REVIEW ARTICLE

Correlation between skeletal maturity assessed by spheno-occipital synchondrosis (SOS) fusion and cervical vertezzbrae maturation index (CVMI)? A systematic review and meta-analysis

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ABSTRACT
This review aims to systematically collect and analyze studies investigating the correlation between the skeletal age assessed by spheno-occipital synchondrosis (SOS) fusion and CVMI (cervical vertebrae maturation index). Based on PECO, a research question was framed as "Is there a correlation between skeletal maturity assessed by spheno-occipital synchondrosis (SOS) fusion and cervical vertebrae maturation index (CVMI)?" The review was submitted for registration in PROSPERO (receipt 550152). Keywords: skeletal maturity; spheno-occipital synchondrosis; and cervical vertebrae maturation were used to search data in the search engines: PubMed Central, Lilac, EBSCOhost, Science Direct, and Google Scholar. The search question was formulated as "skeletal maturity" AND "spheno-occipital synchondrosis" (OR "SOS") AND "cervical vertebrae maturation" (OR "CVMI"). The data extracted from the articles was tabulated and a meta-analysis of correlation was performed. Overall, a strong positive correlation ($r = 0.876$) between SOS fusion and CVMI was found, with significant statistical support ($p < 0.01$). Gender-specific analyses also showed strong correlations for both males ($r = 0.898$) and females ($r = 0.877$), however, high heterogeneity was observed, suggesting variability among studies. This systematic review demonstrates a strong positive correlation between SOS fusion and CVMI, suggesting that SOS fusion can be a reliable indicator of skeletal maturity. However, the considerable heterogeneity observed, particularly in gender-specific analyses, warrants further investigation with a homogenous population and larger sample size.

KEY WORDS: skeletal maturity, spheno-occipital synchondrosis, cervical vertebrae maturation index

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INTRODUCTION
In orthodontics and orthopedics assessment of skeletal maturity is crucial for determining growth status and planning appropriate treatment strategies. The gold standard for assessing skeletal maturity is the hand-wrist (HW) maturation method. However, HWM assessment exposed patients to an unnecessary dose of radiation hence, the cervical vertebral maturation (CVM) in the lateral cephalometric radiographs was evaluated for its correlation to the skeletal maturity as an alternative [1, 2]. The lateral cephalometric radiograph is routinely required for orthodontic diagnosis and treatment planning and, therefore, no extra radiograph is needed. But, this method is not sensitive in detecting the growth maturity in periods away from the growth spurt [3].

The spheno-occipital synchondrosis (SOS) located in the midline between the sphenoid and occipital bones and is considered the most important growth center in the cranial base because of its late ossification and contribution to post-natal cranial base growth [1, 2]. The cranial base is the template for facial development; therefore, it is directly related to the maxillary and mandibular growth. Understanding the correlation between SOS-assessed skeletal age and cervical vertebrae maturation index (CVMI) is thus, crucial for refining clinical assessments and treatment planning in orthodontics and orthopedics. While both methods aim to assess skeletal maturity, variations in their application and interpretation exist. Therefore, a systematic review and meta-analysis was deemed essential to synthesize existing evidence and evaluate the strength of correlation between these two measures.

AIM
This review systematically collects and analyzes studies investigating the correlation between the

skeletal age assessed by SOS fusion and CVMI. By synthesizing these findings, we aim to provide clinicians with a comprehensive understanding of the relationship between these two methods of skeletal maturity assessment.

MATERIALS AND METHODS

The review was submitted for registration in PROSPERO (Registration Id: CRD42024550152). PRISMA guidelines were followed for conducting this review [4].

RESEARCH QUESTION: PECO

P (Problem): Healthy participants
E (Exposure): SOS
C (Comparison): CVMI
O (Outcome): Correlation between skeletal maturity assessed by SOS and CVMI

On the basis of PECO, research question was reframed as "**Is there a correlation between skeletal maturity assessed by spheno-occipital synchondrosis (SOS) fusion and cervical vertebrae maturation index (CVMI) among healthy participants?**"

SEARCH STRATEGY

Using keywords: skeletal maturity; spheno-occipital synchondrosis; cervical vertebrae maturation, search engines: PubMed Central, Lilac, EBSCOhost, Google Scholar, and Science Direct were used by applying the Boolean operator "AND". The search question was formulated as "skeletal maturity" AND "spheno-occipital synchondrosis" (OR "SOS") AND "cervical vertebrae maturation" (OR "CVMI"). Cross-sectional or longitudinal studies that compared the skeletal maturation assessed by SOS fusion and CVMI in healthy patients were included. Studies using data of syndromic patients, cleft lip/palate, scoliosis, or other skeletal abnormalities, and those with a history of fracture in craniofacial base were excluded. Abstracts, dissertation, theses, patents, convention abstracts, opinion articles, commentaries, article not in English language, and animal study were also excluded.

The literature was reviewed in the entirety up to 31st May 2024 for clinical studies evaluating correlation between skeletal maturity assessed between SOS fusion and CVMI, irrespective of the method used. Title and abstract screening was done by two authors independently (A.S and S.V), followed by retrieval of full text reports of the eligible articles. All the available full text was compiled and thoroughly scrutinized.

Table 1. Summary of studies evaluating the correlation between SOS fusion and CVMI

Author	Year	Population	Sample size (n)	n (M)	n (F)	mean age	mean age (M)	mean age (F)	Age range (year)	Test used	r	r (M)	r (F)	SOS method	SOS stages	CVMI method	CVMI stages
Kocasarac	2016	Turkish	116	43	73		15.13	16.39	8 to 28	Spearman correlation		0.851	0.618	Franklin and Flavel	4	Hassel and Farman	6
Perez	2016	North American	315	167	148	15.6+_7.3			6 to 23	Spearman correlation	0.89	0.89	0.88	Bassed et al	5	Baccetti	6
Fayad	2020	Lebanese	117	55	62		13.7	12.6	8 to 18	Spearman correlation	0.852	0.839	0.868	Franklin and Flavel	4	Baccetti	6
Kim SM	2023	Korean	630	308	322	6.0-18.0				Spearman correlation		0.955	0.964	Bassed et al	5	Baccetti	6

Source: Authors' own work

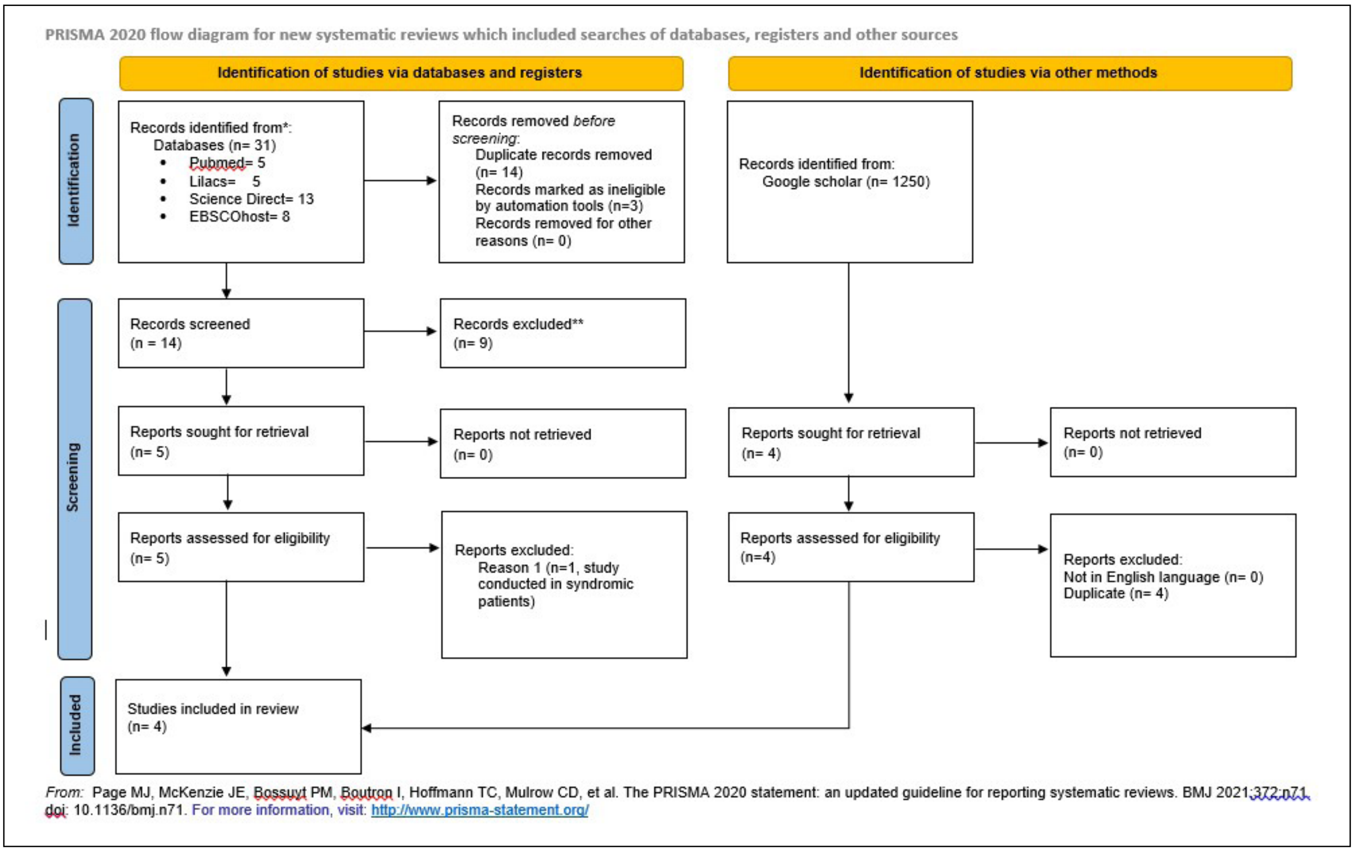

Fig. 1. Search strategy
Source: [4]

DATA EXTRACTION

Two authors (A.S and S.V) independently searched the data. A third author (S.A.M) resolved any conflict arising in case of disagreement amongst the two authors regarding eligibility of an article. The data was entered in the specially designed excel sheet. The characteristics of the studies: author, year, country, sample size (n), age (range/ mean, standard deviation), gender, method used for skeletal maturity assessment (SOS and CVMI), spearman correlation value (r) both combined and separately for males and female, and any other reported outcome measures were recorded (Table 1). RevMan (Review Manager Computer program version 5.4.1 The Cochrane Collaboration, 2020) was used for risk of bias assessment of individual studies [5]. Quality assessment was done using QUADAS-2 tool [6].

DATA ANALYSIS

Meta-analysis of correlation coefficient obtained was performed in the Medcalc software v 12.7.8 (Medcalc software, Ostend, Belgium). Hedges-Olkin method was used as it reduces the risk of Type 1 error as compared to Schmidt-Hunter method if the studies are homogenous. Heterogeneity was assessed using I^2 statistic.

REVIEW

LITERATURE SEARCH

After applying the aforementioned filters and removing duplicates, five articles were left for screening. From these, one article was removed after reading the title and abstract. Four articles were assessed for eligibility. Thus, a total of four articles were found suitable for the review (Fig. 1).

Quality assessment of the selected articles was done using RevMan software [5]. The studies were critically appraised under four categories: patient selection, index test, reference standard, and flow and timing. Each category was further evaluated under the following domains: description, signaling questions ("yes", "no," or "unclear"), risk of bias ("high", "low" or "unclear"), and concerns about applicability ("high", "low" or "unclear"). All studies showed low risk of bias and low applicability concerns suggesting that the result of the studies are reliable and valid (Fig. 2-3).

For SOS assessment, two studies (Kim and Perez) [7, 8] used Frankel and Flavin's [9]method, and two (Fayad and Kocasarac) [10, 11] used Bassed et al's method [12]. Both these methods determine skeletal maturity, but differ in their level of details for assessment. Franklin and Flavel used a three- point scoring method (unfused, partly fused, completely fused) providing a broad

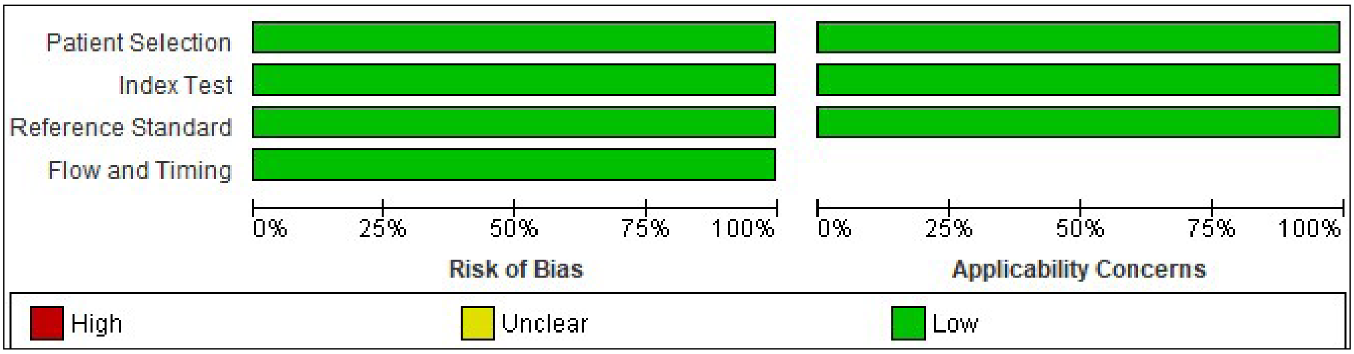

Fig. 2. Risk of bias and applicability concerns graph: review authors' judgements about each domain presented as percentages across included studies
Source: Authors' own work

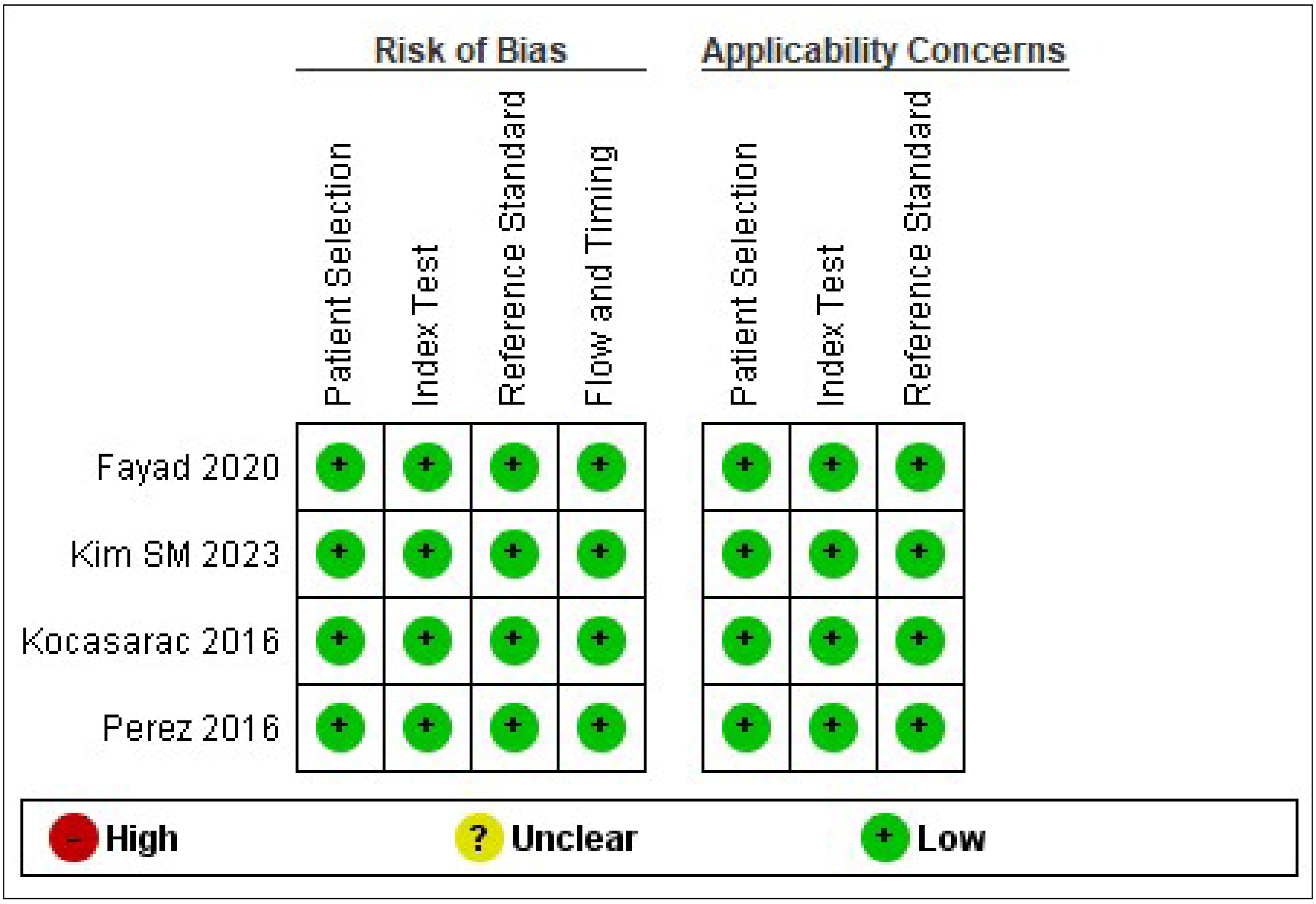

Fig. 3. Risk of bias and applicability concerns summary: review authors' judgements about each domain for each included study
Source: Authors' own work

classification of fusion stages. In contrast, Bassed et al's system used a detailed five stage scoring system (completely open, initial ossification, partial fusion, nearly complete fusion, and complete fusion).

For CVMI, three studies [7, 8, 10] used Bacceti et al's method [13] while one (Kocasarac) [11] used Hassal and Farman's method [2]. As compared to Hassel Farman, Baccetti et al's method uses more detailed description of morphology of vertebrae and can be considered superior to former.

Of the four studies, correlation between SOS fusion and CVMI was higher in males [8,10,11], except in the study by Kim SM [7]. They also found that SOS fusion stages were more advanced in females as compared to males.

The correlation coefficient from the combined studies was 0.876 with 95% confidence interval, suggesting a strong positive relationship between SOS and CVMI (Figure 4). The p value was <0.01 which is statistically significant (Table 2a). The I^2 value is 52.34% implicating moderate heterogeneity (Table 2b).

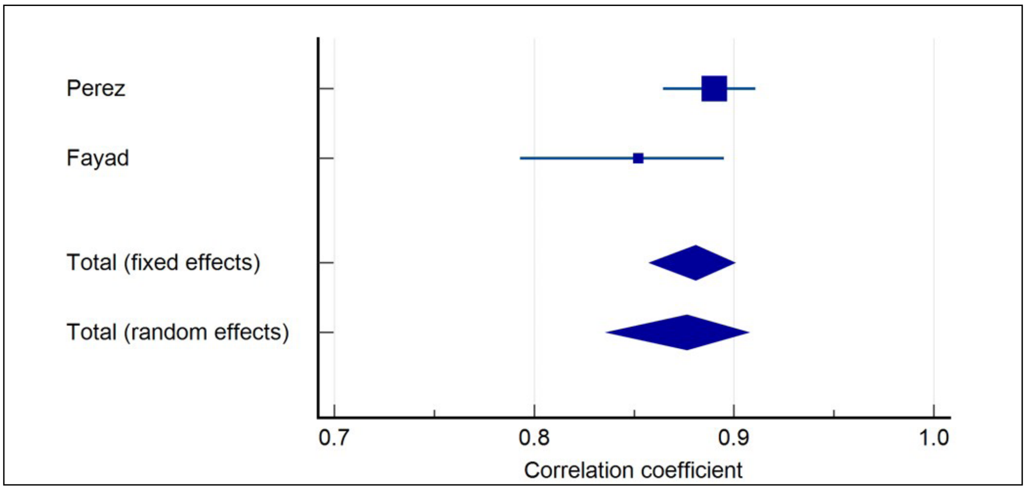

Fig. 4. Forest plot without gender specification
Source: Authors' own work

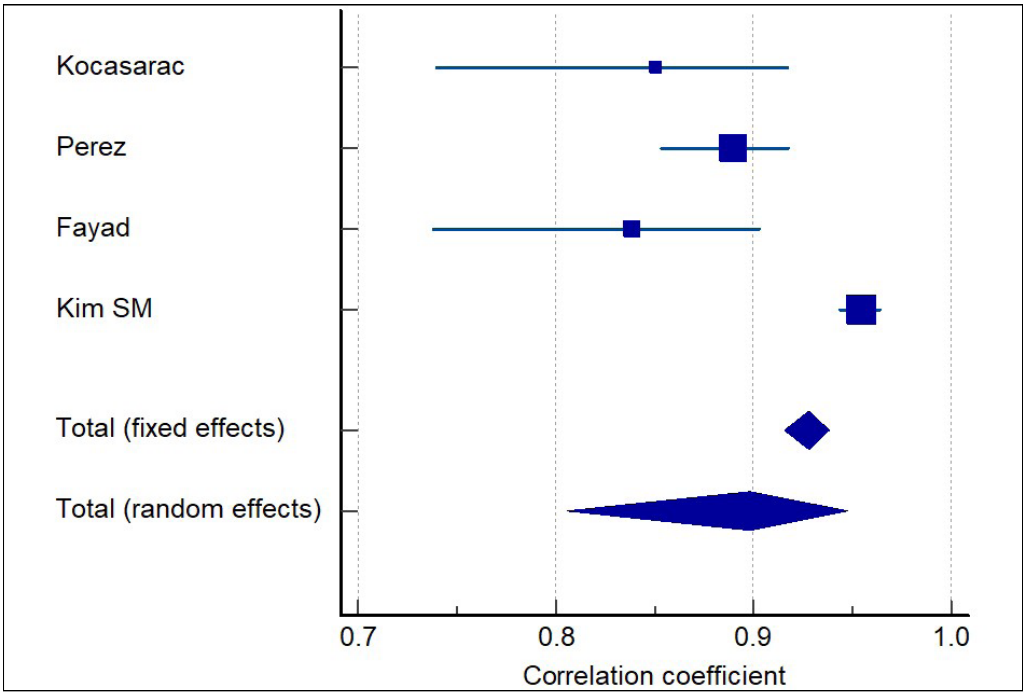

Fig. 5. Forest plot for males
Source: Own materials

The meta-analyses was also conducted separately for males and females. For males, the meta-analysis yielded a correlation coefficient (r value) of 0.898 with 95% confidence interval, suggesting a strong positive correlation (Fig. 5). The p value was <0.01 which is statistically significant (Table 3a). The I^2 value of 92.73% suggests considerable heterogeneity among the studies included in the meta-analysis (Table 3b).

For females, the meta-analysis yielded a correlation coefficient (r value) of 0.877 with 95% confidence interval, suggesting a strong positive correlation (Fig. 6). The p value was <0.01 which is statistically significant (Table 4a). The I^2 value of 97.42% suggests considerable heterogeneity among the studies included in the meta-analysis (Table 4b).

Kocasarac et al., [11]in addition to determining correlation between SOS and CVMI, also found a strong correlation between chronological age and third molar mineralization, age and SOS fusion, age and CVMI fusion, TMM and SOS fusion, and TMM and CVMI.

DISCUSSION

Lateral cephalometric radiographs have been an integral part of orthodontic treatment. Therefore, CVMI gets seamlessly integrated into the clinical set up, eliminating the need for additional mode of investigation for skeletal age assessment [13]. Previous studies have established its simplicity and reliability in assessing skeletal maturity [2, 14].

However, CVMI has its own limitations. Since CVMI is based on visual assessment of morphological changes in vertebrae, it is at risk for subjective variability [15]. Also, it is inadequate in determining small changes in skeletal maturity over short periods of time, hence cannot be used in conditions where precise growth

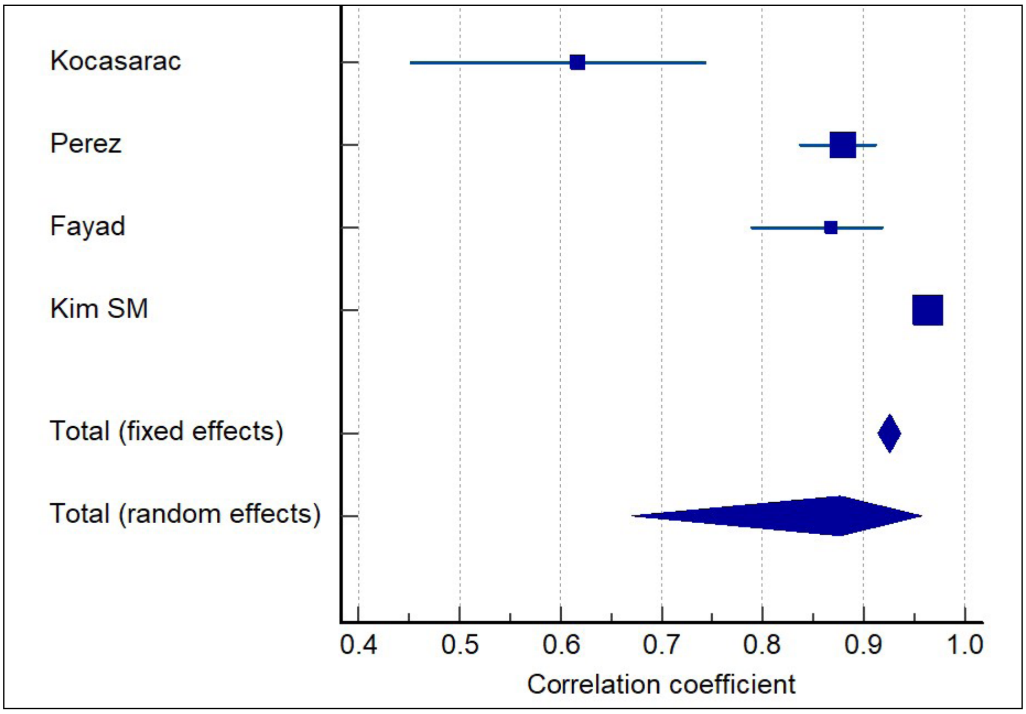

Fig. 6. Forest plot for females
Source: Own materials

assessment is needed. Since CVMI varies with age and gender, it cannot be used in patients who do not follow typical growth patterns [14].

SOS located in the base of the skull is the nidus of craniofacial growth. SOS undergoes distinct sequential changes corresponding closely to somatic changes hence, is considered a reliable indicator of pubertal growth spurt [1]. SOS fusion is more of an objective assessment as compared to CVMI which is subjective in nature. The assessment of SOS not only provides an insight of skeletal maturity but also the craniofacial growth making it more comprehensive as compared to other skeletal assessment markers [16].

The present systematic review aimed to evaluate the correlation between SOS and CVMI in assessing skeletal maturity.

CORRELATION BETWEEN SOS AND CVMI

The overall analysis indicated a strong correlation between SOS fusion and CVMI. The combined correlation coefficient value was 0.876. The 95% confidence interval and a p value of <0.01 reinforce the statistical significance and strength of this relationship. The moderate heterogeneity (I^2 value of 52.34%) is considered acceptable, suggesting that the variability among the studies does not significantly impact the overall findings.

GENDER SPECIFIC META-ANALYSIS

For males, the correlation coefficient 0.898 with a 95% confidence interval and a p value of <0.01, indicating a strong positive correlation. However, the high I^2 value of 92.73% suggests considerable heterogeneity, indicating significant variability among the studies.

For females, the correlation coefficient was 0.877 with a 95% confidence interval and a p value of <0.01, also indicating a strong positive correlation. Similarly, the I^2 value of 97.42% suggests considerable heterogeneity among the studies.

The strong positive correlations in both the overall and gender-specific analyses underscore the potential utility of SOS fusion as an indicator of skeletal maturity alongside CVMI. However, the considerable heterogeneity in the gender-specific analyses highlights the need for cautious interpretation. The high heterogeneity could be attributed to variations in study designs, population demographics, or assessment methodologies.

Given the strong positive correlation between the two methods, for routine cases, clinicians especially orthodontists can consider CVMI over SOS fusion for assessing skeletal maturity. In cases requiring precise measurement of craniofacial growth or cases where CBCT is indicated for other concomitant factors, the clinicians can rely on SOS fusion.

CLINICAL IMPLICATIONS

The assessment of skeletal maturity is crucial for timing growth-dependent therapies. In orthodontics, functional appliances for mandibular retrognathia, rapid maxillary expansion (RME), headgear for Class III malocclusion, and vertical growth control procedures are

Table 2a. Spearman correlation (r) without gender specification

Study	Sample size	Correlation coefficient	95% CI	z	P	Weight (%)	
						Fixed	Random
Perez	315	0.890	0.865 to 0.911			73.24	61.08
Fayad	117	0.852	0.793 to 0.895			26.76	38.92
Total (fixed effects)	432	0.881	0.858 to 0.900	28.473	<0.001	100.00	100.00
Total (random effects)	432	0.876	0.836 to 0.907	17.599	<0.001	100.00	100.00

Source: Authors' own work

Table 2b. Test for heterogeneity

Q	2.0981
DF	1
Significance level	P = 0.1475
I^2 (inconsistency)	52.34%
95% CI for I^2	0.00 to 88.07

Source: Authors' own work

Table 3a. Spearman correlation (r) for males

Study	Sample size	Correlation coefficient	95% CI	z	P	Weight (%)	
						Fixed	Random
Kocasarac	43	0.851	0.740 to 0.917			7.13	22.78
Perez	167	0.890	0.853 to 0.918			29.23	26.40
Fayad	55	0.839	0.738 to 0.903			9.27	23.77
Kim SM	308	0.955	0.944 to 0.964			54.37	27.04
Total (fixed effects)	573	0.928	0.916 to 0.939	38.930	<0.001	100.00	100.00
Total (random effects)	573	0.898	0.806 to 0.948	8.255	<0.001	100.00	100.00

Source: Authors' own work

Table 3b. Test for heterogeneity

Q	41.2634
DF	3
Significance level	P < 0.0001
I^2 (inconsistency)	92.73%
95% CI for I^2	84.61 to 96.57

Source: Authors' own work

Table 4a. Spearman correlation (r) for females

Study	Sample size	Correlation coefficient	95% CI	z	P	Weight (%)	
						Fixed	Random
Kocasarac	73	0.618	0.452 to 0.742			11.80	24.68
Perez	148	0.880	0.838 to 0.912			24.45	25.27
Fayad	62	0.868	0.789 to 0.919			9.95	24.48
Kim SM	322	0.964	0.955 to 0.971			53.79	25.58
Total (fixed effects)	605	0.926	0.914 to 0.937	39.671	<0.001	100.00	100.00
Total (random effects)	605	0.877	0.671 to 0.957	4.854	<0.001	100.00	100.00

Source: Authors' own work

Table 4b. Test for heterogeneity (females)

Q	116.1848
DF	3
Significance level	P < 0.0001
I^2 (inconsistency)	97.42%
95% CI for I^2	95.52 to 98.51

Source: Authors' own work

most effective when carried out during pubertal growth spurt. For instance, beginning functional treatment too early in a pre-pubertal child may prolong the therapy with limited skeletal effect, whereas delaying treatment until after growth cessation may eliminate the possibility of orthopedic correction altogether. In pediatric dentistry and craniofacial anomaly management, understanding the growth status aids in sequencing surgical, orthodontic, and prosthetic interventions to achieve stable long-term results. Thus, skeletal maturity indicators help clinicians decide whether to initiate, delay, or alter the treatment modality directly impacting treatment outcomes. Incorporating these tools into clinical decision-making enhances the ability of the clinician to customize therapies to individual growth potential, optimizing both functional and aesthetic outcomes

LIMITATIONS

Despite the robust findings, the review has certain limitations. Although all the included four studies scored well in the quality assessment tool, it is to be noted that all of them had used convenience sampling, and were cross-sectional studies. None of the studies have been carried out in a longitudinal manner. All studies represented different population groups thus, generalization of the results should be done with caution. The considerable heterogeneity in the gender-specific analyses suggest the need to conduct further studies with larger sample sizes. The use of different methodologies for assessment could have also introduce variability in the results.

CONCLUSIONS

This systematic review demonstrates a strong positive correlation between SOS fusion and CVMI, suggesting that SOS fusion can be a reliable indicator of skeletal maturity. However, the considerable heterogeneity observed, particularly in gender-specific analyses, warrants further investigation. Due to its practicality and established methodology clinicians can use CVMI for general assessments. For cases requiring detailed analysis of craniofacial growth, incorporating SOS assessments can provide a more comprehensive evaluation. Also, skeletal maturity assessment must be done using the method that uses a detailed description of morphological changes.

FUTURE DIRECTIONS

Based on the findings of this review, future research should aim to

1. Establish uniform protocols for assessing CVMI and SOS
2. Increase the sample size to enhance generalizability of the results
3. Conduct longitudinal studies to understand the temporal relationship between SOS fusion and CVMI.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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