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ORIGINAL ARTICLE

New insights into the variability of upper airway morphology in modern humans

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Abstract

The biological adaptation of the human lineage to its environment is a recurring question in paleoanthropology. Particularly, how eco-geographic factors (e.g., environmental temperature and humidity) have shaped upper airway morphology in hominins have been subject to continuing debate. Nasal shape is the result of many intertwined factors that include, but are not limited to, genetic drift, sexual selection, or adaptation to climate. A quantification of nasal airway (NA) morphological variation in modern human populations is crucial to better understand these multiple factors. In the present research, we study 195 in vivo CT scans of adult individuals collected in five different geographic areas (Chile, France, Cambodia, Russia, and South Africa). After segmentation of the nasal airway, we reconstruct 3D meshes that are analyzed with a landmark-free geometric morphometrics method based on surface deformation. Our results highlight subtle but statistically significant morphological differences between our five samples. The two morphologically closest groups are France and Russia, whose NAs are longer and narrower, with an important protrusion of the supero-anterior part. The Cambodian sample is the most morphologically distinct and clustered sample, with a mean NA that is wider and shorter. On the contrary, the Chilean sample forms the most scattered cluster with the greatest intra-population variation. The South African sample is morphologically close to the Cambodian sample, but also partially overlaps the French and Russian variation. Interestingly, we record no correlation between NA volume and geographic groups, which raises the question of climate-related metabolic demands for oxygen consumption. The other factors of variation (sex and age) have no influence on the NA shape in our samples. However, NA volume varies significantly according both to sex and age: it is higher in males than in females and tends to increase with age. In contrast, we observe no effect of temperature or humidity on NA volume. Finally, we highlight the important influence of asymmetries related to nasal septum deviations in NA shape variation.

KEYWORDS

climate adaptation, deformation-based models, evolution, modern humans, nasal airway

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1 | INTRODUCTION

Since its appearance between 2.4 and 1.8 million years ago in Africa, the genus *Homo* has undergone significant climatic fluctuations that have influenced its evolution (Potts & Faith, 2015; Winder et al., 2015). How these environmental changes shaped hominins morphology has been a recurring question in paleoanthropology research for decades. The exact nature of the influence of eco-geographic factors, their interaction with other processes causing morphological variation (i.e., genetic and biomechanical factors), and the extent of their respective influence on the phenotype are highly debated questions.

One of the anatomical areas that has received particular attention regarding environmental adaptation is the craniofacial skeleton. Specifically, many authors have demonstrated the influence of climate on the morphology of the internal nasal region (Bastir et al., 2011; Butaric et al., 2010; Carey & Steegmann, 1981; Cottle, 1955; Crognier, 1981a, 1981b; Davies, 1932; Evteev et al., 2014; Franciscus & Long, 1991; Harvati & Weaver, 2006; Jaskulska, 2014; Maddux & Butaric, 2017; Marks et al., 2019; Negus, 1960; Noback et al., 2011; Roseman & Weaver, 2004; Thomson & Buxton, 1923; Weiner, 1954; Wolpoff, 1968; Yokley, 2009; Zaidi et al., 2017), which is in direct contact with the external environment. The influence of some climatic factors (e.g., environmental temperature and humidity) on nasal morphology are generally interpreted in relation to two physiological functions: air conditioning (Butaric et al., 2010; Butaric & Klocke, 2018; Churchill et al., 2004; de Azevedo et al., 2017; Elad et al., 2008; Evteev & Grosheva, 2019; Heuzé, 2018; Keck et al., 2000; Maddux et al., 2016; Naftali et al., 2005; Shea, 1977; Yokley, 2009), and respiratory energetics (Froehle et al., 2013; Hall, 2005; Wroe et al., 2018). Air conditioning is the process by which the inspired air is warmed to body core temperature and fully saturated in water vapor to protect the lower airways from thermal injuries (Elad et al., 2008; Hildebrandt et al., 2013; Proetz, 1951; Walker & Wells, 1961; Williams, 1998; Wolf et al., 2004). This function is ensured by the highly vascularized respiratory mucosa lining the bony nasal cavity (NC) (Froehle, 2008; Holton et al., 2013). In addition to climatic conditions, several physiological factors such as blood pressure or nasal cycle can modify the thickness of the nasal mucosa (Elad et al., 2008; White et al., 2015). This also affects the morphology of the soft tissue nasal passageway through which the air flows and which is called the nasal airway (NA). The second physiological function that can be linked to a response to environmental variation is respiratory energetics. The nasal cavity is involved in meeting the energetic demands of the body in that it is the upper part of the respiratory system that regulates the amount of air inhaled (Froehle et al., 2013; Hall, 2005; Wroe et al., 2018). An increase in the energetic demands of the body, which are needed, for example, in colder and/or drier environments, would therefore imply a more voluminous NA (Hall, 2005).

Both air conditioning and respiratory energetics functions can therefore lead to variation in the size and shape of the NA, which will directly affect the velocity, volume, and direction of inspired

airflow. Because these physiological functions are dependent on climatic factors, nasal morphological variation is an important indicator for understanding the climatic adaptation of modern and extinct human species. This has been demonstrated in numerous studies on dry skulls investigating the link between environmental factors and nasal cavity morphology. The results of these studies have shown that in colder and drier environments, humans display a longer, taller, and narrower NC (Churchill et al., 2004; Doorly et al., 2008; Evteev & Grosheva, 2019; Franciscus, 1995; Holton et al., 2011, 2013; Yokley, 2009). This morphology would improve the air conditioning capacity by increasing the ratio of mucosal surface area relative to air volume (SA/V) (Lindemann et al., 2009; Schroter & Watkins, 1989), but also the occurrence time and the turbulence of the airflow in the NC (Inthavong et al., 2007; Noback et al., 2011). Such a morphology could also benefit respiratory energetics, in that higher nasal cavities have been observed in populations with higher metabolic oxygen demands. These higher demands could be linked to a larger lean body mass or a higher level of physical activity in these populations, but also to more demanding climatic conditions (Bastir et al., 2011; Bastir & Rosas, 2016; Froehle, 2008; Holton et al., 2016). Additionally, the shape of the nasal turbinates, which are curled structures that extend from the lateral and upper walls of each side of the nasal cavity, also seems to be affected by climatic factors (Marks et al., 2019). However, the morphology of these structures has been very scarcely studied in humans.

While NC morphology and its environmental fitness has been extensively discussed, our knowledge on NA morphological variation is still incomplete. A study on in vivo data showed non-significant differences in the SA/V ratio between individuals from European and African descent, unless the nasal airway was completely decongested, which is more indicative of NC morphology rather than NA (Yokley, 2009). This raises the question of the covariation between the volumes and the shapes of NC and NA. The study of a small sample from France addressed this question by studying the correlation between NA and NC volumes. When including the ethmoidal air cells, which are olfactory anatomical structures closely connected to the respiratory NA, Heuzé reported a non-significant correlation between NC and NA volumes. When excluding the ethmoidal air cells, this correlation was significant but rather low (Heuzé, 2018). These findings call for caution when interpolating climatic explanations of NA morphology based on NC morphology. A quantification of NA climate-related variation and covariation between NA and NC are therefore crucial steps to be able to discuss the climatic adaptation of this anatomical area.

The study of archaeological series or anatomical collections does not allow to solve these questions entirely, because soft tissues are absent. However, medical computed tomography (CT) of living individuals, whose age and sex are reliably known, allows us to study both hard and soft tissues. In this research study, we use CT data to quantify the extent of NA morphological variation in five samples from different modern human populations. Our goal is not to investigate climatic adaptation per se, as the populations we study are genetically different and geographically widely dispersed.

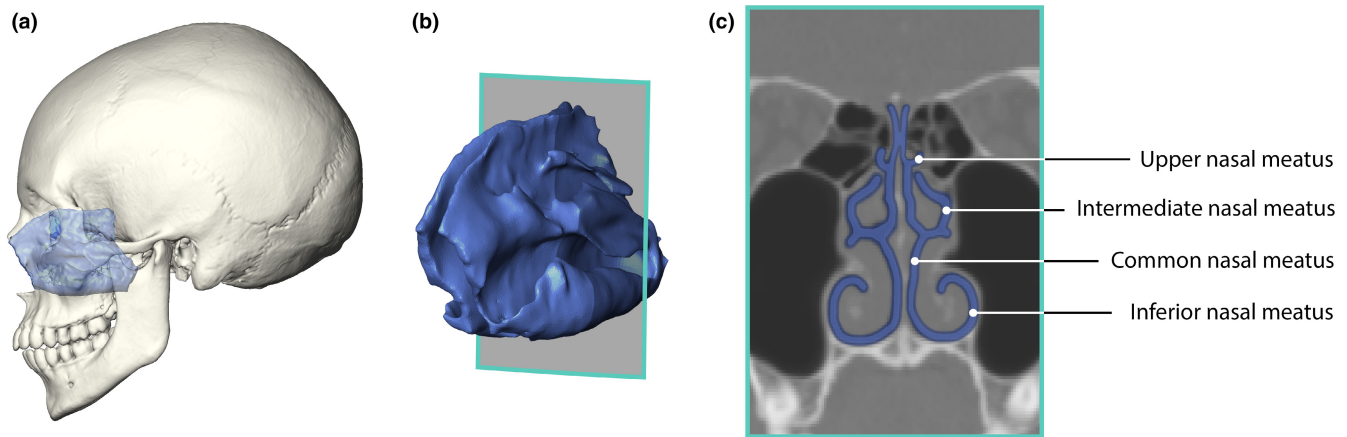


FIGURE 1 Anatomy of the nasal airway. Localization of the nasal airway inside the craniofacial skeleton (left lateral view) (a). Note that the nasal airway is delimited by the nasal mucosa visible on the *in vivo* CT images. The anterior limit is defined by the piriform aperture and the posterior limit by the choanae. 3D reconstruction after segmentation of the nasal airway (b). Coronal slice (c) of the nasal airway along the plane figured in (b).

However, we expect that the genetic and geographic diversity of our sample will impact the morphological variation in the NA. On an intra-population scale, we expect morphological variation in the NA related to seasonality and characterized by an increase in the nasal resistance and a reduction of nasal patency in cold or dry conditions (Fontanari et al., 1996; Olsson & Bende, 1985; Salman et al., 1971). We also anticipate morphological variation related to size that could be associated with different energetics demands. On this matter, we expect for instance to observe sexual dimorphism in NA morphology (Bastir et al., 2020; Holton et al., 2014, 2016). Finally, we will explore the potential influence of aging on NA morphology, that could be linked to the atrophy of nasal mucosa throughout life (Schrödter et al., 2003).

2 | METHODS

2.1 | Materials

The present study is based on 195 *in vivo* CT scans of adult individuals aged between 20 and 95 years old. These CT images were collected in five different geographic areas: Santiago, Chile ($N = 35$), Bordeaux, France ($N = 40$), Phnom Penh, Cambodia ($N = 40$), Moscow, Russia ($N = 40$), and Cape Town, South Africa ($N = 40$). The data were collected after local IRB approval (ethical agreements references: DC 2015/172 (CHU Bordeaux); 090 (Hospital of the University of Chile); N19/12/158 (Tygerberg Hospital); National Scientific and Practical Center of Children's Health of Moscow (see Evteev et al., 2018). No ethical clearance was required for a retrospective and anonymized study on data from Phnom Penh Central Hospital). The CT images were anonymized and the only information collected was the age and sex of the individuals. Additionally, the month at which the scans were performed were used to determine the local average temperature and humidity (The World Bank Group, 2021). We excluded the patients displaying nose and sinus

disorders such as nasal fractures, rhinitis, or choanal atresia causing an obstruction of the NA, or sinusitis. We also excluded patients under respiratory assistance or scanned with their mouths open, to ensure a functional nasal breathing. The application of these criteria led to the exclusion of 56% of the data collected. Among the remaining individuals, we selected males ($N = 99$) and females ($N = 96$) over the age of 20 and divided them into three age categories based on those commonly used in biological anthropology (Buikstra & Ubelaker, 1994): 20–35 years ($N = 66$), 36–50 years ($N = 64$), and 51+ years ($N = 65$) (see Figure S1 for detailed composition of the selected sample). The voxel size of the CT-scans ranges from 0.42 to 0.52 mm perpendicular to the axial scan direction and from 0.63 to 1.25 mm in the axial direction.

2.2 | Segmentation of the nasal airway

NA surfaces were produced through semi-automatic segmentation and 3D mesh reconstruction in the software Avizo v.9.0.1 (Figure 1). First, a threshold-based segmentation was used for filling the air in the negative space delimited by the nasal mucosa. Depending on the acquisition parameters of the original CT scans, the threshold values set on the basis of the histogram were slightly adjusted visually to find the best fit to the segmented structures. As a next step, volumes were inspected and corrections were manually made to include areas that were not initially selected to the final volumes corresponding to the NA. We excluded all ducts connecting the NA with paranasal sinuses. The NA was delimited anteriorly by the piriform aperture and posteriorly by the choanae. The ethmoidal air cells, located in the ethmoid labyrinth (also known as the olfactory labyrinth), were not included in this model, as they are covered with olfactory mucosa rather than respiratory mucosa (Jankowski, 2013). In the case of a connection between the ethmoidal air cells and the common and/or upper nasal meati, the ethmoidal air cells and the ducts connecting these structures were manually excluded. All

the segmentation process was performed by one observer (LM) and an intra-observer test (Figure S2) confirmed the repeatability of the procedure.

In order to observe the morphological variation in the NA in real physiological conditions, we did not decongest or average the NA to exclude the potential effect of the nasal cycle, as it has been done in several studies (Patel et al., 2015; Yokley, 2009). The labels resulting from the segmentation were used to build a surface mesh by applying the marching cubes algorithm (Lorensen & Cline, 1987) ("Generate Surface" module in Avizo v.9.0.1). The number of triangles was set to 75.000 faces for each individual's NA to reduce computation time while maintaining sufficient morphological accuracy. These surface models were smoothed using a smoothing algorithm allowing minimal surface shrinkage (Taubin, 1995) ("Smooth Surface" module in Avizo v.9.0.1). As a pre-processing step, all surfaces were rigidly aligned in position, orientation, and scale with respect to a reference surface (randomly selected) using an Iterative Closest Point algorithm ("Align Surface" module in Avizo v.9.0.1). We then exported each simplified, scaled and aligned surface in PLY file format and converted them into VTK files on Paraview v.5.7.0.

2.3 | Surface-based morphological comparison

The NA shape was analyzed with a landmark-free method based on the construction of a surface representing the mean shape of a sample and its deformation to each individual surface (Beaudet et al., 2016; Durrleman et al., 2012, 2014). This deformation is modelled as a diffeomorphism: it is not based on a point-to-point correspondence between shapes but on a smooth and invertible deformation of the entire 3D surface (Durrleman, 2010). This method was shown to increase the statistical power of shape comparison and to increase its precision by allowing the observation of non-homologous features of shapes (Braga et al., 2019; Vaillant et al., 2007). The mean shape is computed with the software Deformetrica from a set of surfaces, based on a set of control points located near the most variable parts and a set of momenta (or vector fields) representing the deformation from the global mean shape (GMS) to each individual. We also calculated population mean shapes (PMS) for each geographic group, based on the mean of the momenta within each population.

2.4 | Exploratory multivariate analysis

To test the effects of geographic origin, demographic factors (sex and age), and environmental factors (mean temperature and humidity) on NA morphology, statistical analyses were carried out using R v.4.0.5 (R Core Team, 2021) and the packages RToolsForDeformetrica (Dumoncel, 2020), ade4 (Bougeard & Dray, 2018; Chessel et al., 2004; Dray et al., 2007; Dray & Dufour, 2007; Thioulouse et al., 2018), vegan (Oksanen et al., 2020), and pairwiseAdonis (Martinez

Arbizu, 2020). We quantified inter-population variation by performing a principal component analysis (PCA) on the GMS-to-individuals NA deformations of the whole sample. Intra-population variation was explored by performing a PCA on the deformation fields from PMS to the individuals. Deformed shapes along the PCs illustrate how the GMS (inter-population) or the PMS (intra-population) varies from the mean to one time the standard deviation. Color maps onto the NA surfaces rendered the magnitude of the displacements caused by the deformation. To represent an accurate vision of our data and make it accessible to people with color-vision deficiencies (Cramer et al., 2020; Moreland, 2016) we use the viridis color map (van der Walt & Smith, n.d.) for our data visualization. Permutational multivariate analyses of variance (PERMANOVAs) were used to explore the variables influencing the distribution of the individuals on the main PCs (i.e., geographic group, sex, age, temperature, humidity). The effect of allometry on the shape variation was tested via bivariate regressions (Pearson correlation) between PC scores and the log-transformed volume of NA (Urciuoli et al., 2020). We also explored NA volume variation among and within populations with ANOVAs. To be able to normalize these volumes by the size of the facial skeleton, we measured 11 landmarks on the facial skeleton of each individual and used centroid size as a proxy for size (Figure S3). Centroid size is defined as the square root of the sum of squared distances of all the landmarks of an object from their centroid. These landmarks were measured by one observer (LM) and their repeatability was assessed by an intra-observer test (Figure S2).

3 | RESULTS

3.1 | Nasal airway shape variation among geographic groups

The PCA analysis of NA shapes performed among all the geographic groups shows a strong overlap of the five populations. Nevertheless, we can observe differences in the distribution of these groups on several PCs, including PC1, PC2, and PC3 accounting for 18.59%, 6.91%, and 5.26% of total shape variance, respectively (Figure 2). Due to the high overlap of the groups on the PCA scatterplot, we also represented the distribution of the individuals with boxplots showing their scores on the first three PCs. In addition to quantitative comparisons, we also computed the mean shapes for each geographic group (Figure 3) to provide a qualitative comparison of these shapes with the corresponding GMS-to-PMS deformations. These comparisons can be visualized with colormaps and vectors showing the magnitude and orientation of the variation.

PC1 highlights major variation in NA length, width, and height as well as the degree of protrusion of the anterosuperior part of the common nasal meatus (Figure 2). The Cambodian and South African samples have the highest scores on PC1 (Figure 2) because of the anteroposteriorly contracted and mediolaterally extended morphology of their NAs (Figure 3). The reduction in the anteroposterior axis

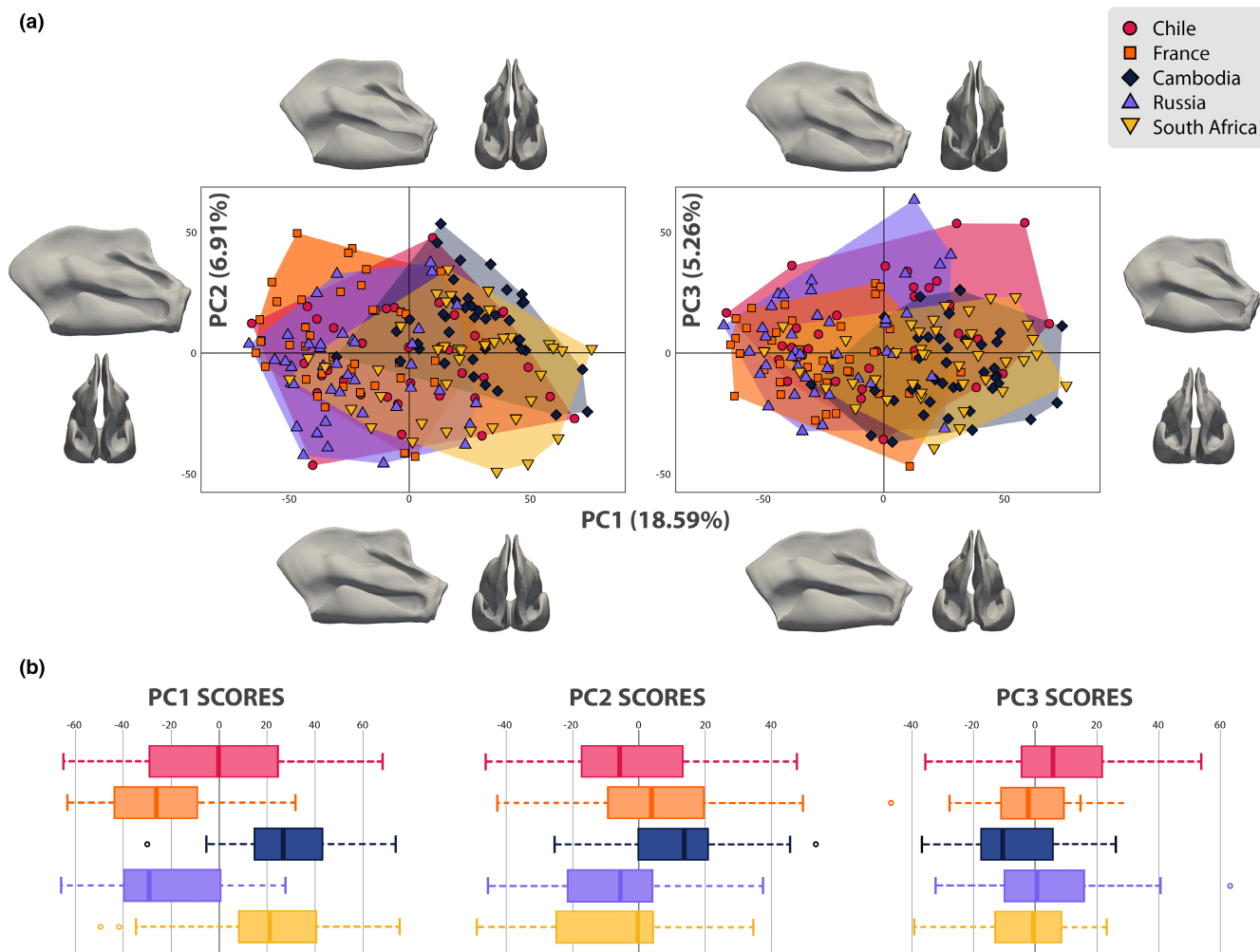


FIGURE 2 Shape differences between groups. Principal component analysis (PCA) of the deformation-based shape comparison made on the NA of the five populations (Chile, France, Cambodia, Russia, South Africa) (a) and boxplots showing the distribution of the PC scores on PC1, PC2 and PC3 (b).

is due to an anterior displacement of the choanae and a posterior displacement of the piriform aperture. The mediolateral elongation is related to a lateral displacement of the inferior and intermediate meati, while the common meati approximately remain in the same position. The French and Russian samples are found rather in the negative values (Figure 2) because their NAs have a longer and narrower shape and show significant protrusion of the anterosuperior part of the common meati (Figure 3). The lower part of the common meati is displaced downward, contributing to a slight overall increase in height. Individuals from Chile spread out all along PC1 with a median centered at 0 (Figure 2). The Chilean PMS shows the lowest rate of variation compared to the GMS (Figure 3).

PC2 captures variation in NA height, length and width, but also in the morphology and relative position of the meati. Individuals from Cambodia are mainly found in the positive values on PC2 (Figure 2) because of their morphology being relatively larger in the superior-inferior dimension, shorter in the anterior-posterior dimension and wider in the medial-lateral dimension. The elongation in the superior-inferior plane is due to an upward displacement of

the superoposterior portion of the common meati, which are proportionally much higher than in the negative values (Figure 3). This part of the common meati also shifts significantly forward. PC2 discriminates the Cambodian and South African samples because the latter, although wider and shorter than the GMS, is found rather in the negative values (with a median centered at 0) because of its contraction in the superior-inferior plane. Individuals from Russia are also predominantly found in the negative values (Figure 2) because their PMS shows an increase in overall NA length and a reduction in NA width. Their shape is also defined by a displacement of the intermediate meati floor, implying a relative position that is closer to the inferior meati. The curvature of the intermediate meati is also more curled toward the common meati, especially at their posterior part.

PC3 accounts for the asymmetry in the shape of the NA. On this PC, all populations are more equally distributed (Figure 2). Negative values characterize wider inferior meati and narrower intermediate and upper meati. The upper and anterior part of the common meati is displaced to the left while the middle part is displaced to the right. This creates a torsion of the overall shape. The choanae are displaced

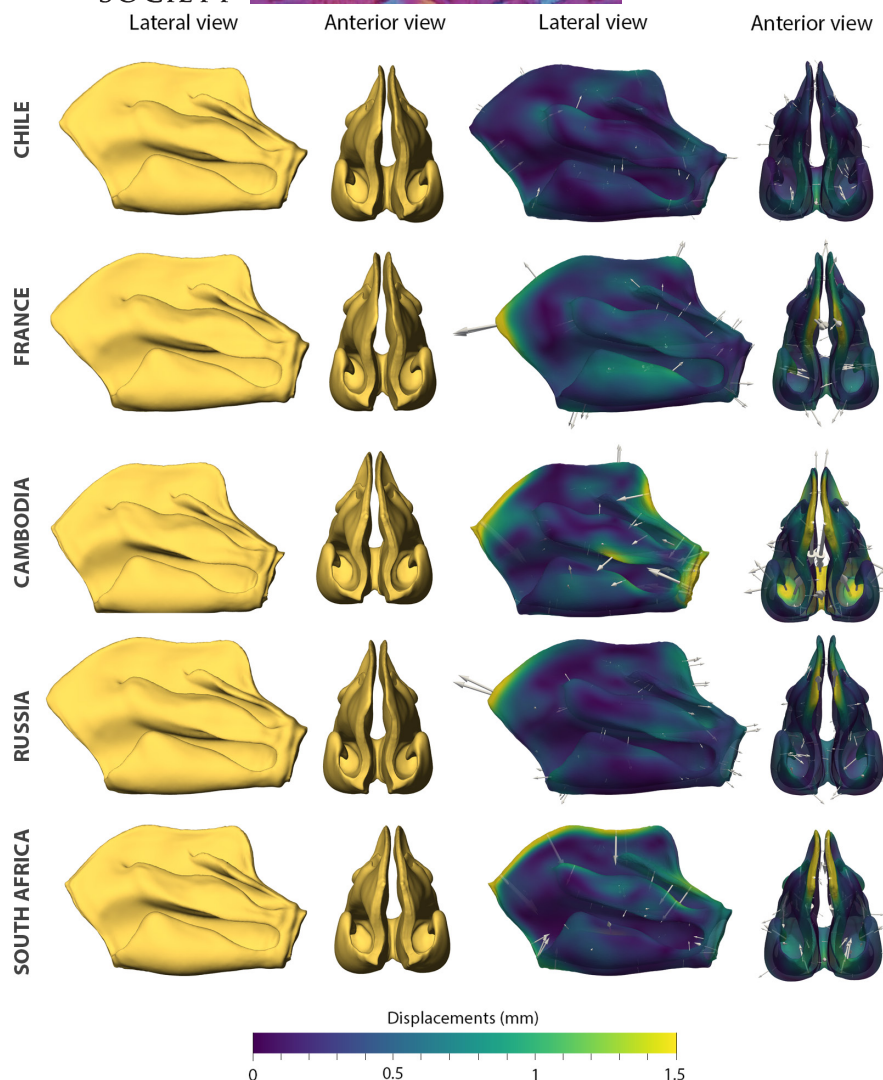


FIGURE 3 Population mean shapes. Mean shapes computed for each population (PMS) (left) and comparative maps of morphological deformations from the global mean shape (GMS) computed for the total sample to the PMS (right). Deformation from the GMS is rendered by a colormap ranging from dark blue (lowest values) to yellow (highest values) at the surfaces of each PMS. The magnitude and orientation of the deformation from the GMS to the PMS is represented by the white vectors (scale factor set to 5 for a better visualization). The range of the color bar (from 0 to 1.5 mm) has been homogenized to best represent global and local deformation, even if some recorded deformations exceeded this value.

upward and the anterior part of all meati is displaced downward. In positive values, there is a mirror-like variation.

The PERMANOVAs performed on all the PC scores (Table S1) of the morphospace confirm what we observe on the PCA by revealing statistically significant differences between geographic groups ($R^2 = 0.12$, $p = 0.001$) and, to a lesser extent, between sexes ($R^2 = 0.01$, $p = 0.04$). These PERMANOVAs also show that the temperature at the time of scanning significantly influences the distribution of individuals in the morphospace ($R^2 = 0.08$, $p = 0.001$). However, this last factor is strongly correlated with the geographic groups. Individuals scanned at the highest temperatures (over 25°C) are only found in the Cambodian sample and the individuals scanned below 0°C all belong to the Russian sample. Finally, the PERMANOVAs on all the PC scores do not highlight an influence of age or mean humidity at the time of scanning on the distribution in the morphospace.

The morphological distances between the geographic groups can be represented by the F value of the pairwise PERMANOVAs between group levels and by the regularity value associated with the deformation-based shape comparison and representing the amount of deformation from GMS to each PMS (Table 1). The groups that are the closest in the morphospace and thus show greatest morphological similarities are Russia and France. The pairs of groups that are the most distant in the morphospace are Cambodia-Russia (cf. regularity value) and Cambodia-France (cf. F value). When performing post hoc tests between the temperature categories (Table S1), we find redundancy in this information: the pairs of groups that are significantly the most distant are patients scanned between 0 and 9°C (i.e., almost exclusively French and Russian individuals) and patients scanned above 25°C (all the Cambodian individuals). The two significantly closest groups are patients scanned between 0 and 9°C .

and between 20 and 25°C (mainly individuals from Chile, but also from France and Russia).

When performing PERMANOVAs on each PC (Table S2) from PC1 to PC8 (which all account for more the 3% of the overall variation), we observe that the geographic groups influence the distribution of the individuals on all the PCs, except PC5. On PC1 (18.59% of the overall variance), the affiliation to a geographic group explains 42% of the distribution of the individuals. PC3 (5.26% of overall variance) is the only PC to be moderately but significantly correlated with sex ($R^2 = 0.02$, $p = 0.03$). To quantify the effect of allometry on the sample distribution in the morphospace, we also performed bivariate regressions between each PC and the log-transformed volume of NA (Table S3). Of the first three PCs, only PC2 ($R^2 = 0.057$, $p < 0.001$) and PC3 ($R^2 = 0.069$, $p < 0.001$) show a significant correlation between these two factors and, therefore, an influence of allometry.

3.2 | Factors of volume variation in the total sample

The ANOVAs performed on NA volumes (Table S4) highlighted that NA volume is not influenced by geographic group affiliation. However, NA volume varies significantly according both to sex ($F = 26.57$, $p < 0.001$) and age ($F = 9.16$, $p = 0.003$). NA volume is overall higher in males than in females and tends to increase with age (Figure 4). When we normalize NA volume by the centroid size of the facial skeleton, we obtain the same results, that is, no influence of geographic group on normalized NA volume, but a significant influence of sex ($F = 10.10$, $p = 0.002$) and age ($F = 12.99$, $p < 0.001$).

3.3 | Factors of shape variation within geographic groups

After analyzing variation between geographic groups, we quantified the influence of sex, age, and temperature and humidity at the

time of scanning on morphological variation within each population. Temperature and humidity factors were not observable on the South African individuals, as the scans were all acquired during the same month. Similarly, we could not observe the correlation between temperature and NA morphology in the Cambodian population, as there was only one temperature category represented. According to the PERMANOVAs (Table S5), the only sample subject to the influence of one of these factors is the Russian population, whose morphology is significantly correlated with temperature at the time of scanning ($R^2 = 0.10$, $p = 0.03$). PCA analysis performed on the NA shapes of this sample (Figure 5) shows the clear distinction of the group containing individuals scanned during months with temperature above 20°C from the other three groups scanned during colder months. This is confirmed by a post-hoc test on the results of the PERMANOVA (Table S5), showing that individuals scanned at more than 20°C are significantly different from the groups scanned at <0°C ($R^2 = 0.08$, $p = 0.04$) and 10–19°C ($R^2 = 0.12$, $p = 0.04$). On the PCA, this group (>20°C) is localized in negative values on PC1, which can be illustrated by a NA shape that is more contracted antero-posteriorly and that shows an asymmetry in the width of the two sides of the NA. The same group is located in positive values on PC3, in which we observe an even greater asymmetry in NA width.

All the variance that cannot be explained by inter-group variability (i.e., 88% of overall variance) must be explained by within-group factors that we do not have access to. As in the total sample, allometry plays a role in the morphological distribution inside the geographic groups, except for the South African sample (Table S3). This factor accounts for 12.4% (PC3 vs. $\ln(\text{Vol})$, Russia) to 18.6% (PC2 vs. $\ln(\text{Vol})$, Chile) of the variance in the analyzed PCs.

3.4 | Factors of volume variation within geographic groups

Within each population, NA volume varies significantly with sex, age, or both (Table S4). In contrast, we observe no effect of temperature or

TABLE 1 Between-groups morphological distances.

Pairs of geographic groups		Regularity	F	R ²	p
Cambodia	Russia	850.90	12.303	0.136	0.002*
Cambodia	France	825.20	13.425	0.147	0.002*
South Africa	France	677.40	10.046	0.114	0.002*
South Africa	Russia	585.80	8.241	0.096	0.002*
Chile	Cambodia	404.50	5.770	0.073	0.002*
Chile	France	354.20	4.306	0.056	0.002*
Chile	South Africa	254.20	3.312	0.043	0.002*
Cambodia	South Africa	238.10	3.520	0.043	0.002*
Chile	Russia	223.30	2.664	0.035	0.002*
Russia	France	133.40	1.872	0.023	0.005*

Note: Pairwise distances represented by: The regularity values (sorted from highest to lowest) associated with the between-groups shape comparison; and the results of the pairwise PERMANOVAs performed on all the PCs. The results were considered significant (*) when $p < 0.05$.

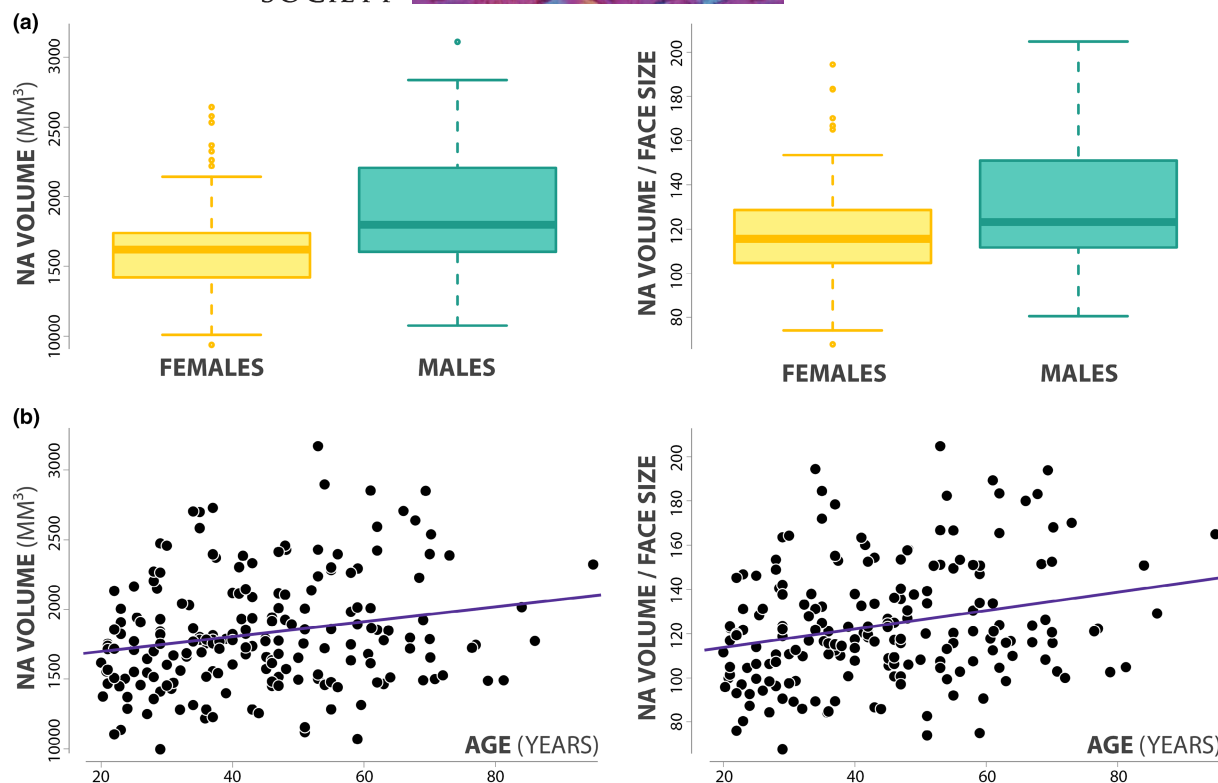


FIGURE 4 Factors of volume variation. Box-whisker plots (a) representing sexual dimorphism in NA volume (left) and in NA volume normalized by the centroid size of the facial skeleton (right) of the five populations. Regressions between NA volume and age (left) and NA volume normalized by the centroid size of the facial skeleton and age (right) among the five populations (b).

humidity on NA volume. We record sexual dimorphism in NA volume for populations from France ($F = 8.98$, $p = 0.005$), Cambodia ($F = 4.70$, $p = 0.037$), Russia ($F = 7.61$, $p = 0.009$), and South Africa ($F = 4.03$, $p = 0.052$). Age influences NA volume in samples from Chile ($F = 4.12$, $R^2 = 0.11$, $p = 0.05$) and Russia ($F = 10.21$, $R^2 = 0.21$, $p = 0.003$). We observe the same pattern of variation to that observed for the total sample, with greater NA volume in males than in females (Figure S4) and NA volume increasing with age (Figure S5). When we normalize NA volume by the centroid size of the facial skeleton, we obtain slightly different results. We still record significant sexual dimorphism in normalized NA volume for the population from France ($F = 4.31$, $p = 0.045$) but no longer for the populations from Cambodia, Russia, and South Africa. Age still influences normalized NA volume in samples from Chile ($F = 5.26$, $R^2 = 0.14$, $p = 0.03$) and Russia ($F = 8.85$, $R^2 = 0.19$, $p = 0.005$), but also the population from France ($F = 5.08$, $R^2 = 0.12$, $p = 0.03$).

4 | DISCUSSION

4.1 | Inter-population variation in the nasal airway

To our knowledge, no study had investigated the extent of NA morphological variation in large samples ($N > 100$) from different modern human populations. Our results highlight subtle but significant morphological differences between the five geographic groups we studied. We can observe two groups showing strong morphological

similarities, which are France and Russia. These two samples are broadly overlapping in the PCA and the distance between them is the smallest of all pairwise distances. Their PMS are anteroposteriorly larger and mediolaterally smaller compared to the GMS. They both show an important protrusion of the superior-anterior part of the common meati, which can be reasonably linked to the relative position of the nasal bones and the shape of the external nose. The sample that diverges the most from the French and Russian groups is the Cambodian sample, which is the most distant in the morphospace. The Cambodian PMS is anteroposteriorly contracted and superoinferiorly and mediolaterally extended compared to the GMS. Cambodian population is also the most clustered group on the PCA, indicating that it is the sample with the least shape variation, that is, the most homogenous population. In contrast, Chile individuals spread all along each PC and form a very scattered cluster. When we look at Chile PMS, which is very close to the GMS, we get the impression that the morphological variation within this sample is very low. On the contrary, the PCA rather indicates a great deal of morphological diversity that averages in a shape that is very close to the GMS. Finally, the South African PMS is morphologically close to the Cambodian PMS, although more contracted in the superoinferior dimension. On the PCA, South African sample tends to overlap greatly with the Cambodian sample, with a shift of some individuals toward the negative values on PC1, that is, toward French and Russian morphology.

Obviously, morphological variation among these five modern populations cannot be explained in a unifactorial manner. As stated

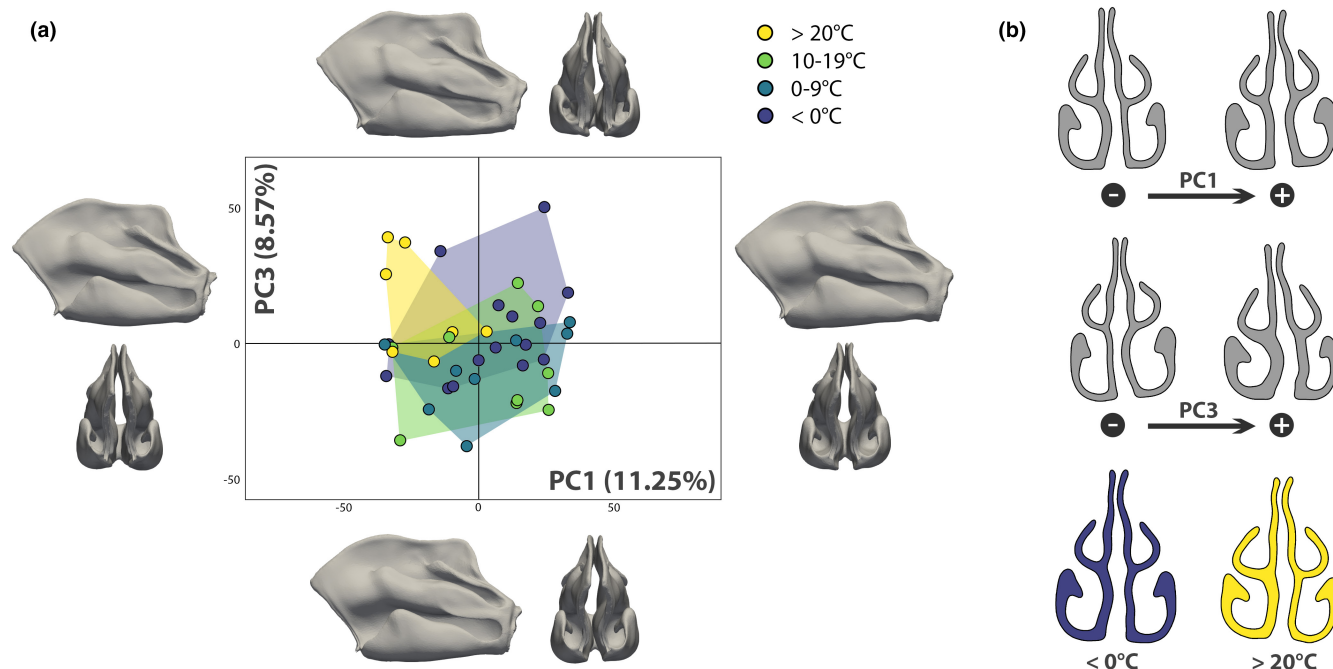


FIGURE 5 Seasonality. PCA of the deformation-based shape comparison made on the NA of the sample from Russia (a). Colors represent the temperature at the time of the scan. NA cross-section at the extreme values on PC1 and PC3 and of the groups scanned below 0°C and above 20°C (b).

in our introduction, we are aware of the limitations of our sample composition: first, the location where the patients were scanned does not provide information about their geographic and genetic background. We, therefore, have to consider that our samples can be more or less heterogeneous. Furthermore, other data that could influence the morphology of the NA, such as lifestyle (e.g., diet, smoking habits, etc), medical history or air quality are out of our reach. Other environmental factors can also influence NA morphology, such as altitude, which we were unable to observe either. Indeed, the locations from which the data were obtained are coastal or valley environments, which limits the elevation variation between 19 m (Phnom Penh, Cambodia) and 561 m (Santiago, Chile) (OpenStreetMap, 2022). However, keeping in mind all these limitations and the fact that the observed variation has a multiple etiology, we discuss two factors that could partially explain this variation and that are difficult to disentangle from each other: genetic and climatic factors.

Genome-wide association studies have found significant association for multiple facial traits including nose-related traits and have identified several genes involved in craniofacial development (Adhikari et al., 2016; Shaffer et al., 2016). This implicates a genetic basis for craniofacial morphology, which makes us hypothesize that the genetic traits of individuals will condition in part the morphology of their NA. From this point of view, one could expect that the populations of this study which are genetically the closest will also be the closest morphologically. This hypothesis seems to be verified in the morphological proximity of the populations from France and Russia, which also share a lot of similar ancestry components (Cavalli-Sforza & Piazza, 1993) despite the genetic differences between Western

Europeans and Balto-Slavic populations (Kushniarevich et al., 2015). The three other populations have very different ancestral histories linked to historical migration patterns. The Chilean population has a genetic structure defined by 40.43% of European ancestries, 57.11% of Native-American ancestry, and 2.46% of African ancestry (Eyheramendy et al., 2015). It is thus rather coherent to find this population so widely distributed in our morphospace. As for the South African population, it includes 79.2% of black southeastern Bantu-speakers, 8.9% of an admixed population (with major ancestral components that are predominantly Khoesan [32%–43%], Bantu-speaking Africans [20%–36%], European [21%–28%], and Asian [9%–11%] [de Wit et al., 2010]), 8.9% of whites of European origin, and 2.5% of a population originating from the Indian subcontinent (Choudhury et al., 2017). As for all our geographic groups, we have no information on the composition of this sample. We can therefore only suppose that it is heterogeneous, and that the distribution we observe in the morphospace reflects this diversity. Finally, the Cambodian population is morphologically the most distant from the European populations and the least variable for NA shape, which reflects the fact that there is no recent admixture with European populations. The homogeneity observed in between and within different Cambodian ethnic groups (Kloss-Brandstätter et al., 2021), indicating early genetic isolation of the whole population, can also be observed morphologically in this study.

Even if the distribution of our individuals in the morphospace reflects to a certain extent these genetic affinities, we can still raise the question of the part played by climate adaptation in the phenotypes. This question is relevant, especially in view of the results of a study on the external nose, having demonstrated with Qst-Fst

comparisons that nares width is more differentiated across populations than expected under genetic drift alone (Zaidi et al., 2017). This study also proved that the width of the nares is correlated with temperature and absolute humidity. It appears that some aspects of nose shape may indeed have been driven by local adaptation to climate, in addition to other non-neutral forces such as sexual selection.

As stated above, we do not have the right sample to address climatic adaptation. For that purpose, we would need to constitute a comparative sample of genetically close groups living in more variable environments (Evtsev & Grosheva, 2019). However, two of our samples, that are genetically and geographically rather close, could raise such discussion: France and Russia. According to Köppen-Geiger climate classification, Bordeaux (France) benefits from a warm temperate climate and Moscow (Russia) from a continental, colder climate (Dfb) (Table 2). Yet, their morphology is very close and the volume of their NA is not significantly different. As expected, the link between NA morphology and climate is not straightforward and we may consider that the part of the variation resulting from climatic adaptation lies in the subtle morphological differences between these two populations.

We can raise this question of climatic adaptation for all the samples in our study and ask what aspect of the morphology of each population can be explained by this factor and in which proportion. The antero-posteriorly contracted and mediolaterally extended Cambodian mean shape could be linked to a reduction of nasal resistance and time occurrence of the airflow in order to improve air conditioning in a tropical climate. This interpretation would be coherent with the observations made on bone nasal cavity in previous studies (Franciscus & Long, 1991; Maddux et al., 2016). However, our data also highlight the fact that morphological variation is not limited to these three main dimensions. It also lies in the overall curves, protrusions and retrusions of the different parts of the NA, as well as in the relative position and the curvature of the meati. Concerning the latter, our results do not allow us to make a straightforward connection with the observations made on the nasal turbinates, which define, to a certain extent, the morphology of the meati. Marks et al. (2019) showed that individuals from the Arctic Circle possessed superoinferiorly and mediolaterally larger inferior turbinates compared to Equatorial individuals, which reflects climate-mediated evolutionary demands on heat and moisture exchange. An interesting avenue of research would be to study the covariation between soft tissues meati and bony nasal turbinates, to further confirm the functional expectations in this area of the NC.

TABLE 2 Climatic data.

Location	Mean T° (°C)	Cls	Main climate	Precipitation	Temperature
Santiago (CL)	10.5	Cfa	Warm temperate	Fully humid	Hot summer
Bordeaux (FR)	14.2	Cfb	Warm temperate	Fully humid	Warm summer
Phnom Penh (KHM)	28.8	Am	Equatorial	Moonsoonal	
Moscow (RUS)	6.2	Dfb	Snow	Fully humid	Warm summer
Cape Town (SA)	17.3	Csb	Warm temperate	Summer dry	Warm summer

Note: Annual mean temperature (The World Bank Group, 2021), Köppen-Geiger classification (Cls) (Kottek et al., 2006; Rubel et al., 2017) and corresponding climate for the five regions of origin of the populations studied.

Interestingly, we record no correlation between NA volume and geographic groups. This implies that the modification of NA shape between the studied populations does not impact the volume of air that can pass through the NA. As higher metabolic demands for oxygen requirements (e.g., linked to higher body mass or colder and/or drier environments) may place constraints on the size of the nasal cavity (Bastir et al., 2011; Froehle et al., 2013; Holton et al., 2014, 2016), we expected to observe NA volume variation due to the climatic and ancestry diversity of our samples. However, the populations constituting those samples are not subject to strong constraints, whether environmental (e.g., extreme climatic conditions), genetic (e.g., low degree of genetic admixture), or biomechanical (e.g., mechanically challenging diet, see Brachetta-Aporta & Toro-Ibacache, 2021). The absence of volume variation and high level of stress lead us to hypothesize that the NA shape variation between modern human populations may not be primarily driven by a functional role. As proposed by Eyquem et al. (2019), the reduction of functional constraints might actually be a key to greater degree of shape variation in modern populations. Our findings suggest that volume might be more of a conserved trait constrained by a sex and age effect, whereas the shape associated with this volume would be the element that varies among populations. This hypothesis could be verified by comparing our results with body mass index variation, but also by conducting population-scale airflow simulations to understand how airflow is distributed in this morphology (e.g., de Gabory et al., 2020; Keck & Lindemann, 2010).

4.2 | Seasonal reactivity of the nasal mucosa

In this study, one important aspect to explore was the way environmental temperature can, in a very short time period, affect the morphology of nasal mucosa and, subsequently, the morphology of the NA. The only sample that allowed us to do so was the Russian sample, as it is the only one that contains individuals that were scanned throughout the year and therefore in different seasons. Of course, we do not know at what temperature the individuals were scanned in the hospital and consider that this data must be controlled to study this question. However, we sought to observe the potential volume or shape variation that could have been linked either to the temperature of the outside environment or, conversely, to the use of air conditioning or heating in the hospital during certain seasons.

We found that this population displayed a correlation between the average temperature at the time of the scan and the NA shape and that individuals scanned above 20°C separate from the other groups in the morphospace. However, by observing the extreme shapes on PC1 and PC3, we saw that the morphology of this group is mainly characterized by an asymmetry in the sectional width of the meati. This asymmetry is related to the nasal cycle, which is an alternative partial congestion and decongestion of the right and left sides of the nasal airway during breathing (Watelet & Cauwenberge, 1999; White et al., 2015). Yet, two of the three individuals in the >20°C group that fall outside of the morphological variation and that drive the signal of this group toward negative values on PC1 and positive values on PC3 have been scanned at a strongly asymmetric moment of their nasal cycle. This signal could therefore highlight a sample composition bias or indicate a higher activity of the nasal cycle when the temperature is warmer. We can point out, however, that the volume of the NA is not correlated with environmental temperature or humidity, as would have been expected knowing that cold-dry conditions tend to increase nasal resistance and to reduce nasal patency (Fontanari et al., 1996; Olsson & Bende, 1985; Salman et al., 1971).

4.3 | Causes of intra-population variation in the nasal airway

Sex had no influence on NA shape, but did influence their volume. Males have on average 17% larger NAs than females (10% when normalized by the size of the facial skeleton), which can be explained by the fact that they have higher energetic demands, requiring higher air volume intakes (Bastir et al., 2011, 2020; Holton et al., 2014, 2016). Previous studies (Bastir et al., 2020; Keustermans et al., 2018) demonstrated sexual dimorphism in the shape of the soft tissues of the upper respiratory tract. Nevertheless, they all included in their 3D analysis the inflow region (external nose) and the outflow region (behind the choanae) and stated in their results that these two regions showed stronger sexual dimorphism than the NA (Bastir et al., 2020). Our results corroborate these observations, as we show no sexual dimorphism in NA morphology.

Our results highlight that age has no effect on NA shape but influences its volume. NA volume tends to increase by 11% between younger (20–35 years) and older (51+ years) individuals. This would indicate that nasal mucosa tends to shrink with age, thus increasing the negative volume that constitutes NA. This alteration of the nasal mucosa has been observed in previous histological and histochemical studies showing a significant atrophy of the epithelium in older individuals (Schrödter et al., 2003; Toppozada, 1988). This atrophy of the nasal epithelium can be linked to age-related differences in the molecular signature associated with ciliation and mucin biosynthesis (Balázs et al. 2022). This result underscores the importance of taking into account the influence of age on NA morphology in future studies.

Finally, in order to observe possible asymmetries related to deviations of the nasal septum, we did not symmetrize the two nasal

hemi-cavities. On the PCA performed on the total sample, these asymmetries are well reflected by PC3, accounting for 5.26% of the overall variance. This underlines their importance in NA shape variation, even if it has been demonstrated that they do not affect the heating function of the nose (Keustermans et al., 2020). PC3 is moderately but significantly correlated with geographic group affiliation, which explains 9% of the distribution on this PC. This tenuous link between populations and asymmetries indicates that the latter are fairly randomly distributed in our five samples. We can note however that, while populations from France, Russia, and South Africa tend to average around 0, the sample from Chile is slightly displaced toward the positive values. This tends to indicate a higher occurrence for rightward torsions in NA shape in the Chilean sample of this study, probably related to nasal septum deviations. On the contrary, the sample from Cambodia tends to be more toward negative values, which represents a leftward torsion of the NA shape.

4.4 | Perspectives

The results of our study show complex patterns of variation in nasal airway morphology. At the inter-population level, we quantify shape variation between our five samples that we could connect to genetic background and climate. This shape variation is surprisingly not associated with volume variation, which questions the climate-related metabolic demands for oxygen consumption. At the intra-population level, sex and age have no influence on the NA shape, but do influence NA volume, which is higher in males than in females and tends to increase with age. These factors of variation, to which we can add temperature and asymmetries, do not have the same role and/or the same magnitude for all the samples. The quantification of these patterns of variation allows us to take a step toward a better understanding of the multiple factors driving the morphological variation and evolution of the upper airways. To take this a step further and link a phenotype to air conditioning and respiratory energetic capacities, we could use the population mean shapes we produced with our data in a computational fluid dynamics (CFD) study (Chen et al., 2010; de Gabory et al., 2020; Inthavong et al., 2007; Keck & Lindemann, 2010). This would allow us to numerically simulate airflow patterns in modern humans on a population scale. After taking this first step, we could consider transposing these research questions to the fossil record. A better knowledge of the etiologies and intricacies of modern nasal shape variation could lead to more accurate reconstructions of the functional NA of fossil hominins. This could allow, ultimately, to apply CFD techniques on these reconstructions to get an insight into the breathing of fossil hominins.

AUTHOR CONTRIBUTIONS

Laura Maréchal carried out study design, data processing and analysis, results interpretation, manuscript drafting, and revision. Jean Dumoncel and Frédéric Santos were involved in data analysis, results interpretation and manuscript revision. Williams Astudillo

Encina, Rudolph G. Venter, Andrej Evteev, Viviana Toro-Ibacache, and Alice Prevost were involved in data collection and manuscript revision. Yann Heuzé carried out project conception, data collection, result interpretation, and critical revision of the manuscript.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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