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Systematic review and meta-analysis

The relationship between the dimensions of frontal air sinus and skeletal malocclusions: A systematic review and meta-analysis

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ABSTRACT

Objective: The goal of this systematic review and meta-analysis was to assess whether the dimensions of the frontal air sinus correlate with skeletal malocclusion.
Study selection: PubMed, Scopus, Embase, and Google Scholar were searched for relevant studies published up to May 23, 2023. The review included observational studies that compared the dimensions of the frontal air sinus between different skeletal malocclusions. The PECOS method was used in this study ("Population, Exposure, Comparator, Outcome, and Study design"). The search was done using the following English keywords: "frontal sinus" AND "lateral cephalometric" AND "malocclusion" AND "surface area".
Results: Seven studies were included, which involved 1101 participants, of whom 403 were class I, 375 were class II, and 323 were class III. These studies had a moderate risk of bias. The surface area of the frontal sinus in class III was significantly larger than in class I (standardized difference in means (SDM) = −0.971; 95 % CI = −1.147− −0.796; P < 0.001) and in class II (SDM = −1.535; 95 % CI = −1.732− −1.337; P < 0.001).
Conclusion: Class III malocclusion is associated with a larger surface area of the frontal sinus compared to classes I and II.

1. Introduction

1.1. Rationale

Vertical and horizontal growth are the two main cranio-facial growth patterns. Horizontal patterns play a more important role in the formation of skeletal malocclusion, which refers to growth and developmental deviations affecting the jaws and teeth and resulting in variances in their position [1]. The prediction of skeletal jaw patterns is a developing field, and markers that are related to changes in

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mandibular and maxillary development are being sought, which would enhance orthodontic diagnosis and treatment planning [2].

Numerous craniometric investigations demonstrate an intimate relationship between sinus enlargement and craniofacial development [3,4]. There are four pairs of paranasal sinuses in the human body: the maxillary, frontal, sphenoidal, and ethmoidal sinuses. They are mucosa-lined air spaces within the face and skull bones and grow in the same way as the bones [5]. The development of the frontal sinuses is linked to the development of the nasal cavity and maxilla, which are effective at sculpting the final contour of the face [6–10].

Frontal air sinuses are air chambers in the frontal bone in the posterior portions of the superciliary arcs. They are located between the internal and external faces of the frontal bone and directly connect to the nasal cavity [11]. The frontal air sinuses continue to develop until the age of around 18–20 years and do not change thereafter [12,13]. However, Brown et al. claimed that the growth of the frontal air sinus terminates at 15.5 years in boys and at 13 years in girls [7].

The dimensions of the frontal air sinus are influenced by two primary factors: genotype and the development of maxillofacial structures [14]. Moreover, there are many factors that might influence sinus growth, such as environmental factors, trauma, allergies, acquired diseases, diet, and medication use [15]. Some studies have reported a relationship between the morphology of the frontal sinus and skeletal growth patterns [4, 16, 17]. Rossouw et al. [18] investigated the relationship of mandibular, maxillary, condylar, and symphysis widths with frontal air sinus size and found that the frontal air sinus may be a useful predictor of mandibular development.

Lee et al. reported abnormality in the width of the frontal air sinus in association with facial asymmetry [19]. Moreover, the size of the frontal air sinus differs according to sex, being larger in men [13,19], which makes it a good indicator for distinguishing between sexes in forensic studies [20]. Radiography has long been a popular method for identifying human anthropological structures, and forensic medicine relies significantly on radiographic recognition when fingerprints and DNA samples are unavailable [21]. Typically, a standard frontal view can be used to examine differences in size, morphology, symmetry, border shape, and the presence and number of septa and cells [22].

The effect of the frontal air sinuses' formation on the development of various skeletal malocclusions has been studied [13,23–25], but the results have been controversial. Some studies report a relationship with class III skeletal malocclusion [13,23–26], and other studies report a relationship with class II skeletal malocclusion [27–29]. Other studies have linked the frontal sinus with the vertical

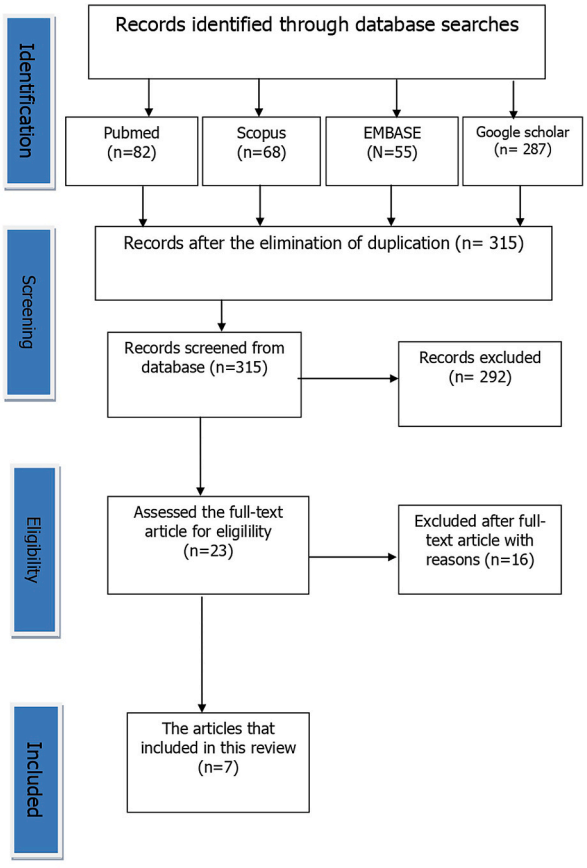

Fig. 1. PRISMA flow diagram.

growth pattern [30–32].

1.2. Objective

The goal of this systematic review and meta-analysis was to assess whether the dimensions of the frontal air sinus correlate with skeletal malocclusion.

2. Material and methods

2.1. Protocol and registration

This systematic review and meta-analysis adhered to the guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) [33] (Fig. 1). The protocol was registered in PROSPERO, the International Prospective Register of Systematic Reviews (CRD42023413531). The PECOS method was used in this study. The PECOS research question was, "Is there a relationship between the dimensions of the frontal air sinus and the different skeletal malocclusions?" PECOS refers to the following components in this study: P (population): healthy adolescent subjects, E (exposure): any skeletal malocclusion (class I, class II and class III), C (comparator): involvement of skeletal malocclusion other than those included in the population component, O (outcome): dimensions of the frontal sinus in different skeletal malocclusions, and S (study design): observational studies (cross-sectional and retrospective studies).

2.2. Research strategy

A thorough and comprehensive search was conducted on May 23, 2023, in PubMed, Scopus, Embase, and Google Scholar to retrieve relevant studies. Combinations of the following terms were used: "frontal sinus" AND "lateral cephalometric" AND "malocclusion" AND "surface area". The electronic search was later augmented with a manual search of the reference lists of the relevant studies. The detailed inclusion and exclusion criteria are summarized in (Table 1).

2.3. Study selection

The electronically retrieved studies were imported into the program Endnote 20, and any duplicates were removed. The titles and abstracts of the remaining studies were screened independently by two authors (AL and MS), and the irrelevant studies were excluded. Full texts of the remaining potential studies were evaluated for inclusion by the two authors independently. Moreover, the reference lists of the subsequent included studies were manually searched for additional studies. Any disagreements were solved via discussion between the two authors.

2.4. Data extraction

The following data were independently extracted from the included studies by two reviewers (AL and FT): author and date of publication, journal, sample size, age, sex, study design, diagnosis of the skeletal malocclusions, and the dimensions of the frontal sinus. Any disagreements were resolved via discussion between the two authors.

2.5. Quality assessment

The included studies were independently and critically appraised by two authors (AL and NM) according to the Newcastle-Ottawa Scale (NOS) [34]. Observational studies were graded using three categories from this measure: selection (maximum 5 stars), comparability of study groups (maximum 2 stars), and outcome (maximum 3 stars). The maximum score was 10 stars. Accordingly, the studies were considered as having a high risk of bias if the score was <4 stars, a moderate risk if the score was between 4 and 7 stars, and a low risk if the score was >7 stars.

Table 1
Detailed inclusion and exclusion criteria.

Inclusion Criteria	Exclusion Criteria
Published articles until May 23, **2023**	Published articles after May 23, 2023 not included.
The articles that address the relationship between the frontal sinus and skeletal malocclusion	The articles that **address** the relationship between paranasal sinuses, other than the frontal sinus, and skeletal malocclusion
Original article: retrospective, longitudinal or cross-sectional studies	Other study designs: Case reports, animal studies, experimental studies, commentaries, review articles, Comments, letters to the editors, editorials, and brief messages
Lateral Cephalometric radiograph	Other evaluation (imaging) approaches
Studies on humans	Non-human studies
Studies that assessed the frontal sinus quantitatively (dimensions and/or surface area)	No quantitative measurements.

2.6. Summary measures

The height, depth, and surface area of the frontal sinus were considered as the outcome variables. The exposure variable was various types of skeletal malocclusion.

2.7. Statistical analysis

Statistical analyses were conducted using the computer software Comprehensive Meta-analysis version 3.3.070 (Biostat, Englewood, NJ, USA, 2014). The standardized mean difference (SMD) in surface area of the frontal sinus between two given groups along with the 95 % confidence interval (CI) were calculated. The heterogeneity across the included studies was evaluated using a chi-squared test and the I-squared index (I^2). A random-effects model was used when the heterogeneity was significant ($I^2 > 50$ %); otherwise, a fixed-effects model was applied. A P-value of <0.05 was considered statistically significant.

3. Results

3.1. Study selection

Fig. 1 shows the PRISMA workflow for choosing studies. The search yielded a total of 492 articles. There were 315 papers left after removal of the duplicate studies (177 duplicates). Screening by the titles and abstracts resulted in the exclusion of 292 studies. The full texts of the remaining 23 studies were assessed for potential inclusions, and 16 studies were excluded due irrelevance (Table 2). Ultimately, the systematic review and meta-analysis included 7 articles.

Table 2
Excluded studies with reasons.

Reference	Reason for Exclusion
Rossouw PE, Lombard CJ, Harris AM. The frontal sinus and mandibular growth prediction. American Journal of Orthodontics and Dentofacial Orthopedics. 1991;100(6):542-6.	No quantitative measurement for frontal sinus dimension (width and length).
Rothstein T, Yoon-Tarlie C. Dental and facial skeletal characteristics and growth of males and females with Class II, Division 1 malocclusion between the ages of 10 and 14 (revisited)—Part I: Characteristics of size, form, and position. American Journal of Orthodontics and Dentofacial Orthopedics. 2000 ;117(3):320-32.	No quantitative measurement for frontal sinus dimensions.
Prado FB, Rossi AC, Freire AR, Groppo FC, De Moraes M, Caria PH. Pharyngeal airway space and frontal and sphenoid sinus changes after maxillomandibular advancement with counterclockwise rotation for class II anterior open bite malocclusions. Dentomaxillofacial Radiology. 2012;41(2):103-9.	No quantitative measurement for various skeletal malocclusion
Salehi P, Heidari S, Khajeh F. Relationship between frontal sinus surface area and mandibular size on lateral cephalograms of adults. Journal of Isfahan Dental School, 2012, 244-250.	No quantitative measurement for frontal sinus dimensions.
Al-Sheakli II, Mohammed SA, Taha SS. The frontal sinus dimensions in mouth and nasal breathers in Iraqi adult subjects. Journal of baghdad college of dentistry. 2013;25(2):155-63.	No quantitative measurement for various skeletal malocclusion
Kapasiawala N, Raval NR, Patil AS. Comparative analysis of dimension of frontal sinus with different skeletal patterns. International Journal of Current Research, 2016, 8 (12): 42947-51.	No quantitative measurement for frontal sinus dimensions.
Nathani R, Diagavane P, Shrivastav S, Kamble R, Gupta D, Korde S. Evaluation of frontal sinus as a growth predictor in horizontal, vertical, and average growth pattern in children from 8 to 11 years: A cephalometric study. Journal of Indian Orthodontic Society. 2016;50(2):101-5.	No quantitative measurement for frontal sinus dimensions.
Tehranchi A, Motamedian SR, Saedi S, Kabiri S, Shidfar S. Correlation between frontal sinus dimensions and cephalometric indices: A cross-sectional study. European journal of dentistry. 2017;11(01):064-70.	Not measure the frontal sinus size in various skeletal malocclusion
Said OT, Rossouw PE, Fishman LS, Feng C. Relationship between anterior occlusion and frontal sinus size. The Angle Orthodontist. 2017;87(5):752-8.	No quantitative measurement for frontal sinus dimensions.
Büyük, S. Kutalmış; Karaman, Ahmet; Şimşek, Hüseyin. farkli sagittal iskeletsel ilişkiye sahip pediatrik ortodontik bireylerde frontal sinüs boyutlarinin incelenmesi. Atatürk Üniversitesi Diş Hekimliği Fakültesi Dergisi, 2018, 28 (2): 144-149.	Other evaluation (imaging) approaches (Postero-anterior cephalometric radiograph(
Göymen M, Büyüknacar GB, Güleç A. Effect of vertical growth pattern on maxillary and frontal sinus sizes. European Journal of Therapeutics. 2019;25(3):197-200.	Not measure the frontal sinus size in various skeletal malocclusion
Bhangare J, Ambekar A, Kangane S et al. Frontal sinus: Indicator of growth pattern.IOSR Journal of Dental and Medical Sciences, 2019, 18(4): 45–48.	Not measure the frontal sinus size in various skeletal malocclusion
Metin-Gürsoy G, Akay G, Baloş Tuncer B. Frontal sinus: is it a predictor for vertical malocclusions?. Anatomical Science International. 2021;96(1):62-9.	CBCT study
Abate A, Gaffuri F, Lanteri V, Fama A, Ugolini A, Mannina L, Maspero C. A CBCT based analysis of the correlation between volumetric morphology of the frontal sinuses and the facial growth pattern in caucasian subjects. A cross-sectional study. Head & Face Medicine. 2022;18(1):1-2.	CBCT study
Ijaz K, Babar A, Rasool G, Ijaz M, Ali F. relationship between frontal sinus width and skeletal jaw pattern: a lateral cephalometric study. Journal of Khyber College of Dentisrty, 2022;12(2):29-34.	No quantitative measurement for frontal sinus dimension (length and surface area).
Sawada M, Yamada H, Higashino M, Abe S, Tanaka E. Volumetric assessment of the frontal sinus in female adolescents and its relationship with craniofacial morphology and orthodontic treatment: A pilot study. International Journal of Environmental Research and Public Health. 2022;19(12):7287.	CBCT study

Table 3
Characteristics of the included studies.

Authors Country	Date of publication	Study design	Gender of participants	Age range	Number of subjects in each malocclusion class	Assessment Methods and Software	Main conclusion
Anil Prashar et al. [23] India	2012	Comparative Cross-sectional study	Male-Female	16 to 25	Patient record files, 80 pre-treatment lateral head cephalograms Skeletal Class I 30 Skeletal Class II 30 Skeletal Class III 20	Measurements of the frontal sinus's surface area, width and length on lateral cephalometric radiographs with manual tracing	Skeletal Class III malocclusions subjects had a greater frontal air sinus area than those with Class II and Class I skeletal malocclusions, and larger frontal air sinuses were related to large size mandibles.
Indu Dhiman et al. [24] India	2015	Comparative retrospective study	Male-Female	16 to 25	240 patients Skeletal Class I 80 Skeletal Class II 80 Skeletal Class III 80	Measurements of the frontal sinus's surface area, width and length on lateral cephalometric radiographs with AutoCAD Software	When compared, the frontal air sinus had a significant correlation with skeletal malocclusion (P 0.05). Skeletal Class III malocclusion had larger frontal air sinus area greater than in skeletal malocclusion Classes II and I.
Aishwarya Sabharwal et al. [37] India	2019	Comparative Cross-sectional stud	Male-Female	16–30	120 lateral cephalograms Skeletal Class I 40 Skeletal Class II 40 Skeletal Class III 40	Measurements of the frontal sinus's surface area, width and length on lateral cephalometric radiographs with manual tracing	There is a significant variability in height, width, and area of the frontal sinus region among classes I, II, and III after evaluating the linear dimensions. As a result, we may conclude that the frontal sinus is important in the representation of skeletal malocclusions.
Soghra Yassaei et al. [13] Iran	2019	Comparative Cross-sectional stud	Male-Female	15–20	A total of 116 digital lateral cephalograms Skeletal Class I 38 Skeletal Class II 40 Skeletal Class III 38	Measurements of the frontal sinus's surface area, width and length on lateral cephalometric radiographs with AutoCAD 2016 software	The frontal air sinuses in patients with Class III skeletal malocclusion had larger dimensions and surface areas than those in other groups. The width of the frontal air sinus was shown to be related to the anterior cranial base.
Alka Gupta et al. [35] Nepal	2021	Comparative Cross-sectional stud	Male-Female	16–30	A total of 195 lateral cephalometric radiographs Skeletal Class I 65 Skeletal Class II 65 Skeletal Class III 65	Measurements of the frontal sinus's surface area, width and length on lateral cephalometric radiographs with manual tracing	It was discovered that Class III had the biggest frontal sinus area while Class II had the smallest. The diagnostic and treatment planning of orthodontic and orthognathic situations should take into account these differences in frontal sinus dimensions.
Algahefi et al. [26] Yemen and China	2022	Comparative retrospective study	Male-Female	15 to 25	290 adolescent Caucasians and Chinese patients with 145 each. Skeletal Class I 65 Skeletal Class II 50 Skeletal Class III 30 Skeletal Class I 20 Skeletal Class II 20 Skeletal Class III 20	Measurements of the frontal sinus's surface area, width and length on lateral cephalometric radiographs with Winceph version 8.0 software	Compared to skeletal class I and class II malocclusions, the frontal air sinus surface area was much larger in skeletal class III malocclusions.
Tunca M et al. [36] Turkey	2022	Comparative retrospective study	Male-Female	17 to 25	In total, 60 patients Skeletal Class I 20 Skeletal Class II 20 Skeletal Class III 20	Measurements of the frontal sinus's surface area, width and length on lateral cephalometric radiographs with NemoCeph NX 2005 software	The length and height of the frontal sinus were found to be greater in skeletal Class III people than in skeletal Class I and skeletal Class II people, which may be a sign of the mandibular potential growth still present.

3.2. Study characteristics

The seven included studies were retrospective cross-sectional studies. They were conducted in six nations, with India having the highest number (n = 3)[23,24,35]. The rest of the studies were carried out in Iran [13], Nepal [35], Yemen [26], China [26], and Turkey [36]. There was a total of 1101 participants, who were examined with cephalometric X-rays and had different skeletal malocclusions.

There were 403 class-I, 375 class-II, and 323 class-III participants. The age range was 15–30 years. The majority of subjects in the studies were selected from universities (n = 5) [13,23,24,35,36] and hospitals (n = 1) [26]. Only one study did not include the location of recruitment [37]. Detailed characteristics of the included studies are presented in (Table 3).

3.3. Risk of bias assessment

Table 4 displays the results of the evaluation of risk of bias of the included studies based on the NOS. The seven studies had a medium score for risk of bias. Two received a score of 7/10, three received a score of 6/10, one received a score of 5/10, and one received a score of 4/10.

3.4. Results of the meta-analysis

No significant differences were detected in the frontal sinus surface area between class-I and class-II skeletal malocclusions (The Standardized Mean Difference (SMD) = 0.021; 95 % CI = −0.136−0.178; P = 0.796) (Fig. 2). In contrast, the surface area of the frontal sinus of class-III skeletal malocclusion was larger than that of class I (SMD = −0.971; 95 % CI = −1.147− −0.796; P < 0.001) (Fig. 3). In addition, the surface area of the frontal sinus of class-III skeletal malocclusion was larger than that of class II (SMD = −1.535; 95 % CI = −1.732− −1.337; P < 0.001) (Fig. 4).

4. Discussion

A range of morphological changes in paranasal sinuses (frontal and maxillary sinuses) and their relationship with skeletal malocclusion has been reported. Most prior investigations have measured the morphological alterations of the paranasal sinuses using 2-dimensional conventional radiography [13,24]. Of the few articles identifying the morphological change of the frontal sinus surface area in the different types of skeletal malocclusion, we included only studies that used cephalometric radiographs to measure the difference in the frontal sinus surface area in different skeletal malocclusions [13,23,24,26,35–37].

The present study is the first systematic review and meta-analysis to determine whether the dimensions of the frontal air sinus correlate with skeletal malocclusion. The results indicated that the surface area of the frontal sinus of class-III skeletal malocclusion was larger than that of class I and class II, and there were no differences between class I and class II. A recent study reported a smaller surface area of the maxillary sinus in class III compared to class I and class II [38].

Based on this, the results of the current study imply that the body compensates for this by increasing the dimensions of the frontal sinus in class III. This is mostly because class-III malocclusion is due to retruded maxilla, a combination of a retruded maxilla and prognathic mandible, and, to a lesser extent, mandibular prognathism. This explains the decreased maxillary sinus dimensions in this form of malocclusion, which are compensated for by an increase in the size of the frontal sinus to maintain normal function [39]. However, this contradicts the results of Yassaei et al., who reported larger frontal and maxillary sinuses in class III compared to class I

Table 4
Quality criteria of included studies.

Authors	Selection				Comparability	Outcome		Score
	Representativeness of the sample *	Sample size *	Nonrespondents *	Ascertainment of exposure * *	Based on design and analysis **	Assessment of outcome **	Statistical test *	
Anil Prashar et al. [23]	–	*	–	*	*	*	–	**4**
Indu Dhiman [24]	*	*	–	–	* *	*	*	**6**
Aishwarya Sabharwal et al. [37]	*	–	–	*	*	*	*	**5**
Soghra Yassaei et al. [13]	*	*	–	*	* *	*	*	**7**
Alka Gupta et al. [35]	*	*	–	*	*	*	*	**6**
Ahmed lotf Algahefi [26]	*	*	–	*	* *	*	*	**7**
Tunca M et al. [36]	*	*	–	*	*	*	*	**6**

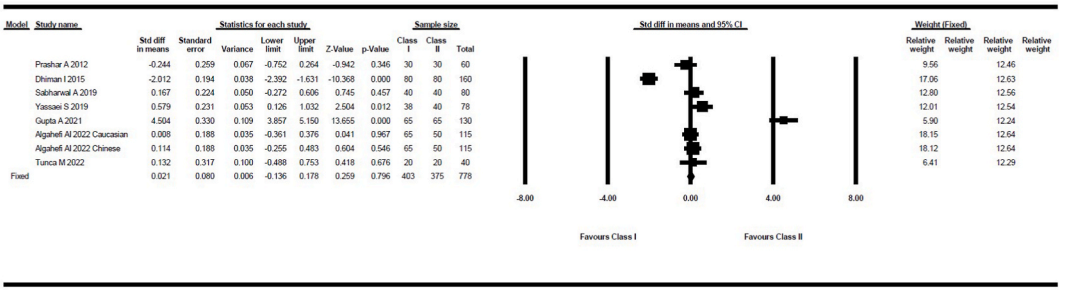

Fig. 2. Comparison of frontal sinus surface area between class-I and class-II malocclusion.

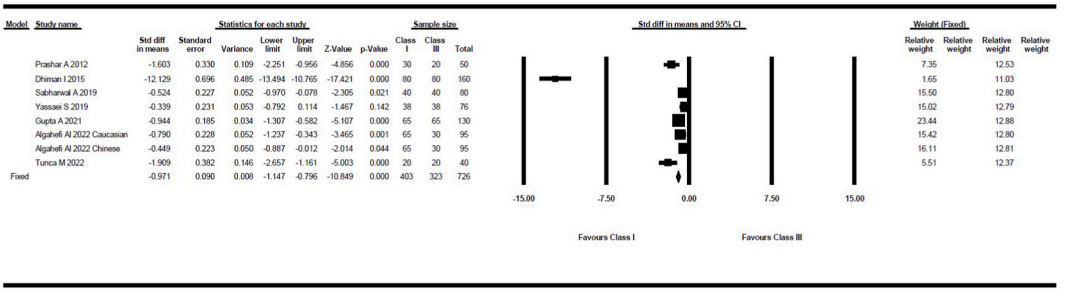

Fig. 3. Comparison of frontal sinus surface area between class-I and class-III malocclusion.

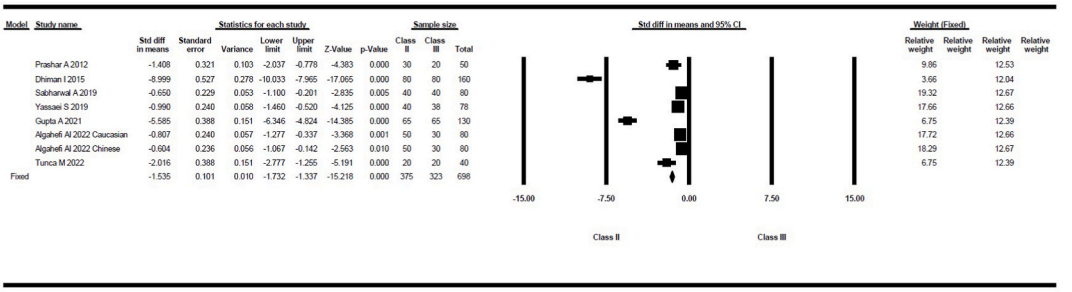

Fig. 4. Comparison of frontal sinus surface area between class-II and class-III malocclusion.

and class II [13].

Most of the included articles in this study demonstrated that the frontal surface area was larger in class-III skeletal malocclusion [13,23,26,35–37]. Besides what has been already mentioned above, this result may be attributed to the lack of anterior occlusion in class-III skeletal malocclusion, leading to a lack of transmission of mastication force to the frontal sinus area. The development of paranasal sinuses is a result of the skull's biomechanical requirements. As a result, the masticatory forces are a significant contributor to mechanical stress, so it is important to consider their size and direction. The amount of pneumatization is influenced by these mechanisms [31].

In addition, Said et al. [40] found a significant correlation between anterior occlusion and the size of the frontal sinus, with the sinus size being significantly smaller in the class-I group compared to all other malocclusion groups except the skeletal class-III edge-to-edge group and the bimaxillary protrusion group. Furthermore, Prado et al. [12] found that there was a decrease in the size of the frontal sinus six months after maxillomandibular advancement and counterclockwise rotation to repair a class-II open-bite malocclusion. All of these authors found that the frontal sinus size alteration resulted from adapting to the stresses resulting from a harmonized occlusion. These results support our findings.

Individuals with a vertical growth pattern were shown to have a smaller frontal sinus [4,31]. However, Goymen et al. claimed that the size of the frontal sinuses are not affected by a varied vertical growth pattern. This result conflicts with the theory that the size of the frontal sinus is altered by stresses forced by a harmonized occlusion [41].

Regarding the significant association between the frontal sinus size and skeletal malocclusion, it was emphasized that there was a correlation between the size of the frontal sinus and the mandibular protrusion, and the frontal air sinus may be useful as a supplementary indication for predicting mandibular development [18,32]. These findings are consistent with ours. In contrast with our

results, Andiappan [29] found that class-II skeletal malocclusion has a significant positive correlation with frontal sinus surface area, aiding in the assessment of class-II skeletal malocclusion.

4.1. Strengths and limitations

This study's strengths include that it is the first meta-analysis to examine the relationship between frontal sinus surface area and skeletal malocclusion. This study used a comprehensive search approach employing several databases, which should increase the strength and accuracy of the aggregated results. The limitations of the study include the limited number of studies, insufficient data, missing patient information, and the use of a two-dimensional imaging (cephalometric X-ray) rather than a three-dimensional imaging (cone beam computed tomography). Notably, there were different methods for measuring the surface area of the frontal sinuses among the included studies: three studies used manual measurement, while the other studies measured it using software. This might be a limitation as it raises questions regarding the measurement precision. The low certainty of evidence obtained from the observational studies represents another limitation of this study.

Although methodological shortcomings were found, this systematic review and meta-analysis came to the conclusion that there is a connection between the frontal sinus surface area and skeletal malocclusion. Nevertheless, more research is required in this area due to the low certainty of the evidence for such a correlation. These findings may help orthodontists: they have to consider the size of the frontal air sinus during orthodontic treatment planning for proper results. The study recommends to involve three-dimensional imaging methods, as these methods describe more accurately and three-dimensionally the overall facial spaces either air or soft tissue filled spaces including the frontal air sinuses [42, 43].

5. Conclusion

The frontal sinus surface area may vary significantly among individuals with different types of skeletal malocclusions. The surface area of the frontal air sinuses is more linked with class-III skeletal malocclusion than other kinds of skeletal malocclusions (classes I and II).

Data availability statement

Data will be available by direct request from the corresponding author whenever required.

CRediT authorship contribution statement

Ahmed lotf Algahefi: Writing – original draft, Visualization, Resources, Investigation, Formal analysis, Conceptualization. **Mohammed sultan Alak'hali:** Writing – review & editing, Methodology, Data curation. **Esam Halboub:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Fei Tong:** Writing – review & editing. **Abeer A. Almashraqi:** Writing – review & editing. **Labib hazaa ghaleb:** Methodology. **Li Zhihua:** Writing – review & editing, Investigation, Funding acquisition, Conceptualization. **Maged S. Alhammadi:** Writing – review & editing, Investigation.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Zhihua Li reports financial support was provided by Health Commision of Jiangxi province. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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