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Digit ratio (2D:4D) and maxillary sinus volume: A link between prenatal sex steroids and a paranasal reservoir of nitric oxide?

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ABSTRACT

Background: The paranasal sinuses serve as a reservoir for nitric oxide (NO), a vasodilator associated with cardiovascular health and exercise performance. Digit ratio (2D:4D), a proxy for first trimester testosterone and estrogen, is also a correlate of cardiovascular health and exercise performance. There are sex differences in the volume of fractional exhaled NO (FeNO: males>females) and in mean 2D:4D (males<females). Here we consider the relationships between 2D:4D and the volume of the largest paranasal sinus, i.e. the maxillary sinus (MS), in men and women.

Methods: 30 male and 30 female participants, mean age of 38.4 ± 11.8 years, who had a paranasal sinus computer tomography (CT) scan were included. The MS volumes were calculated from the scans using GE software. The 2D:4D ratios were obtained from direct measurements of the 2nd and 4th digits.

Results: Sex differences were not significant in 2D:4D or MS volumes. In males, 2D:4D correlated negatively with right MS volume (right and left 2D:4D, r = −0.58) and left MS volume (right 2D:4D r = −0.45, left 2D:4D r = −0.40). After removal of the effects of age, BMI and digit length all correlations for the right MS remained significant as did that between right 2D:4D and left MS. There were no significant correlations in females.

Conclusion: We have found that low (androgenized) 2D:4D in men is associated with high MS volumes with stronger effects for the right MS. Our findings indicate that in men high prenatal testosterone relative to estrogen is related to high MS volume. We suggest that 2D:4D may be negatively related to FeNO volume produced by the MS.

1. Introduction

There are four paired paranasal sinuses; maxillary, frontal, sphenoid and ethmoid [1]. The paranasal sinuses have been the subject of studies regarding the production of nitric oxide (NO) [2], a powerful vasodilator associated with cardiovascular health [3,4] and continuous exercise training [5]. All four paranasal sinuses are formed prenatally [6]. Digit ratio (2D:4D) is widely thought to be a proxy of first trimester levels of sex steroids such that 2D:4D is negatively related to prenatal testosterone and positively related to prenatal estrogen [7,8]. In common with fractional exhaled NO (FeNO), the 2D:4D is also associated with cardiovascular health [9] and performance in aerobic exercise [10,11]. The links between 2D:4D, cardiovascular function and FeNO suggest that 2D:4D may be a correlate of the volume of one important site of FeNO production, i.e. the paranasal sinuses. The maxillary sinus (MS) is the first paranasal sinus to appear in the 10th week of gestation [6]. Therefore, its development may be influenced by first trimester sex steroids.

The nose and paranasal sinuses form a functional unit. The volumes of the latter have been reported to be sexually dimorphic (males>females: maxillary, [12]; frontal, [13]; sphenoid, [14]; ethmoid, [15]). The maxillary, ethmoid and frontal sinuses all drain via ostia into the ostium meatal unit. The MS is the largest of the air-filled, mucosa-lined spaces within the maxillofacial region and skull. It lies within the

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maxillary bone, and the alveolar process of the maxilla forms the inferior boundary of the sinus [16].The MS originates in the 10th week of gestation, when the mucosa located at the anterior end of the ethmoid infundibulum, presents with invaginations and by the 11th week, the fusion of the invaginations creates a single cavity which represents the MS primordium [6]. At birth, the MS is an aerated slit, situated inferomedial to the orbit. Its development lasts until young adulthood, and it is proportional to growth of the facial bones [17].

In common with the MS the 2D:4D ratio and its sex difference is first established around week 10 to 11 [7,8,18,19]. It has been suggested that the sexual dimorphism in 2D:4D is dependent on allometry through sex differences in digit length (males>females [20] and elaborated by [21]). However, during ontogeny the differences in digit lengths varies thus: males<females; males = females and males>females. The sexual dimorphism in 2D:4D (males<females) does not follow this pattern rather it arises prenatally and subsequently remain more or less fixed across the life cycle [7,22]. Large sample studies employing a range of measurement techniques in children and adults across several ethnicities have not replicated the Kratochvil & Flegr [20] effect [23–27]. Regarding the origin of the sex difference in 2D:4D, it is widely thought that 2D:4D is a negative correlate of first trimester sex steroids, i.e. it is negatively related to testosterone and positively related to estrogen (see reviews in support [28,29] and against [30]). Experimental studies with rodents have reported that the 2D:4D ratio is established in a narrow time window during early gestation [31].

There is evidence that the pattern of effects of FeNO produced by the paranasal sinuses is like those reported for 2D:4D. Thus, the volume of produced FeNO and values of 2D:4D are both sex dependent (FeNO, males>females [32]: 2D:4D, males<females [7]). With regard to oxygen metabolism, upper airways FeNO from the paranasal sinuses improves oxygen uptake and reduces pulmonary vascular resistance [33], while low 2D:4D has been reported to be correlated with high VO_2max [34–36]. Control of blood pressure is in part dependent on the interaction of NO with the angiotensin-converting enzyme (ACE) I/D polymorphism and 2D:4D has been reported to correlate with the latter. Thus, men who are homozygous with the D/D genotype have higher systolic blood pressure, lower NO metabolites and higher 2D:4D than those who are heterozygous I/D carriers [37,38]. Furthermore, there is considerable evidence that both NO and 2D:4D are related to aerobic sports performance. Aerobic exercise training induces intrinsic NO which has a positive effect on cardiovascular health and exercise efficiency [39]. Runners who are trained in nasal breathing achieve higher physiological economy and ventilatory efficiency than mouth-breathing controls [40]. Marathon running causes cardiac fatigue and cardiac fatigue correlates with low pulmonary levels of NO and pulmonary inflammation [41]. Regarding 2D:4D, there are reports of negative relationships with performance in distance running [42] and rowing [11].

There has been one report of a relationship between 2D:4D and the MS. Hasan et al. (2018) [43] found significant negative associations between 2D:4D and MS volume. This suggests that high prenatal testosterone and low prenatal estrogen are correlated with large MS volumes. However, the study was confined to males only. Here we extend this, in order to clarify relationships between 2D:4D and MS volume in both males and females. Specifically, our aim was to clarify the relationship between 2D:4D and MS volume in both males and females. Additionally, we consider our findings in the light of a possible association between 2D:4D and FeNO production.

2. Method

2.1. Sample size calculations

Based on the correlations reported by Hasan et al. (2018) [43], we performed power calculations. The criteria included were the power of test (0.8); correlation coefficient (0.5) (although the lowest reported was 0.58, a more conservative approach was used); error type I (alpha) ($p < .05$). We concluded that the minimum number of participants was 29.

2.2. Recruitment of participants

CT scans involve exposure to X rays. In order to minimize X ray exposure, we recruited participants who were healthy but required routine CT scans. The sample included women and men who were admitted between January 2022 and December 2023 to a Plastic Surgery Out-patient Clinic due to posttraumatic nose deformity. We emphasize that care was taken to ensure that the nasal trauma had not affected the maxillary sinuses or the zygomatic bones. Thus, the participants were recruited to the study if: (1) they were qualified for paranasal sinus computed tomography (CT), (2) their history of nose trauma was after the age of 18 years old so that the development of their maxilla (and sinuses) was not affected by trauma, (3) had isolated nose trauma, without a fracture of maxillary and zygomatic bones (which could affect the morphology of the sinuses), (4) the trauma was at least a year before the planned CT (CT before a planned rhinoplasty, at least year after the injury, is performed after completion of healing of the tissues, to exclude post-trauma edema and overlapping scarring process), (5) did not suffer from any laryngological conditions (e.g. polyps, chronic sinusitis). Exclusion criteria included: lack of the criteria above and lack of patient's consent for using CT scans for additional measurements and for measuring digits directly. There were 60 individuals (30 women and 30 men) who gave written informed consent for participation.

The protocol of the study included body and hand anthropometric measurements and the analysis of right and left MS volumes, based on CT scans. Those who reported hand injuries were excluded from the study. All the participants were White. The protocol was agreed by the local ethics committee (RNN/04/22/KE).

2.3. MS measurements

Single phase CT scan of paranasal sinuses was performed with GE Light Speed 64 VCT scanner (GE Healthcare, Milwaukee, WI, US; kV 120, mA 10, mAs - dynamic), with 0.625-mm layer width and 0.6-mm pitch, without adding intravenous contrast. Acquired images were evaluated at a physician's console with the aid of AW 3.2 GE software. The volume of maxillary sinuses (ml) was manually evaluated during analysis of MPR (multiplanar reformation) reconstructions (Fig. 1).

2.4. Hand and body measurements

Hand measurements were taken directly twice: 2nd- and 4th-digits' lengths (2D and 4D) (right (R) and left hand (L)). One experimenter (AKT) made all measurements blind to results from CT scans. Based on the digit measurements the following were calculated: 2D:4D for the right (R) and left (L) hand (finger 2nd length [cm]/finger 4th [cm]) (2D:4D R, 2D:4D L) and right minus left 2D:4D (Dr-l) were calculated. All measurements were made directly with GPM anthropological instruments. For the digits, vernier calipers measuring to 0.01 mm were employed. Measurements were performed on the palmar side of the hand using anthropometric points lying on the digit axis: pseudophalangion – a point in the finger metacarpophalangeal crease, dactylion – the most distal point on the fingertip. Height was measured in a standing position with an anthropometer, body mass with Tanita SC331S Body Composition Analyzer and BMI (mass divided by the square of height) was calculated (kg/m^2).

2.5. Statistical analysis

Means and standard deviations (SD) were calculated for all the parameters. The normality assumption was verified by calculating skewness and kurtosis. Intra-class correlation coefficients (ICC) (absolute agreement) between the first and second 2D:4D's of the right and left

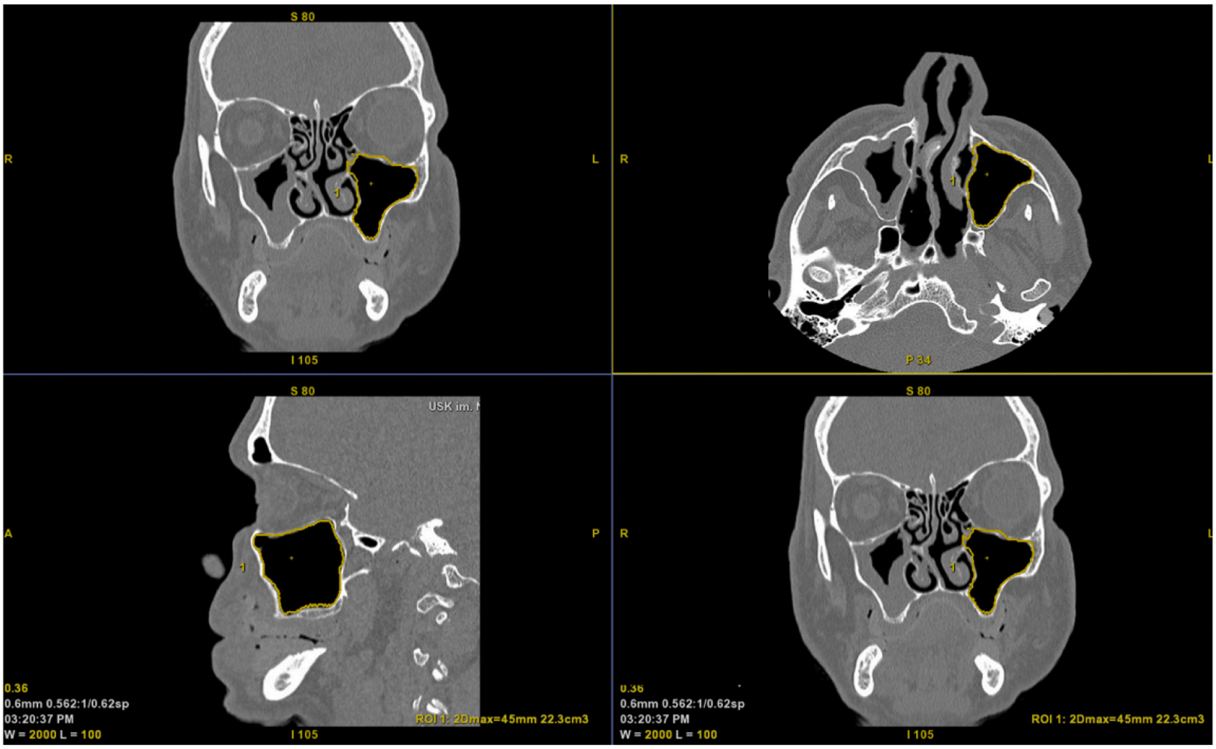

Fig. 1. CT scans with marked outline of the MS for the purpose of MS volume calculation.

digits were calculated. Pearson-product moment correlation coefficients (r)were used to calculate associations. Correlations were described as trivial (0–0.1), small (0.1–0.3), moderate (0.3–0.5), large (0.5–0.7), very large (0.7–0.9), nearly perfect (>0.9) and perfect (1.0) [44]. Multiple regression analyses were performed, the dependent variable was MS volume, and the independent variables were digit ratio, age, BMI, and mean digit lengths. The level of significance was set at $p < .05$.

3. Results

3.1. Repeatability

We calculated intra-class correlation coefficients (ICC's) of digit ratios from first- and second-digit measurements. The ICC's were high and significant for the ratios: right2D:4D, ICC = 1.0, left 2D:4D, ICC = 1.0, for digits' lengths: from ICC 0.996 for 2D L to 0.997 for 2D R and 0.956 for Dr-l (all $p < .0001$. Therefore, we assumed measurement error was small compared to digit ratio differences between individuals. The means of digit ratios 1 and 2 were obtained and used in all subsequent statistical analyses.

3.2. Sex differences in variables

Mean age did not differ between the sexes. Values of 2D:4D and MS showed low skewness and kurtosis in both males and females. For the former this varied from 0.08 to 0.31 for skewness and 0.03 to 0.61 for kurtosis. For the latter, skewness varied from 0.02 to 0.41 and kurtosis from 0.40 to 0.50. Right and left 2D:4D showed the usual pattern of lower values for males compared to females. The differences were close to significance for right 2D:4D (males.98[0.03], females1.00 [0.03], $p = .06$) but not for left 2D:4D (males 0.98 [0.04], females 0.99 [0.03], $p = .16$). The MS volumes did not differ between females and males. Body size variables (weight, height, digit lengths and BMI) showed greater values for males compared to females (Table 1).

Table 1
Descriptive characteristics of the variables.

Variable	Women			Men			
	$\bar{X}$	SD	SE	$\bar{X}$	SD	SE	p
right maxillary sinus volume [ml]	20.57	5.6	1.04	19.55	5.5	0.998	0.48
left maxillary sinus volume [ml]	20.6	4.7	0.86	19.15	6.6	1.21	0.33
2D R [mm]	69.5	3.6	0.65	75.73	4.7	0.85	<0.0001
4D R [mm]	69.7	4.1	0.75	77.07	5.1	0.92	<0.0001
Mean Right Digits [mm]	69.6	3.7	0.67	76.40	4.7	0.86	<0.0001
2D L [mm]	69.2	3.7	0.67	75.30	4.5	0.82	<0.0001
4D L [mm]	69.83	3.9	0.71	77.00	5.2	0.94	<0.0001
Mean Left Digits [mm]	69.50	3.7	0.67	76.17	4.6	0.84	<0.0001
2D:4D R	1.00	0.03	0.006	0.98	0.03	0.005	0.06
2D:4D L	0.99	0.03	0.005	0.98	0.04	0.007	0.16
Dr-l	0.01	0.03	0.005	0.004	0.02	0.004	0.62
Age [years]	36.27	12.1	2.21	40.63	11.2	2.05	0.15
Weight [kg]	64.93	13.2	2.42	87.70	11.8	2.15	<0.0001
Height [cm]	169.3	6.2	1.14	180.1	7.2	1.3	<0.0001
BMI [kg/m^2]	22.62	4.4	0.81	27.02	3.1	0.56	<0.0001

3.3. MS volume vs. body size and digit ratio

3.3.1. Males

Pearson's r showed significant moderate correlations between 2D:4D and MS volume (all $p < .05$). Regarding right 2D:4D, there was a large negative correlation ($r = -0.58$, Fig. 2) with right MS volume and a moderate negative correlation ($r = -0.45$) with left MS volume. Left 2D:4Dalso showed a moderate negative correlation with right MS volume ($r = -0.58$) and a moderate negative correlation with left MS volume ($r = -0.40$). There were no significant correlations between Dr-l and MS volume (Table 2). There were no significant associations between age or body size variables (BMI, mean digit lengths of right or left hand) and right or left MS volumes (values of r varied from 0.05 to 0.22 for right MS volume and 0.10 to 0.36 for left MS volume, $p > .05$).

Multiple regressions were conducted as follows:

Right 2D:4D; two multiple regressions with dependent variables right MS volume or left MS volume and independent variables right 2D:4D, age, BMI and mean of right digit lengths. The standardized regression coefficient (b) for right 2D:4D vs right MS volume was −0.57, $p = .001$. There were no significant relationships between the remaining independent variables and right MS volume (values of b varied from −0.05 to −0.17) (Table 3). Regarding right 2D:4D vs left MS volume, the value of b was −0.41, $p = .02$. There were no significant associations between the remaining independent variables and left MS volume (b varied from 0.01 to 0.29) (Table 3).

Left 2D:4D; two multiple regressions with dependent variables right or left MS volumes. The independent variables were left 2D:4D, age, BMI and mean of left digit lengths. The value of b for left 2D:4D vs right MS volume was −0.61, $p = .001$.There were no significant relationships between the remaining independent variables and right MS volume (values of b varied from −0.10 to −0.20) (Table 4).Regarding left 2D:4D vs left MS volume, there were no significant associations (b varied from −0.004 to −0.35 (Table 4).

3.3.2. Females

There were no significant associations between digit ratios (right hand, left hand, or Dr-l), age or body size variables (BMI, mean digit lengths of right or left hand) and right or left MS volumes. Values of r varied from −0.06 to 0.30 for right MS volume and 0.028 to −0.27 for left MS volume, $p > .05$).

4. Discussion

We did not find significant sex differences for 2D:4D or MS volumes. This is likely to have arisen as a result of our small sample sizes and the medium effect sizes associated with sexual dimorphism in digit ratios [7] and MS volumes [12]. Correlations between 2D:4D and MS volume

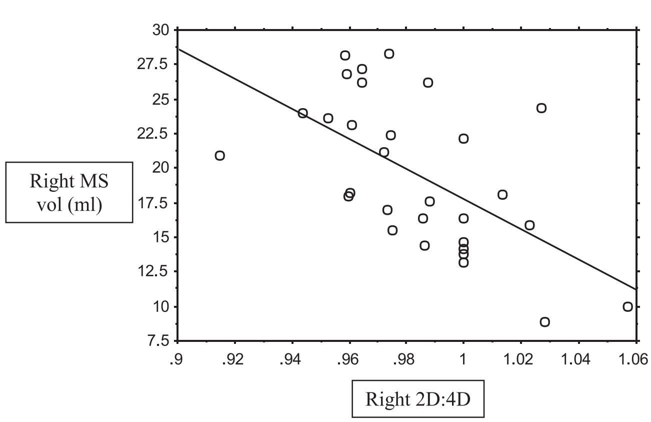

Fig. 2. The relationship between right 2D:4D and right MS volume in 30 males. The formula for the line is: $y = -108.652\times + 126.389$, $r^2 = 0.34$.

($r > -0.50$: Hassan et al., 2019) would suggest that we should detect within-sex associations between 2D:4D and MS volumes with sample sizes of around $n = 30$.

Replicating the findings of Hassan et al. (2018) [43], we have found moderate negative associations between 2D:4D and MS volumes in men. Age, BMI and mean digit lengths were not significantly related to right or left MS volumes. The large associations between right and left 2D:4D and right MS volume were not weakened by removal of the effects of age, BMI and mean digit lengths. Regarding left MS volume, removal of the effects of age, BMI and mean digit lengths had little effect on the correlation with right 2D:4D but removed significance from the association with left 2D:4D. Therefore, the overall pattern suggests that both right and left 2D:4D were negatively associated with MS volumes with greatest effect sizes for right MS volume. In contrast to the associations in men, we found no significant relationships between digit ratios and MS volumes, nor were there any correlations between age or body size (BMI, mean digit lengths) and MS volumes.

Our focus in this study was to describe the relationship between 2D:4D and MS volume. However, we feel that the large negative correlations between 2D:4D and MS volume in men suggest that 2D:4D may be a correlate of MS function, i.e. the secretion of FeNO. Both the MS and 2D:4D have their origin in the 1st trimester (MS [6]: 2D:4D [8]). Thus, it is possible that 2D:4D is linked to MS function. The exact function of the paranasal sinuses has been the subject of controversy for 1800 years. They have been suggested to: humidify and warm inspired air, increase the area of the olfactory membrane, absorb shock applied to the head for protection of sensory organs and lighten the bones of the skull for maintenance of balance of the head. None of these hypotheses are accepted to be the reason for their existence. The paranasal sinus epithelium continuously generates large amounts of NO. Gas from the nose and sinuses is inhaled with every breath and reaches the lungs where it increases oxygen uptake via local vasodilation. Therefore, a physiological role of the paranasal sinuses in regulation of pulmonary function is suggested [33]. The effect of sex on FeNO is significant, with FeNO levels approximately 25 % less in females. The sex difference remains after removing the effect of other factors such as current smoking and atopy [32].The finding that FeNO has a sex dependent regulatory effect on pulmonary function suggests links to 2D:4D. Men typically show lower 2D:4D than women and athletes of both sexes tend to have lower 2D:4D ratios compared to non-athletes [45]. Low 2D:4D has been reported in athletes with high aerobic capacity and high VO_2max. In contrast, associations between low 2D:4D and measures of strength (e.g. sprinting speed and hand-grip strength) are significant but weaker than reported for aerobic capacity [46]. Cardiorespiratory fitness is strongly associated with lower risk for a variety of chronic conditions such as heart failure [47] while high 2D:4D is correlated with early myocardial infarction in men [9,48–50]. Recent meta-analysis showed that 2D:4D is a proxy for cardiorespiratory fitness measures, i.e. exercise tolerance measured by ventilatory threshold and performance, but not other aspects such as aerobic capacity and efficiency [51].

Regarding limitations of our study, our sample size is small (total $n = 60$, males $n = 30$). However, the power calculation on Hasan et al. [43] findings indicate that a significant effect for 2D:4D and MS should be obtained in a sample of 30 males. We replicated this finding suggesting that it is indeed a real effect. We did not find a significant effect for the relationship between 2D:4D and MS in our sample of 30 females. This null finding should be replicated. These male and female associations were the first focus of our study. They form the basis of the second focus, i.e. our suggested hypothesis that 2D:4D is a negative correlate of FeNO.

In conclusion, we have found that in men right and left hand 2D:4D are negatively related to right and left MS volume with a moderate to large correlation. This suggests that male MS volume is influenced by prenatal sex steroids such that high volume is associated with high testosterone and low estrogen in the 1st trimester. There were no relationships between 2D:4D and MS volume in women. The paranasal sinuses (including MS) are sex dependent sites of production of FeNO

Table 2
Pearson's r for hand and sinus variables in women and men.

	Women				Men			
	right maxillary sinus volume [ml]		left maxillary sinus volume [ml]		right maxillary sinus volume [ml]		left maxillary sinus volume [ml]	
	r	p	r	p	r	p	r	p
2D:4D R	−0.06	0.76	−0.27	0.14	−0.58	0.0008	−0.45	0.01
2D:4D L	0.011	0.96	0.028	0.89	−0.58	0.0008	−0.40	0.03
Dr-l	−0.10	0.60	0.20	0.30	0.17	0.37	0.05	0.78
Age [years]	0.07	0.71	0.08	0.67	−0.18	0.34	−0.14	0.46
BMI [kg/m^2]	0.09	0.65	0.03	0.90	0.05	0.81	0.10	0.60
Mean Right Digits [mm]	0.29	0.12	0.24	0.21	0.22	0.24	0.34	0.07
Mean Left Digits [mm]	0.30	0.11	0.22	0.24	0.22	0.25	0.36	0.052

Table 3
Two multiple regressions in males: Independent variables right 2D:4D, age, BMI and mean right digit length; dependent variables right maxillary sinus volume or left maxillary sinus volume.

	Right Maxillary Sinus [ml]					Left Maxillary Sinus [ml]				
Trait	b*	SE	b	t	p	b*	SE	b	t	p
2D:4D R	−106.01	29.63	−0.57	3.58	0.001	−93.04	38.42	−0.41	2.42	0.02
Age [years]	−0.09	0.08	−0.17	1.11	0.28	−0.08	0.10	−0.14	0.83	0.41
BMI [kg/m^2]	−0.09	0.29	−0.05	0.30	0.77	0.01	0.37	0.01	0.03	0.97
Mean Right Digits [mm]	0.18	0.18	0.16	0.99	0.33	0.40	0.24	0.29	1.68	0.11

Table 4
Two multiple regressions in males: Independent variables left 2D:4D, age, BMI and mean left digit length; Dependent variables right maxillary sinus volume or left maxillary sinus volume.

	Right Maxillary Sinus [ml]					Left Maxillary Sinus [ml]				
Trait	b*	SE	b	t	p	b*	SE	b	t	p
2D:4D L	−92.54	25.28	−0.61	3.66	0.001	−64.59	33.91	−0.35	1.91	0.07
Age [years]	−0.10	0.08	−0.20	1.31	0.20	−0.10	0.10	−0.17	0.95	0.35
BMI [kg/m^2]	−0.21	0.29	−0.12	0.74	0.47	−0.01	0.39	−0.004	−0.02	0.98
Mean Left Digits [mm]	0.12	0.19	0.10	0.64	0.53	0.42	0.25	0.29	1.65	0.11

(males>females), a gas which is inhaled and enhances vasodilation and pulmonary oxygen uptake. Low 2D:4D is correlated with high cardiorespiratory fitness. Therefore, we suggest that further work should consider whether 2D:4D is a negative correlate of FeNO production in males.

CRediT authorship contribution statement

Anna Kasielska-Trojan: Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Marcin Majos:** Writing – review & editing, Visualization, Software, Methodology, Investigation, Data curation, Conceptualization. **Aneta Sitek:** Writing – review & editing, Validation, Formal analysis, Data curation. **Bogusław Antoszewski:** Writing – review & editing, Supervision, Resources, Conceptualization. **John T. Manning:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Formal analysis, Conceptualization.

Funding information

The research was carried out without a financial relationship.

Declaration of competing interest

The authors declare no conflict of interest.

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Data availability

The data are available from the corresponding author upon reasonable request.

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