)	0.0003	22241 (21116, 23366)	19102 (17668, 20536)	0.0001
Partial volumes†	Genioglossus (mm ³)	101302 (99118, 103486)	91576 (88436, 94715)	<0.0001	101664 (99212, 104115)	90383 (87055, 93710)	<0.0001
	Other tongue (mm ³)	31328 (29932, 32724)	24812 (22774, 26850)	<0.0001	31395 (29866, 32925)	24395 (22313, 26477)	<0.0001
	RP lateral walls (mm ³)	14563 (13653, 15473)	15235 (13927, 16543)	0.4197	14695(13751, 15639)	14929 (13599, 16259)	0.7798
	RG lateral walls (mm ³)	13567 (12806, 14329)	14195 (13063, 15327)	0.3936	14082 (13262, 14901)	13153 (11933, 14372)	0.2411

Significant p-values are given in bold.

AP, anteroposterior, CI, confidence interval, ODI, oxygen desaturation index, RG, retroglossal, RP, retropalatal.

*Bonferroni corrected significance level: $p < 0.0071$ (equals 0.05/7).

†Bonferroni corrected significance level: $p < 0.0125$ (equals 0.05/4).

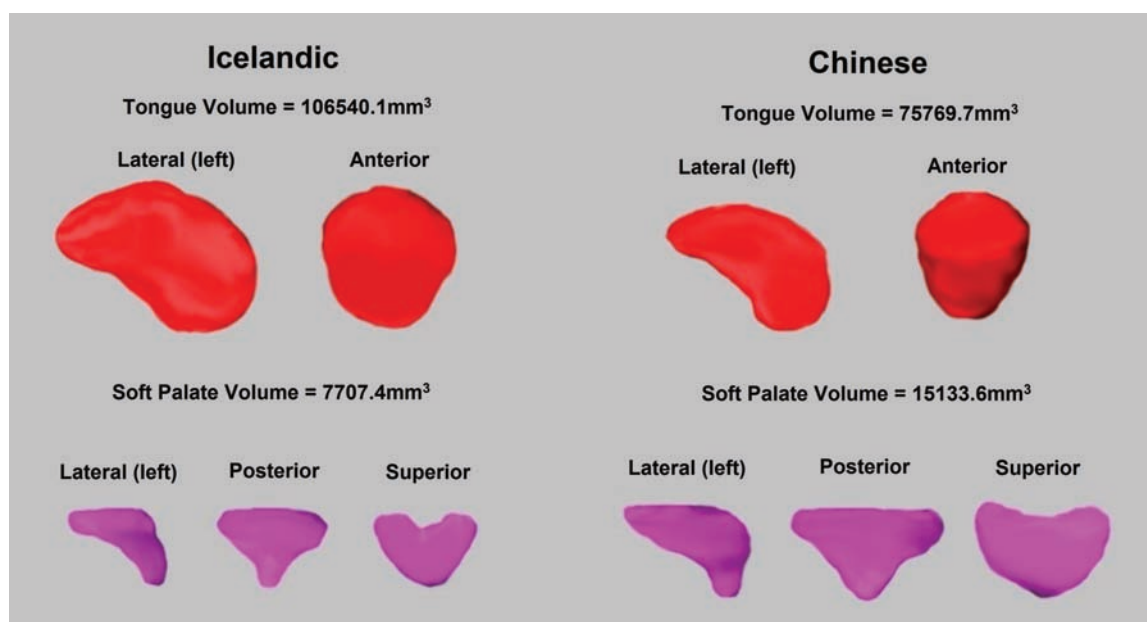


Figure 2. Three-dimensional reconstruction of tongue [genioglossus muscle] and soft palate volumes in representative age, gender, and ODI matched Icelandic and Chinese patients. The Icelandic patient (left), is a 26 years-old male with BMI of 35.2 kg/m² and ODI of 10.8 events/h. The Chinese patient (right) is a 25 years-old male with BMI of 23.8 kg/m² and ODI of 13.6 events/h. Reflecting our results, the Chinese patient had a smaller tongue but larger soft palate than the Icelandic patient.

Table 4. Adjusted comparisons of craniofacial angles between Icelandic and Chinese patients matched for age, gender, and ODI

Variable	Model 1: age, ODI, height Adjusted mean (95% CI)		p	Model 2: age, ODI, BMI Adjusted mean (95% CI)		p
	Icelandic	Chinese		Icelandic	Chinese	
SNA angle (°)	84.49 (83.57, 85.41)	85.99 (84.66, 87.32)	0.0825	84.74 (83.82, 85.66)	85.50 (84.19, 86.81)	0.3686
SNB angle (°)	81.29 (80.40, 82.19)	81.34 (80.04, 82.64)	0.9537	81.37 (80.48, 82.26)	81.19 (79.89, 82.48)	0.8256
ANB angle (°)	3.18 (2.62, 3.74)	4.97 (4.15, 5.78)	0.0009	3.38 (2.83, 3.92)	4.60 (3.80, 5.40)	0.0196
Saddle angle (°)	125.7 (124.4, 126.9)	125.7 (123.9, 127.5)	0.9940	124.5 (123.2, 125.7)	128.0 (126.2, 129.8)	0.0023
ACB:HP (°)	12.89 (11.68, 14.10)	10.39 (8.624, 12.15)	0.0314	11.79 (10.71, 12.88)	12.50 (10.93, 14.07)	0.4939

Bonferroni corrected significance level: $p < 0.01$ (equals 0.05/5). Significant p-values are given in bold.

ACB, anterior cranial base, ANB, Subspinale–Nasion–Supramentale (the difference between SNA and SNB), BMI, body mass index, CI, confidence interval, HP, horizontal plane, ODI, oxygen desaturation index, SNA, Sella (S)–Nasion (N)–Subspinale (A), SNB, Sella (S)–Nasion (N)–Supramentale (B).

interactions ($p < 0.10$) were observed in adjusted (Table 10) or unadjusted (Supplementary Table S4) analyses. Adjusting for age, ODI, and height, gender-specific ethnic differences

were identified for RP minimum anteroposterior (AP) distance ($p = 0.020$), soft palate volume ($p = 0.006$), mandibular length corpus ($p = 0.046$) and ramus ($p = 0.014$), mandibular

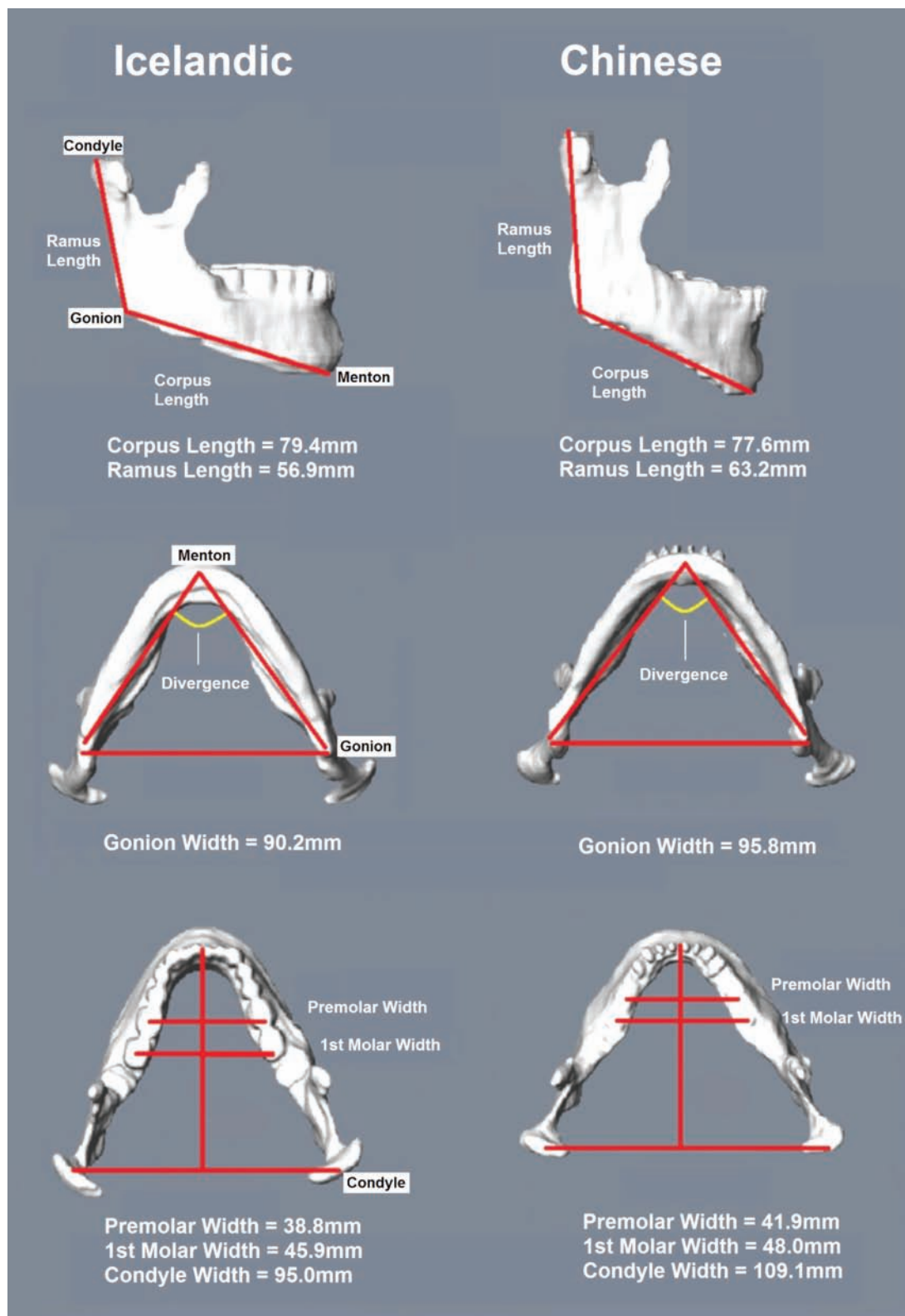


Figure 3. Three-dimensional reconstruction of the mandible in representative age, gender and ODI matched Icelandic and Chinese patients. The Icelandic patient (left) is a 59 years-old female with a BMI of 26.0 kg/m² and ODI of 28.8 events/h. The Chinese patient (right) is a 58 years-old female with BMI of 26.0 kg/m² and ODI of 31.1 events/h. As in our results, the Chinese patient has a longer ramus length, shorter corpus length, and greater mandibular widths than the Icelandic patient.

width at the first molar ($p = 0.071$), mandibular divergence ($p = 0.098$) and hyoid-to-sella distance ($p = 0.019$). Results were similar when adjusting for BMI instead of height: the gender effect on hyoid-to-sella distance became

nonsignificant, but a borderline interaction on maxillary depth emerged ($p = 0.099$). Ethnic differences in mandibular lengths and width were significant in both genders; larger differences in length were seen in males and a larger

Table 5. Adjusted comparisons of mandibular measurements between Icelandic and Chinese patients matched for age, gender and ODI

Variable	Model 1: age, ODI, height Adjusted mean (95% CI)			Model 2: age, ODI, BMI Adjusted mean (95% CI)		
	Icelandic	Chinese	P	Icelandic	Chinese	P
Depth (mm)	76.29 (75.03, 77.55)	75.26 (73.44, 77.08)	0.3907	76.23 (74.98, 77.48)	75.38 (73.57, 77.19)	0.4752
Length corpus (mm)	93.80 (92.79, 94.82)	80.57 (79.09, 82.05)	<0.0001	94.16 (93.10, 95.22)	79.89 (78.35, 81.42)	<0.0001
Length ramus (mm)	45.23 (43.87, 46.60)	67.48 (65.52, 69.43)	<0.0001	46.15 (44.80, 47.50)	65.72 (63.80, 67.63)	<0.0001
Total length (mm)	139.1 (137.5, 140.6)	148.1 (145.9, 150.3)	<0.0001	140.3 (138.6, 142.0)	145.8 (143.5, 148.1)	0.0001
Width second premolar (mm)	38.57 (37.95, 39.18)	41.46 (40.61, 42.31)	<0.0001	38.51 (37.89, 39.13)	41.54 (40.71, 42.37)	<0.0001
Width first molar (mm)	44.77 (44.07, 45.47)	48.62 (47.67, 49.57)	<0.0001	44.73 (44.03, 45.43)	48.65 (47.72, 49.58)	<0.0001
Width gonion (mm)	90.05 (88.94, 91.16)	98.78 (97.17, 100.4)	<0.0001	90.51 (89.36, 91.67)	97.86 (96.22, 99.50)	<0.0001
Width condyle (mm)	102.6 (101.4, 103.7)	110.9 (109.3, 112.6)	<0.0001	103.0 (101.8, 104.2)	110.0 (108.4, 111.7)	<0.0001
Divergence (°)	72.12 (71.04, 73.20)	69.70 (68.23, 71.18)	0.0076	72.03 (70.95, 73.12)	69.88 (68.42, 71.34)	0.0159

Significant p-values are given in bold.
 BMI, body mass index, CI, confidence interval, ODI, oxygen desaturation index.
 Bonferroni corrected significance level: $p < 0.0056$ (equals 0.05/9).

Table 6. Adjusted Comparisons of Maxillary measurements between Icelandic and Chinese Patients Matched for Age, Gender and ODI

Variable	Model 1: age, ODI, height Adjusted mean (95% CI)			Model 2: age, ODI, BMI Adjusted mean (95% CI)		
	Icelandic	Chinese	p	Icelandic	Chinese	p
Depth (mm)	47.64 (46.88, 48.39)	44.83 (43.76, 45.89)	0.0001	47.68 (46.90, 48.46)	44.69 (43.63, 45.75)	<0.0001
Divergence (mm)	55.41 (54.27, 56.55)	58.83 (57.20, 60.45)	0.0011	55.68 (54.57, 56.80)	58.29 (56.70, 59.89)	0.0114
Width second premolar (mm)	40.55 (39.94, 41.16)	44.64 (43.80, 45.47)	<0.0001	40.38 (39.77, 41.00)	44.93 (44.12, 45.74)	<0.0001
Width first molar (mm)	45.18 (44.59, 45.78)	49.52 (48.69, 50.34)	<0.0001	45.14 (44.56, 45.72)	49.59 (48.79, 50.40)	<0.0001

BMI, body mass index, CI, confidence interval, ODI, oxygen desaturation index. Bonferroni corrected significance level: $p < 0.0125$ (equals 0.05/4).

Table 7. Adjusted comparisons of hyoid distances between Icelandic and Chinese patients matched for age, gender and ODI

Variable	Model 1: age, ODI, height Adjusted mean (95% CI)			Model 2: age, ODI, BMI Adjusted mean (95% CI)		
	Icelandic	Chinese	p	Icelandic	Chinese	p
Hyoid to retropogonion (mm)	42.92 (41.69, 44.15)	40.71 (38.89, 42.52)	0.0636	42.76 (41.54, 43.98)	41.01 (39.24, 42.78)	0.1292
Hyoid to C3 (mm)	36.94 (35.94, 37.93)	39.46 (38.03, 40.89)	0.0064	37.12 (36.06, 38.19)	39.03 (37.57, 40.48)	0.0350
Hyoid to sella (mm)	119.3 (117.6, 121.0)	129.3 (126.8, 131.7)	<0.0001	122.4 (120.1, 124.6)	123.1 (120.1, 126.1)	0.6854
Retropogonion to C3 (mm)	72.29 (70.80, 73.79)	65.34 (63.14, 67.54)	<0.0001	71.08 (69.67, 72.49)	67.69 (65.69, 69.70)	0.0080

Significant p-values are given in bold. Bonferroni corrected significance level: $p < 0.0125$ (equals 0.05/4).
 BMI, body mass index, C3, the 3rd cervical vertebrae, CI, confidence interval, ODI, oxygen desaturation index.

Table 8. Adjusted comparisons of craniofacial heights between Icelandic and Chinese patients matched for age, gender and ODI

Variable	Model 1: age, ODI, height Adjusted mean (95% CI)			Model 2: age, ODI, BMI Adjusted mean (95% CI)		
	Icelandic	Chinese	p	Icelandic	Chinese	p
Upper facial height (UFH) (mm)	48.40 (47.66, 49.14)	50.76 (49.68, 51.83)	0.0009	48.85 (48.07, 49.62)	49.87 (48.77, 50.98)	0.1511
Lower facial height (LFH) (mm)	72.31 (71.21, 73.41)	73.90 (72.29, 75.50)	0.1337	73.01 (71.88, 74.13)	72.55 (70.92, 74.19)	0.6716
Anterior facial height (AFH) (mm)	120.9 (119.5, 122.4)	125.4 (123.3, 127.6)	0.0013	122.0 (120.5, 123.5)	123.4 (121.2, 125.6)	0.3177
UFH/AFH	0.401 (0.395, 0.406)	0.405 (0.397, 0.413)	0.4102	0.401 (0.396, 0.407)	0.404 (0.396, 0.412)	0.5421
PNS to anterior arch atlas (mm)	33.14 (32.26, 34.02)	33.22 (31.93, 34.52)	0.9239	32.66 (31.82, 33.50)	34.17 (32.93, 35.40)	0.0633

Bonferroni corrected significance level: $p < 0.01$ (equals 0.05/5). Significant p-values are given in bold.
 BMI, body mass index, CI, confidence interval, ODI, oxygen desaturation index, PNS, posterior nasal spine.

difference in width was seen in females. Interestingly, the smaller RP minimal AP distance ($p \leq 0.002$), larger soft palate volume ($p \leq 0.016$) and smaller mandibular divergence ($p \leq$

0.012) in Chinese compared to Icelandic patients was primarily seen in males, with smaller, nonsignificant differences in females (although the female sample is small).

Table 9. Adjusted comparisons of craniofacial volume and areas between Icelandic and Chinese patients matched for age, gender and ODI

Variable	Model 1: age, ODI, height Adjusted mean (95% CI)		P	Model 2: age, ODI, BMI Adjusted mean (95% CI)		P
	Icelandic	Chinese		Icelandic	Chinese	
Intramandibular volume (mm ³)	181984 (176470, 187498)	175890 (167810, 183970)	0.2249	182813(176867, 188759)	173659 (165358, 181960)	0.0654
Nasooropharyngeal area (mm ²)	8339 (8153, 8525)	8711 (8442, 8981)	0.0344	8499 (8295, 8703)	8399 (8112, 8686)	0.5861
Oropharyngeal area (mm ²)	5876 (5740, 6011)	6224 (6029, 6420)	0.0062	5974 (5828, 6120)	6032 (5826, 6239)	0.6600
Nasopharyngeal area (mm ²)	2465 (2399, 2531)	2487 (2390, 2583)	0.7317	2526 (2456, 2597)	2367 (2266, 2467)	0.0140

Bonferroni corrected significance level: $p < 0.0125$ (equals 0.05/4). Nasopharyngeal area: Nasion-anterior Nasal Spine-Basion-Nasion (Na-ANS-Ba-Na); oropharyngeal area: anterior Nasal Spine-Menton-Third cervical vertebrae-Basion-Anterior Nasal Spine (Na-ANS-Me-C3-Ba-Na); Naso-oropharyngeal area: Na-ANS-Me-C3-Ba-Na. Significant p -values are given in bold.

BMI, body mass index, CI, confidence interval, ODI, oxygen desaturation index.

Table 10. Upper airway measurements with evidence for racial differences modified by gender

Variable*	Inter-action P-value	Male		P	Female		P
		Icelandic N = 84	Chinese N = 44		Icelandic N = 24	Chinese N = 13	
Model 1: age, ODI, height adjusted mean (95% CI)							
RP min. AP distance (mm)	0.0204	7.18 (6.72, 7.65)	5.36 (4.70, 6.01)	<0.0001	5.69 (4.87, 6.51)	5.60 (4.53, 6.66)	0.8830
Soft palate volume (mm ³)	0.0058	10709 (10146, 11271)	12272 (11438, 13106)	0.0051	7870 (7340, 8400)	7174 (6430, 7918)	0.1305
Mandibular length corpus (mm)	0.0460	95.99 (94.79, 97.19)	80.83 (79.03, 82.63)	<0.0001	87.70 (85.73, 89.68)	77.23 (74.41, 80.04)	<0.0001
Mandibular length ramus (mm)	0.0142	45.50 (43.91, 47.10)	68.54 (66.30, 70.78)	<0.0001	45.26 (42.23, 48.28)	62.51 (58.20, 66.82)	<0.0001
Mandibular width first molar (mm)	0.0709	45.46 (44.70, 46.23)	48.66 (47.57, 49.75)	<0.0001	43.08 (41.08, 45.07)	46.65 (44.43, 48.86)	0.0060
Mandibular divergence (°)	0.0977	72.01 (70.77, 73.24)	68.59 (66.82, 70.35)	0.0025	72.37 (69.88, 74.85)	73.46 (70.43, 76.48)	0.4993
Maxillary depth (mm)	0.1343	—	—	—	—	—	—
Hyoid to sella (mm)	0.0192	123.5 (121.6, 125.3)	131.8 (129.0, 134.6)	<0.0001	107.7 (104.6, 110.7)	116.1 (111.8, 120.5)	0.0035
Model 2: age, ODI, BMI adjusted mean (95% CI)							
RP min. AP distance (mm)	0.0252	6.96 (6.51, 7.42)	5.76 (5.14, 6.38)	0.0024	5.73 (4.92, 6.53)	5.53 (4.50, 6.56)	0.7446
Soft palate volume (mm ³)	0.0069	10799 (10244, 11354)	12099 (11285, 12913)	0.0159	7910 (7354, 8467)	7108 (6360, 7855)	0.0682
Mandibular length corpus (mm)	0.0414	95.73 (94.60, 96.87)	81.33 (79.66, 83.00)	<0.0001	87.97 (85.99, 89.96)	76.73 (73.93, 79.52)	<0.0001
Mandibular length ramus (mm)	0.0194	46.10 (44.56, 47.64)	67.37 (65.24, 69.51)	<0.0001	45.98 (43.07, 48.88)	61.19 (57.10, 65.27)	<0.0001
Mandibular width first molar (mm)	0.0872	45.26 (44.55, 45.97)	49.02 (48.04, 50.00)	<0.0001	42.33 (40.43, 44.24)	47.78 (45.60, 49.95)	<0.0001
Mandibular divergence (°)	0.0999	71.77 (70.55, 72.98)	69.05 (67.35, 70.76)	0.0118	72.88 (70.41, 75.34)	72.53 (69.59, 75.48)	0.8206
Maxillary depth (mm)	0.0992	48.03 (47.24, 48.83)	46.45 (45.30, 47.61)	0.0391	45.76 (44.53, 46.99)	40.41 (38.76, 42.06)	<0.0001
Hyoid to sella (mm)	0.1061	—	—	—	—	—	—

Significant p -values are given in bold.

AP, anteroposterior, BMI, body mass index, CI, confidence interval, ODI, oxygen desaturation index, RP, retropalatal.

*Upper airway measurements with suggestive evidence of a gender-by-race interaction in either Model 1 or Model 2.

Discussion

This is the first study to use three-dimensional MRI to explore differences in airway sizes, soft tissue volumes and craniofacial structures between Asian patients from China and European patients from Iceland with similar OSA severity. Results support ethnic-related differences in upper airway anatomy in subjects with OSA. Chinese patients demonstrated narrower airways, particularly in the retropalatal region. Icelandic patients had larger tongue, parapharyngeal fat pads, pterygoid, and combined soft tissue volumes. However, larger soft palate volume was observed in male Chinese patients. Chinese patients demonstrated characteristics consistent with more bony restrictions, including larger ANB angle, shorter mandibular length corpus and shorter maxillary depth in both male and females. Moreover, differently shaped mandible and maxilla were observed between Chinese and Icelandic patients. Ultimately, understanding ethnicity-specific differences in OSA-related

anatomy can play an important role in improving disease identification and treatment in these populations.

Different anatomy in Chinese and Icelandic patients with OSA

Airway dimensions

While airway obstruction during sleep occurs at multiple levels in OSA patients, studies demonstrate particular importance of the retropalatal airway [19–21]. A prior study shows that the minimum retropalatal airway area was significantly smaller in OSA patients than normal subjects [4]. Utilizing dynamic sleep MRI, patients with OSA had retropalatal airway collapse during sleep [20]. This propensity to collapse in the retropalatal region was supported by data showing a smaller retropalatal airway, but not retroglottal airway, in normal subjects [21]. The present study supports ethnic differences in patients with OSA in the

retropalatal region, which was significantly smaller in Chinese than Icelandic patients. Given the association between smaller retropalatal airway and OSA, this suggests retropalatal airway size may be more important in OSA etiology among Chinese patients. In contrast, no robust differences were found in the retroglossal airway. Although the specific causes may vary, the observation of a larger soft palate and smaller mandibular divergence in male Chinese patients may play a role in the observed smaller RP airway minimal AP distance in males.

Soft tissue volumes

Studies have demonstrated enlargement of upper airway soft tissues in OSA patients [1]. In our prior research, increased tongue, lateral pharyngeal wall, and combined soft tissue volumes were important OSA risk factors [1].

In the present study, after matching on age, gender, and ODI and controlling for height or BMI, Icelandic patients demonstrated larger tongues, parapharyngeal fat pads, pterygoids, and combined soft tissue volumes than Chinese. Thus, the differences are not likely explained by greater height or obesity in the Icelandic patients, although there may be differences in regional fat deposition. In contrast, among males, Chinese patients showed larger soft palate volumes than Icelandic patients. The finding of larger soft tissues among Icelandic patients is compatible with previous findings of greater size of the tongue in Caucasian patients compared to Chinese at similar AHI [9]. However, our observation of larger soft palate in male Chinese patients is novel. While this result seemingly contrasts with prior results showing a longer soft palate in Caucasian than Chinese patients [9], this previous study was not able to measure volume, highlighting the novelty of the MRI approach used here. Moreover, despite the difference in overall soft tissue volume, the lateral wall volume was not different between two ethnic groups. This could suggest that the lateral walls, which have previously been shown to be an important OSA risk factor [1], play a similar role in determining OSA risk, independent of ethnicity-specific etiologies. Determining this definitively would require study of controls in each population. Ultimately, results indicate that a number of soft tissue volumes differ between the two ethnic groups studied here. Given that larger soft tissues are seen in Icelandic patients, and increased soft tissue volumes have been previously demonstrated to be a risk factor for OSA [1], our data suggest that soft tissues could be more important in OSA etiology among Caucasians.

Differences in upper airway soft tissues may come from distinct fat distributions between Icelandic and Chinese patients. Chinese adults were shown to have a greater proportion of fat, especially in the trunk region, than Caucasians with similar BMI [22]. Similarly, a recent study found ethnic differences in the propensity to store fat intra-abdominally [23]. Moreover, studies have demonstrated that upper airway soft tissue sizes are in part genetically determined [24, 25]. Thus, future studies should examine the distributions of fat in upper airway structures and the role of genetic factors. It is feasible that more fat is deposited in the soft palate of male Chinese patients or that ethnic differences in genetic factors determining soft tissue size exist.

Craniofacial structures

Certain craniofacial characteristics have been implicated in OSA. Shorter mandibular length and smaller mandibular depth in men, greater hyoid-to-nasion and supramentale-to-hyoid distances in men and women are independent risk factors [7]. A previous two-dimensional cephalometric study found that

Chinese patients had bigger SNA and ANB angles and shorter cranial base, midface length, maxilla, and mandible compared to Caucasians with similar AHI [9].

Our study confirms and extends these prior results [9]. Chinese patients with OSA had more craniofacial bony restriction including larger ANB angle, shorter mandibular corpus length and shorter maxilla depth when compared to Icelandic patients. Using three-dimensional MRI, we also demonstrate differently shaped mandible and maxilla between Chinese and Icelandic patients. Chinese had shorter mandibular corpus length, but longer mandibular ramus and total length. These significant, but opposite differences in length may account for the observation of no significant difference in intramandibular volumes between the two ethnic groups. Our study is the first to compare the 3D intramandibular volume between patients from different ethnicities. Mandibular depth which had been also demonstrated as an independent risk factor of OSA in a previous study [7] was not found to be significantly different between two ethnic groups. As found previously, we observed a gender-specific effect on ethnic differences in mandibular measures [26, 27]. Mandibular divergence was smaller in male Chinese patients. While other differences in mandibular measures were generally significant in both genders, differences in mandibular length were greater in males, while differences in width were greater in females. Chinese also had differently shaped maxilla, with shorter depth and greater width compared to Icelandic patients. The potential role of differences in mandibular and maxillary shape on OSA physiology and airway collapsibility remains to be determined. Evaluating this through dynamic or sleep MRI in association with physiological phenotypes [28] is an important direction for studies in these ethnic groups.

As with soft tissues, craniofacial differences could be driven by genetics. Previous studies have demonstrated familial aggregation of craniofacial structures [18, 24, 29, 30], many of which differ between Chinese and Icelandic patients in our study. Genome-wide significant associations for facial morphology have also been observed [31]. Future studies should address the genetic factors that control craniofacial dimensions in these ethnic groups.

Study limitations

There are several limitations for discussion. First, patients were initially diagnosed with OSA using PSG in China, but portable monitors in Iceland. To account for this difference in diagnostic testing, we recalculated the ODI from PSG in Chinese patients so that it was equivalent to that derived from portable monitoring in Iceland. In particular, in both samples the ODI was calculated as the number of desaturations $\geq 4\%$ per hour of total analysis time, determined as the total recording time beginning 30 min after the start of the study and stopping 5 min prior to the end of the study. The ODI has been demonstrated to be a reliable measure of disease severity in patients with OSA [32].

Second, our study compared Icelandic and Chinese patients with at least moderate OSA (defined as an ODI ≥ 10 events/h); healthy controls and patients with mild OSA were not recruited. Therefore, results are generalizable only to patients with moderate or severe disease. In addition, while data inform ethnic differences in important intermediate OSA anatomic risk factors, the lack of controls means that we cannot directly evaluate the ethnic-specific impact of these factors on the risk of developing OSA. Structural risk factors for OSA have been shown previously

[33, 34]. However, when our results are combined with existing literature, they do implicate specific variables as potentially more or less important in ethnic-specific OSA etiology. Ultimately, future research including controls and patients with mild OSA among the ethnic groups studied here, as well as upper airway analysis, should be conducted to confirm ethnic-specific associations with OSA risk and severity. While there is utility in analyses that include noncases, there are also important benefits of understanding ethnic differences among cases with OSA. Prior studies have used the same design to illustrate ethnic differences in anatomy using cephalometry [9] and physiological measures related to OSA [35]. Results of the present study using three-dimensional MRI can be combined with the prior study by Lee et al. [9] to better understand ethnic-specific differences in upper airway anatomy among cases with similar OSA severity. Importantly, these differences can be leveraged to help to target specific personalized treatments (e.g. mandibular device vs CPAP therapy).

In addition to these limitations, this manuscript represents a secondary analysis of a large, multicenter prospective study in Iceland, combined with a recently recruited sample of Chinese patients from one clinical sleep center in China. The imaging techniques were performed using identical methods and covariate matching was leveraged to increase power and reduce the selection bias. Despite this, it is possible that differences in the upper airway anatomy found here are in part explained by differences in clinical referral patterns between Iceland and our single center in China. Future studies including patients from multiple centers in China are needed to understand differences on a more national scale. Similarly, our analyses focused specifically on patients from China and Iceland, and thus may not be generalizable to all OSA patients of Asian or European ancestry. Finally, a large majority of patients were male, reflecting the expected gender distribution of OSA; while we evaluated the influence of gender on ethnic differences using interaction tests, future studies should recruit more females to robustly assess gender differences and increase generalizability.

Study strengths

Strengths of this study include the robust analysis methods and relatively large sample of patients from two ethnic groups, matched on important clinical factors. In addition, we utilized state-of-the-art three-dimensional MRI techniques to quantify novel measures of upper airway size, soft tissue volumes and craniofacial structures.

Conclusions

In summary, we used three-dimensional MRI to examine differences in upper airway size, soft tissue volumes and craniofacial dimensions between Asian patients from China and European patients from Iceland with similar age, gender and OSA severity. Results are compatible with previous studies [9], and extend these findings by quantifying anatomy with three-dimensional imaging. Chinese patients showed smaller airway size, mainly in the retropalatal region. While Icelandic patients have greater combined volumes of the measured soft tissues in both males and females, our results provide new evidence of a larger soft palate in male Chinese patients. Finally, we found differences in the overall shapes of the mandible and maxilla between the two ethnic groups, and Chinese patients demonstrated evidence of more bony restrictions. Differences in upper airway anatomy should inform therapies and

future studies on the relative efficacy of different treatments (e.g. positive airway pressure vs. oral appliances). Ultimately, our results further the understanding of the ethnicity-specific anatomical characteristics among OSA patients, which can inform potential personalized treatment of OSA within these populations.

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Authors' contribution

Conception and design: A.I.P., T.G. and R.J.S. Data acquisition: Q.L., Z.W., J.W. Analysis and interpretation: A.W., B.S., L.X., B.T.K., B.B., S.J., A.I.P., R.J.S. Drafting of the manuscript: L.X., B.T.K., A.W., A.I.P., T.G. and R.J.S. Revision: L.X., B.T.K., A.I.P. and R.J.S.

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