INSTITUTO UNIVERSITÁRIO EGAS MONIZ

MESTRADO INTEGRADO EM MEDICINA DENTÁRIA

CERVICAL VERTEBRAL MATURITY AS A BIOLOGICAL INDICATOR OF CHRONOLOGICAL AGE: A SYSTEMATIC REVIEW AND META-ANALYSIS

Trabalho submetido por
Maria Inês Ribeiro Magalhães
para a obtenção do grau de Mestre em Medicina Dentária

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Trabalho orientado por
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setembro de 2021

Dedicatory

"Everything is hard before it is easy"

Johann Wolfgang Von Goethe

AGRADECIMENTOS

Antes demais, o meu mais sincero agradecimento à minha orientadora Prof.ª Doutora Ana Delgado pela disponibilidade e excelente orientação ao longo deste projeto desde o início.

À minha coorientadora, Prof.ª Doutora Vanessa Machado, agradeço a disponibilidade, o rigor, a incansável motivação e apoio prestados durante o projeto.

Ao Mestre João Botelho, que espelha um exemplo de trabalho árduo, de motivação, rigor, companheirismo e admiração, quero agradecer por toda a disponibilidade demonstrada.

Ao Instituto Universitário Egas Moniz pelo ensino sublime, pelas oportunidades disponibilizadas enquanto aluna e futura profissional. À Egas Moniz, que foi a casa onde cresci, aprendi e me dediquei à área que sempre sonhei, agradeço de coração cheio.

À minha mãe – Maria João – o meu maior exemplo de força e determinação para toda a vida, ao meu pai – João – o homem que sempre me motivou a realizar os meus sonhos me motivou para ser sempre capaz de alcançar mais. Agradeço de coração cheio aos que sempre incentivaram o meu percurso com entusiasmo.

Ao meu namorado – Marcos – por todo o amor e carinho partilhados neste percurso, por toda a força e determinação transmitidos ao longo destes 5 anos, obrigada de coração.

À minha amiga do coração – Raquel – agradeço pelo apoio imprescindível, inigualável disponibilidade, pelas memórias inesquecíveis e pelas batalhas travadas em conjunto.

Ao meu primeiro colega de Box – Daniel Cruz – pela partilha de conhecimento, pela disponibilidade inquestionável e por todo o carinho e amizade partilhados, agradeço de coração a amizade que surgiu ao longo destes 5 anos. À minha colega de box – Mariana Patrão – pela enorme disponibilidade, carinho e apoio incondicional. Às minhas queridas amigas – Joana Lopes, Madalena Eraclides, Mariana Machete – pela amizade, por todas as memórias risonhas que levo para o resto da vida.

À minha amiga – Inês Miguel – por todo o carinho e motivação que me transmites desde há longos anos. Ao meu amigo – Filipe Caramelo – pelas memórias inesquecíveis que partilhamos juntos. Por último, ao meu amigo – José Furtado – por toda a dedicação, amizade e apoio demonstrados ao longo dos anos, agradeço do fundo do coração.

ABSTRACT

Background: Biological age is a fundamental factor in orthodontic treatment. One of the methods used to determine such parameter is the Cervical vertebral maturation (CVM). By using this exam, it is possible to avoid extra radiation, since it requires a lateral cephalometric radiographic (X-Ray), an exam used to evaluate other orthodontic parameters as well.

Objectives: This systematic review (SR) aimed to appraise the evidence linking the chronological age and each cervical vertebral maturation's stage, according to Baccetti's method from 2005. Moreover, we assessed the gender dimorphism of chronological age and the impact of continents in each CVM stage.

Materials and methods: Five databases (PubMed, Google Scholar, LILACS, CENTRAL and Scopus) were search up to July 2021. Cohort and longitudinal studies on the association of CVM and chronological age were included. The risk of bias (RoB) was assessed using the tool Strengthening the Reporting of Observational Studies in Epidemiology (STROBE), Standards for the Reporting of Diagnostic Accuracy Studies (STARD), and Lagravere's study in 2005. The random effect of single means meta-analysis was performed.

Results: Forty-two articles observational studies fulfilled the inclusion criteria. The overall mean age of CS1 were 9.7 years; CS2 were 10.8 years; CS3 were 12.0 years; CS4 were 13.4 years; CS5 were 14.8 years; and CS6 were15.9 years. A significant difference was noted between females and males, with females presenting an earlier CVM when compared to males. The difference between genders across the continents is also significant.

Conclusion: There is a significant difference between females and males in CVM, with females presenting an earlier CVM when compared to males. The same differences are found all over the continents.

Keywords: Cervical vertebral maturation, Chronological age, Systematic review, Meta-analysis

RESUMO

Contexto: A idade biológica é um fator fundamental no tratamento ortodôntico. Esta pode ser determinada pela maturação vertebral cervical (MVC). Assim, evita-se o uso extra de radiação, visto que requer o uso da radiografia cefalométrica lateral, um exame que avalia simultaneamente outros parâmetros ortodônticos.

Objetivo: Esta revisão sistemática pretende avaliar as evidências que relacionam a idade cronológica e cada um dos estadios de MVC segundo o método de Baccetti em 2005. Avaliamos ainda o dimorfismo de género da idade cronológica e o impacto dos continentes em cada estadio de maturação vertebral cervical.

Materiais e métodos: Cinco bases de dados (PubMed, Google Scholar, LILACS, CENTRAL and Scopus) foram pesquisadas até julho de 2021. Estudos coorte e longitudinais que associassem a maturação vertebral cervical e a idade cronológica foram incluídos. O risco de viés foi avaliado através da ferramenta *Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)*, *Standards for the Reporting of Diagnostic Accuracy Studies (STARD)*, e o estudo de Lagravere em 2005. O efeito aleatório das médias individuais da meta-análise foi realizado.

Resultados: Quarenta e dois estudos observacionais preencheram todos os critérios de inclusão. A média estimada de idade para o CS1 foi de 9.7 anos; para o CS2 foi de 10.8 anos, para o CS3 foi de 12.0 anos; para o CS4 foi de 13.4 anos, para o CS5 foi de 14.8 anos e para o CS6 foi de 15.9 anos. Notou-se uma diferença significativa entre o sexo feminino e masculino. O primeiro apresenta uma maturação vertebral cervical precoce quando comparada com o sexo masculino. A diferença entre géneros nos diversos continentes é igualmente revelante.

Conclusões: Na maturação vertebral cervical, existe uma diferença significativa entre os sexos, sendo que o sexo feminino apresenta uma maturação vertebral cervical mais precoce. Estas discrepâncias são encontradas ao longo dos diferentes continentes.

Palavras-chave: Maturação vertebral cervical, Idade cronológica, Revisão sistemática, Meta-análise

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ABBREVIATION LIST

C2 - Second Cervical

C3 - Third Cervical

C4 - Fourth Cervical

C5 - Fifth Cervical

C6 - Sixth Cervical

CBCT - Cone Beam Computerized Tomography

CENTRAL - Cochrane Central Register of Controlled Trials

CI - Confidence Interval

Co - Condylion

CS - Cervical Stage

CVM - Cervical Vertebral Maturation

CVMI - Cervical Vertebrae Maturation Indicator

CVMS - Cervical Vertebral Maturation Stage

Gn - Gnathion

HWM - Hand Wrist Maturation

LILACS - *Literatura Latino-americana e do Caribe em Ciências da Saúde*

MEDLINE – Medical Literature Analysis and Retrieval System Online

MVC - *Maturação Vertebral Cervical*

PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyses

RCTs - Randomized Clinical Trials

RoB - Risk of Bias

SD - Standard Deviation

SMI - Skeletal Maturity Indicator

SR - Systematic Review

STARD - Standards for Reporting of Diagnostic Accuracy Studies

STROBE - Strengthening the Reporting of Observational Studies in Epidemiology

TW - Tanner Whitehouse

TW-RUS -Tanner Whitehouse – Radius, Ulna and Short Tubular Bones

X-RAY - Radiographic

I. INTRODUCTION

1.1. Craniofacial skeletal maturity

Orthodontics focuses on studying dental-maxillofacial development and treatment of malocclusion, improving the dento-facial appearance (Jawad et al., 2015). Three main orthodontic times of intervention have been investigated separately. Firstly, the early stages of childhood (3 to 4 years old) are mainly preventive. Secondly, interceptive orthopaedic therapies are carried out on young patients with mixed or permanent dentitions, during the growth stages. Thirdly, in adulthood, the orthodontic treatment occurs at the end of the growth process. Therefore, time is a key factor that should be considered by the orthodontist to elaborate a diagnosis, since the constant growth of the patients has a huge impact on the treatment (Smith, 1947).

In order to perform a correct orthodontic course of treatment to manage craniofacial abnormalities and occlusion irregularities, a precise and personalized orthodontic diagnosis is mandatory (Jheon et al., 2017). Thus, skeleton's growth impact in the craniofacial area cannot be underestimated for orthodontic treatment's success. A proper sequencing and timing of orthodontic interventions are critical to optimize outcomes (Sadowsky, 1998).

The development and growth of craniofacial complex begins in the uterus and continues through adulthood. Craniofacial growth usually is described according to three main parameters: 1) magnitude; 2) direction; and 3) velocity. The magnitude criterion is used to characterize the growth in transversal, sagittal and vertical dimension. Furthermore, the direction represents a vector guiding growth, and the velocity is related to rate of growth per unit of time (Manlove et al., 2020).

Skeletal maturation is the magnitude and velocity of peak growth. Each individual skeletal maturation occurs according to her or his own biological time (Moore et al., 1990; Soliman et al., 2014). In other words, all subjects go through the same stages of development and growth but not always at the exact same time (Valadian & Porter, 1977) and, therefore, the chronological age and the skeletal age may not match (Cericato et al., 2015; Gandini et al., 2006; Moore et al., 1990). In 1944, Crampton proposed biological age as an alternative to chronological age to evaluate growth (Crampton, 1944).

The terms "chronological age" and "biological age" are intrinsically related and typically are discussed in tandem, although they are distinct. Conceptually, chronological age corresponds to the age from birth date until the present moment (Chertkow, 1980), while biological age refers to "phenotype age" and is related with cumulative rate of aging on tissues, organs, and blood's real age (Buendía-Roldan et al., 2020). Specifically, biological age reflects a combination of patient's genetic and lifestyle facts and other determinants namely diet and exercise habits. Several methods were reported as an attempt to determine the best indicator of maturation over the years. These methods include sexual maturation (Beunen et al., 2006; Takahashi et al., 2019), dental eruption and/or calcification stages (Demirjian et al., 1973, Demirjian & Goldstein, 1976; Demirjian et al.,1985; Mendes et al., 2010; Nolla, 1960), hand wrist maturation (HWM) (Fishman, 1982; Tanner, 1962; Tanner et al., 1977; Tanner et al., 2001), cervical vertebrae (Baccetti et al., 2002, Baccetti et al., 2005; Hassel & Farman, 1995; McNamara & Franchi, 2018) and biomarkers (Gupta et al., 2012; Himes et al., 1993; Jazwinski & Kim, 2019; Jylhävä et al., 2017).

The craniofacial skeletal maturation is driven by genetic factors, ethnicity, gender, and other factors (Roosenboom et al., 2016), and therefore the timing of patient's growth can occur in different chronological ages. As aforementioned, the biological age should always be considered, to produce the most accurate diagnosis and treatment plan in the orthodontic field.

1.2. Methods to assess craniofacial skeletal maturity

Skeletal maturity is a developmental measure that considers the size, shape, and degree of mineralization of bone (Middleditch, 2010). The determination of skeletal maturity permits to ascertain how close a bone is to its full maturity, and this is fundamental in orthodontics. Many orthodontic steps, such as diagnosis, etiology, modality of treatment and timing of treatment depend on how mature a bone is (Patel & Patel, 2018).

We currently have several bones to estimate skeletal maturity such as hand, cervical vertebrae, foot, knee, elbow, shoulder (Dhiman et al., 2015), middle phalanx of hand's third finger (Leite et al., 1987) or midpalatal suture (Korbmacher et al., 2007). Despite all the previously mentioned bones could be used to estimate skeletal maturation, hand-wrist and cervical vertebrae are those which are widely explored (Dhiman et al., 2015).

Greulich and Pyle (1950) proposed a method to estimate maturation through the hand and wrist skeletal using standard radiographic (X-ray). Despite that, this method has been considered poorly reliable because of subjectivity in their interpretation (Chalala, 2010). Also, the Greulich and Pyle (1950) method showed poor representativeness (Loder et al., 1993).

Later, Tanner (1962) proposed a new classification using specific ossifications from hand and wrist through three distinct scoring systems: 1) the carpals: Tanner Whitehouse (TW) – carpus; 2) radius and ulna and finger bones: TW – Radius, Ulna and Short Tubular Bones (RUS); and 3) fusion of both the carpals with radius and ulna: TW-20 (Tanner, 1962; Tanner et al., 1977; Tanner et al., 2001). Nevertheless, this was reviewed and adjustments were performed (Chalala, 2010; Tanner, 1962; Tanner et al., 1977; Tanner et al., 2001).

Singer also proposed six stages attributing distinct characteristics based on the hand-wrist complex: 1) stage one or early; 2) stage two or prepubertal; 3) stage three or pubertal onset; 4) stage four or pubertal; 5) stage five or pubertal deceleration; and 6) stage six or growth completion (Singer, 1980).

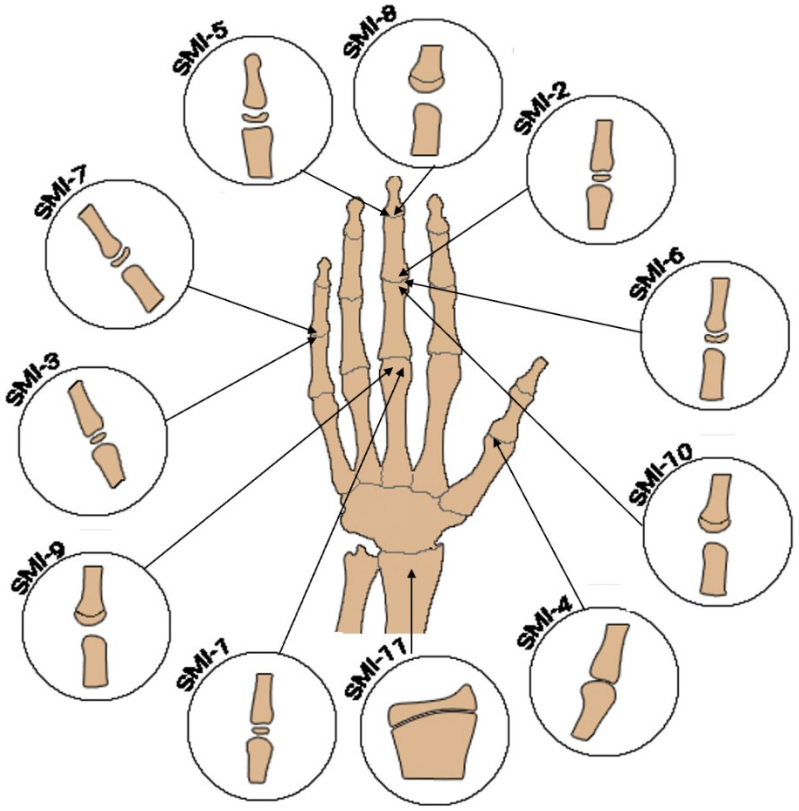
In 1982, Fishman proposed a new method of skeletal maturity indicators (SMI) using X-ray from the hand-wrist, focusing on carpal bones and ossifications (Fishman, 1982). Fishman considered six points on these fingers: thumb, third finger, fifth finger and radius, to evaluate through this method. Overall, eleven stages for hand wrist ossification were presented and could be divided into four groups (Fishman, 1982). SMI has four different phases: 1) Width of epiphysis as wide as diaphysis; 2) Ossification; 3) Capping of epiphysis; and 4) Fusion of epiphysis and diaphysis. The first phase is a progressive evaluation which begins with a little center of ossification in diaphysis. Ossification of adductor sesamoid of thumb, the second phase, comes up as a small point near the ossification center and the junction of epiphysis and diaphysis of the proximal phalanx. Capping, the third phase, happens in a transition phase between widening and fusion of epiphysis and diaphysis. The last phase of skeletal maturation, which corresponds to the fusion between epiphysis and diaphysis, begins in the center and continues until these two bones fuse into one (Fishman, 1982).

In this classification, there are 6 anatomical points (third finger [proximal, middle, distal phalanx], fifth finger [middle phalanx], adductor sesamoid of thumb and radius). In turn all of them are divided into 11 stages which covers the entire period of puberty (Table 1 and Figure 1).

Table 1. Description the of the skeletal maturation indicators. Adapted from Fishman (1982).

Skeletal Maturity Indicators	
Width of epiphysis as wide as diaphysis	
SMI 1	Third finger – Proximal phalanx
SMI 2	Third finger - Middle phalanx
SMI 3	Fifth finger - Middle phalanx
Ossification	
SMI 4	Adductor sesamoid of thumb
Capping of epiphysis	
SMI 5	Third finger – Distal phalanx
SMI 6	Third finger – Middle phalanx
SMI 7	Fifth finger – Middle phalanx
Fusion of epiphysis and diaphysis	
SMI 8	Third finger – Distal phalanx
SMI 9	Third finger – Proximal phalanx
SMI 10	Third finger – Middle phalanx
SMI 11	Radius

SMI - Skeletal Maturity Indicators.



SMI - Skeletal Maturity Indicators.

Figure 1. The maturation of hand wrist through Fishman (1982) method. Adapted from Fishman (1982).

Nowadays, the Fishman's method is not the most used, however it was the standard method before cervical vertebral maturation (CVM) (Baccetti et al., 2002, Baccetti et al., 2005; Fishman, 1982; Hassel & Farman, 1995).

Each hand-wrist method requires additional radiation (Hashim et al., 2018) and are subjective approaches which lead to different rising techniques based on alternative parts of the skeleton. In this sense, the cervical vertebrae gained some interest through the appearance of the CVM method (Baccetti et al., 2002, Baccetti et al., 2005; Hassel & Farman, 1995).

This thesis solely focused on the association between CVM method and chronological age, hence the remaining information is about the CVM method to determine skeletal age, and the chronological age associated with each CVM stage. We will also describe the validity and reliability of CVM method.

1.3. CVM method

The CVM method aims to determine the specific maturational degree of a patient at a specific period during the growth process (McNamara & Franchi, 2018). This method focuses on cervical bone maturation, avoiding the limitations of age as a developmental indicator (Predko-Engel et al., 2015). Each person grows in a different pace, precluding maturity determination using the chronological age (Baccetti et al., 2006).

In an attempt to decrease the use of X-ray incidence (O'Reilly & Yanniello, 1988), Todd, Pyle, Lanier and Taylor proposed an alternative procedure to measure the inferior vertebrae as a way to evaluate skeletal age (Lanier, 1939; Taylor, 1975; Todd & Plye, 1928).

To replace the HWM method, in 1972, Lamparski developed another method using the lateral cephalometric X-ray, mostly used in orthodontics diagnosis. The maturational stages of cervical vertebrae are based on the ratio of vertebral bodies and the depth of the curvature of the inferior part of the vertebrae body. In other words, the CVM method is a visualized diagnostic approach based on two-dimensional cephalogram to determine the maturation according with the second (C2), third (C3), fourth (C4), fifth (C5) and sixth (C6) cervical vertebrae (Lamparski, 1972). The atlas (first cervical vertebrae) is excluded from this evaluation (Dhiman et al., 2015), although there is not a specific reason for this exclusion. However, some authors advance the possibility that there might be a different ontogenetic trajectory (Chatzigianni & Halazonetis, 2009). After the cervical vertebrae X-ray examination, six maturational stages can be defined in this classification (Lamparski, 1972).

The reliability of Lamparski's method was verified and was used as a biological indicator of skeletal maturity (Mânica & Liversigde, 2017). This was the first author that successfully developed a cervical vertebrae maturation indicator (CVMI) (Dhiman et al., 2015).

In the following subsections, we present a historical point of view of CVM methods (Baccetti et al., 2002, Baccetti et al., 2005; Hassel & Farman, 1995). All in all, the Baccetti et al. (2005) method is considered the gold standard technique towards clinical practice and presents higher reliability than the HWM (McNamara & Franchi, 2018; Perinetti et al., 2014).

1.3.1. Hassel and Farman's method (1995)

Later, the Fishman's staging was adapted by Hassel and Farman (1995) establishing a relation between CVM stages and SMI stages (Table 3). This method was based on the analysis of the second (C2), third (C3) and fourth (C4) cervical vertebrae and 6 stages of CVMI were proposed (Table 2 and Figure 2). The vertebras used are the ones which are visible in X-Ray after shielding the patient from radiation with the thyroid collar (Sansare et al., 2011). This method confirms what was stated by Lamparski, except for the shrinking of intervertebral space as age progresses (Hassel & Farman, 1995).

Table 2. Description of cervical vertebral maturation based on Hassel and Farman (1995) method. Adapted from Hassel and Farman (1995).

Cervical Vertebral Maturation Stages	Description
CVMI 1 | Initiation	✓ Lower part of C2, C3 and C4 is plane ✓ The lower part of the vertebrae was losing width from posterior to anterior
CVMI 2 | Acceleration	✓ A concavity arises in the lower part of C2, C3 and C4 ✓ C4 remains flat ✓ The bodies of C3 and C4 becomes more rectangular
CVMI 3 | Transition	✓ The lower part of C2 and C3 have a distinct concavity ✓ The concavity of C4 arises in the inferior part of the vertebra ✓ The vertebras C3 and C4 have a rectangular body shape
CVMI 4 | Deceleration	✓ C2, C3 and C4 have a concavity on the inferior part of vertebras ✓ The body of C3 and C4 becomes a square shape
CVMI 5 | Maturation	✓ The lower part of C2, C3 and C4 have an accentuated concavity ✓ C3 and C4 are almost square shaped
CVMI 6 | Completion	✓ There are deep concavities in the inferior part of vertebras C2, C3 and C4 ✓ C3 and C4 have either a rectangular shape where height is larger than length or squared shaped

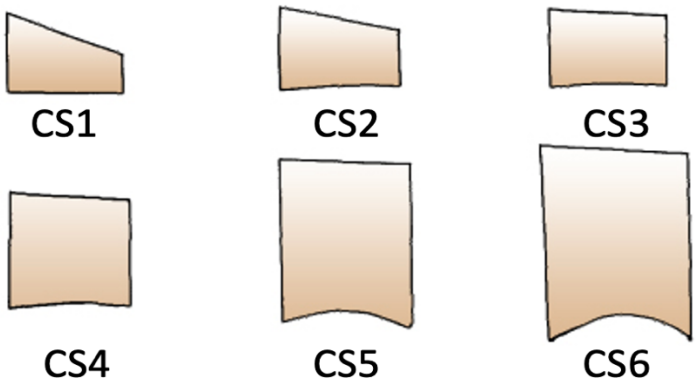
C2 – Second Cervical; C3 – Third Cervical; C4 – Fourth Cervical; CVMI – Cervical Vertebral Maturation Indicator.

Table 3. Description of the relation between cervical vertebral maturation based on Hassel and Farman (1995) method and skeletal maturation indicators based on Fishman (1982) method. Adapted from Hassel and Farman (1995).

Cervical Vertebral Maturation Stages	Fishman's Stages
CVMI 1	Corresponds to stage 1 and 2
CVMI 2	Corresponds to stage 3 and 4
CVMI 3	Corresponds to stage 5 and 6

CVMI 4	Corresponds to stage 7 and 8
CVMI 5	Corresponds to stage 9 and 10
CVMI 6	Corresponds to stage 11

CVMI – Cervical Vertebral Maturation Indicator.



CS – Cervical Stage.

Figure 2. The maturation of cervical vertebrae through Hassel and Farman (1995) method. Adapted from Hassel and Farman (1995).

1.3.2. Baccetti, Franchi and McNamara's method (2002)

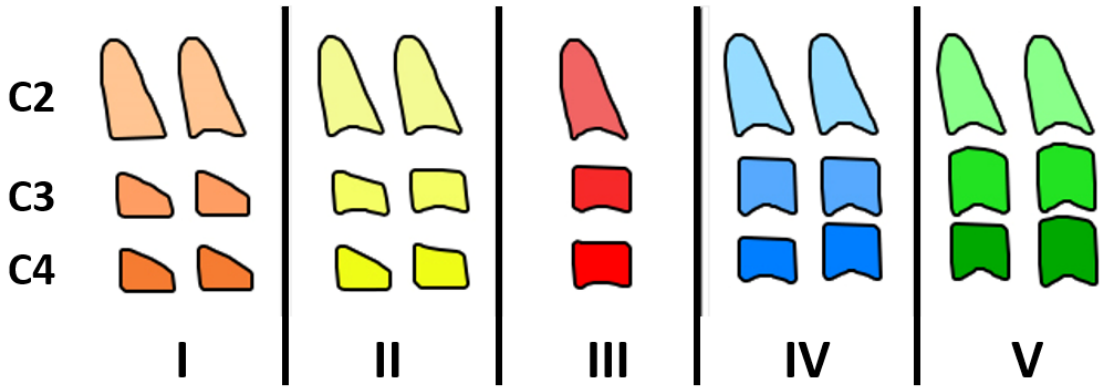
In 2002, Baccetti, Franchi and McNamara proposed an alternative classification of cervical vertebral maturation stages (CVMS). Five stages have been proposed on this classification (Table 4), which meant that the first stage of Baccetti et al. (2002) corresponds to stages 1 and 2 of the method proposed by Lamparski (1972), and every stage after corresponds to Lamparski's scale plus one (Figure 3). This method also has a substantial difference like Hassel and Farman's method, since it only requires C2, C3 and C4 to evaluate CVM, due to the use of thyroid collar, used to protect from radiation (Baccetti et al., 2002; Sansare et al., 2011). The method is also establishing a relation with skeletal maturity of the mandible (Table 5) instead of HWM, as was common among the previous methods. Nevertheless, this method is inadequate in younger children with less than 5-years old, due to the lack of clinical cooperation (Chalala, 2010).

Table 4. Description of cervical vertebral maturation based on Baccetti et al. (2002) method. Adapted from Baccetti et al. (2002).

Cervical Vertebral Maturation Stage	**Description**
CVMS I	✓ The inferior part of C2, C3 and C4 bodies are flat. However, sometimes the lower part of C2 could present a concavity ✓ The bodies shapes of C3 and C4 are trapezoid in form
CVMS II	✓ There are concavities on the lower part of C2 and C3

	✓ The bodies of C3 and C4 could be either shaped similarly to a trapezoid or appeared to be more rectangular in length
CVMS III	✓ There are concavities on the lower part of C2, C3 and C4 ✓ The bodies of C3 and C4 have a rectangular horizontal form
CVMS IV	✓ The concavities in the lower part of the vertebras remain present ✓ The bodies of C3 and C4 assume a square shape or remain in a rectangular horizontal form
CVMS V	✓ The concavities in the lower part of the vertebra's bodies are still evident ✓ The bodies of C3 and C4 becomes rectangular vertical in shape, either that or it will be squared shaped

C2 – Second Cervical; C3 – Third Cervical; C4 – Fourth Cervical; CVMS – Cervical Vertebral Maturation Stage.



C2 – Second Cervical; C3 – Third Cervical; C4 – Fourth Cervical.

Figure 3. The maturation of cervical vertebrae through Baccetti et al. (2002) method: Cervical vertebrae maturation stages (CVMS) – I, II, III, IV, V. Adapted from Baccetti et al. (2002).

Table 5. The skeletal maturity of mandible on each stage of cervical vertebral maturation of Baccetti et al. (2002) method. Adapted from Baccetti et al. (2002).

Cervical Vertebral Maturation Stage	**Skeletal Maturity of Mandible**
CVMS I	The peak of mandibular growth will not happen in the year after this stage
CVMS II	The peak of mandibular growth will happen during the next year after this stage
CVMS III	The peak of mandibular growth happened between one or two years prior to this stage
CVMS IV	The peak of mandibular growth happened in the year prior to this stage
CVMS V	The peak of mandibular growth happened in the two years before this stage

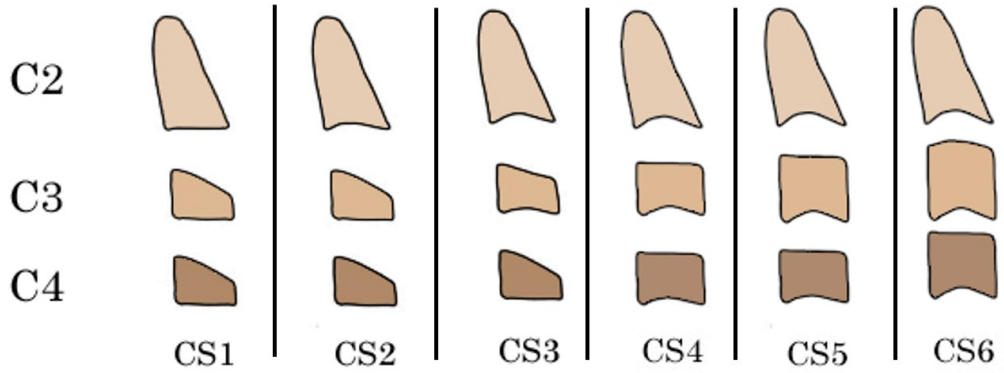
CVMS – Cervical Vertebral Maturation Stage.

1.3.3. Baccetti, Franchi and McNamara's method (2005)

As aforementioned, this method is considered as a user guide in clinical practice (Jaqueira et al., 2010; McNamara & Franchi, 2018; Perinetti et al., 2014). This method was developed based on Lamparski (1972) method. Equal to Lamparski method, Baccetti et al. (2005) also as a 6 cervical stages (CS) classification and evaluates the vertebrae C2, C3 and C4 (Table 6). However, Baccetti et al. (2005) uses the CVM to evaluate mandibular skeletal maturity, so the total mandibular length (Condilary – Gnathion) (Co – Gn) is measured on each patient. The peak of mandibular maturity is illustrated on table 7 according to CVM stage. On CVM, the main characteristic evaluated is the concavity in the inferior border of the third vertebra. Baccetti et al. (2005) adds a special attention to the body shape of the vertebras (Figure 4 and 5).

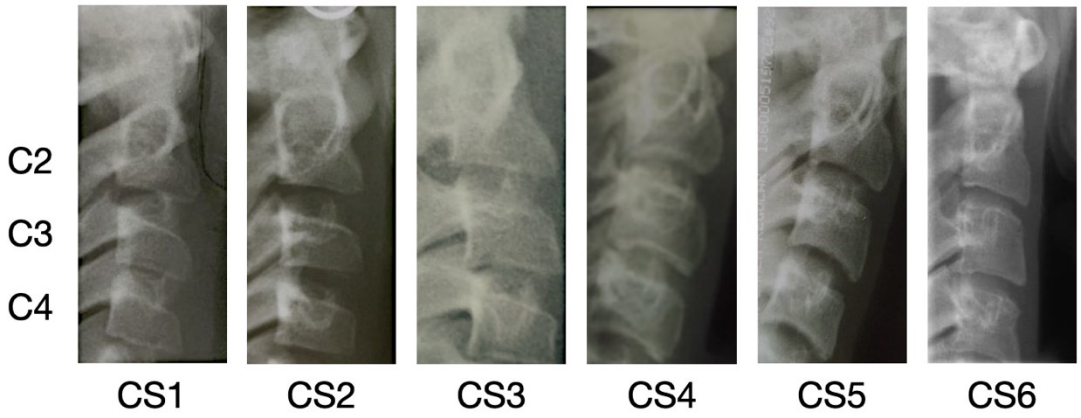
Table 6. Description of cervical vertebral maturation based on Baccetti et al. (2005) method. Adapted from Baccetti et al. (2005).

Cervical Vertebral Maturation Stages	**Description**
CS1	✓ The lower borders of C2, C3 and C4 are flat ✓ The bodies of C3 and C4 are trapezoid shaped (the upper part of the vertebral body is tapered from posterior to anterior)
CS2	✓ There is a concavity in the lower border of C2 ✓ The bodies of C3 and C4 remain in a trapezoidal shape
CS3	✓ Both C2 and C3 show a concavity in the lower border of their bodies ✓ The bodies of C3 and C4 can either present a rectangular or trapezoidal shape
CS4	✓ There are concavities in lower bodies of C2, C3 and C4 ✓ The body shape of C3 and C4 is a horizontal rectangle
CS5	✓ The concavities in the lower borders of C2, C3 and C4 remain ✓ The body shape of C3 and C4 is either square in shape or remains rectangular horizontal
CS6	✓ The concavities in the inferior part of the bodies of C2, C3 and C4 prevail ✓ At least one of the bodies of C3 and C4 is rectangular vertical shaped, the other could either be a rectangle as well or squared shaped instead



C1- First Cervical; C2 – Second Cervical; C3 – Third Cervical; C4 – Fourth Cervical; CS – Cervical Stage.

Figure 4. The maturation of cervical vertebrae through Baccetti et al. (2005) method: Cervical vertebrae maturation (CVM) - I, II, III, IV, V, VI. Adapted from Baccetti et al. (2005).



C1- First Cervical; C2 – Second Cervical; C3 – Third Cervical; C4 – Fourth Cervical; CS – Cervical Stage.

Figure 5. The maturation of cervical vertebrae through Baccetti et al. (2005) method: Radiographic (X-ray) images of cervical vertebrae maturation (CVM) - I, II, III, IV, V, VI. Adapted from Baccetti et al. (2005).

Table 7. The skeletal maturity of mandible on each stage of cervical vertebral maturation of Baccetti et al. (2005) method. Adapted from Baccetti et al. (2005).

Cervical Vertebral Maturation Stages	**Skeletal Maturity of Mandible**
CMV I	The peak of maturity will mostly occur in a period of two years following this stage
CMV II	The peak of maturity will mostly occur in a period of one year following this stage
CMV III	The peak of maturity will mostly occur in the year after this stage
CVM IV	The peak of maturity occurred one or two years previous to this stage

CVM V	The peak of maturity occurred in a period of one year or more previous to this stage
CVM VI	The peak of maturity occurred in a period of two years or more previous to this stage

CVM – Cervical Vertebral Maturation.

1.4. Reliability of CVM

The CVM method was developed recently, so it is important to evaluate if the results obtained are reliable through the comparison with the HWM method. Heretofore HWM, a method that determines skeletal maturation, was used as the main indicator of biological age. However, this method requires more exams, which consequently exposes the patient to extra radiation (Wong et al., 2009). Hence, there was a necessity to explore other options. Several studies have investigated the reliability of CVM methods (Cericato et al., 2015; Ferrillo et al., 2021; Szemraj et al., 2018), so that in the future they might replace the HWM.

Cericato et al. (2015) pretends to collate the reliability of CVM through the comparison with HWM. The methods used to evaluate CVM were Hassel and Farman (1995) and Baccetti et al. (2002), which demonstrated a positive correlation among them and with HWM methods. When gender separation was performed, a higher relation was confirmed in Hassel and Farman (1995) method. However, when it was not separated by sex, a superior relation was observed with the Baccetti et al. (2002) method.

In the other systematic review (SR) (Szemraj et al., 2018), the conclusion was the same, the CVM method is reliable and can replace the HWM. The classification used to evaluate CVM was Baccetti et al. (2002).

On Ferrillo et al. (2021), the purpose of the study was the same, however the methods used to evaluate CVM in this article are Baccetti et al. (2005) method and Hassel and Farman (1995) method. On this article, several methods were used to evaluate HWM (Björk & Helm, 1967; Fishman, 1982; Grave & Brown, 1976; Hägg & Taranger, 1982), the majority of these methods presented a high or significant correlation between them and CVM (Baccetti et al., 2005). The Grave & Brown (1976) method showed no correlation to the CVM method evaluated (Ferrillo et al., 2021).

There is still another SR (Santiago et al., 2012) which evaluates the CVM method, however in this one, the CVM method was not considered reliable to evaluate skeletal age. It is also important to note that the studies included on this SR presented low quality.

In the literature, some of the existent reviews (Cericato et al., 2015; Ferrillo et al., 2021; Szemraj et al., 2018) only evaluate the reliability of CVM methods through comparison of HWM methods. However, there is not any review evaluating the association of chronological age in each stage of CVM. As mentioned before, in the orthodontic area, the orthodontic's treatment timing is fundamental. Thus, it would be helpful to have an estimation of chronological age in each CVM, and therefore this SR review will be the first reporting this information.

1.5. Aims

This SR aims to determine interval ages for each CVM stage according to the classification proposed by Baccetti et al. (2005).

As secondary aims, we explored the effect of sex and geographic location for each CVM stage.

II. MATERIALS AND METHODS

2.1. Protocol and registration

This SR was defined *a priori*, and the protocol was registered at the National Institute for Health Research PROSPERO, International Prospective Register of SR (http://www.crd.york.ac.uk/PROSPERO, ID Number: CRD42021225422. We based our review on Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) (Liberati et al., 2009).

2.2. Focused question and eligibility criteria

We developed a protocol to answer the following PECO questions:

(1) "What is the chronological age associated with each CVM stage? and

(2) "Is there a sex-based and difference in timing of each CVM stage?"

Each question had the respective statements as follows:

(1) Children, adolescents and young adults (Population, P); Lateral cephalometric X-ray or cranium Cone Beam Computerized Tomography (CBCT) (Exposure, E); Chronological age (Comparison, C); chronological age classified into CVM stages (Outcome, O).

(2) Female children, adolescents and young adults (Population, P); Lateral cephalometric X-ray or CBCT of cranium (Exposure, E); Male Children, adolescents and young adults (Comparison, C); chronological age classified into CVM stages (Outcome, O).

Observational studies (case-control, cross-sectional and longitudinal) or interventional studies (randomized clinical trials [RCTs] and non-RCTs) in otherwise healthy humans assessing chronological age related with CVM method on lateral cephalometric X-ray or CBCT of cranium were eligible for inclusion. Only articles in which the CVM is based on Baccetti et al. (2005) method are included.

2.2.1. Exclusion criteria

Non-human studies (animal studies or in-vitro studies), non-original studies (reviews, author responses, comments) or secondary research (SR and meta-analysis), case reports

or case series, thesis, book chapters, editorials, conference papers, meeting abstracts and patents were excluded.

2.3. Information sources search and study selection

To establish potentially relevant studies reporting data related CVM methods and chronological age, we developed detailed search strategies for each database. Medical Literature Analysis and Retrieval System Online (MEDLINE - via PubMed), Scopus, *Literatura Latino-americana e do Caribe em Ciências da Saúde* (LILACS), Google Scholar, Cochrane Central Register of Controlled Trials (CENTRAL) databases were searched up to July 2021. Our PubMed search strategy was based on the algorithm: ['Cervical vertebral maturation' OR 'Baccetti's Method' OR 'Chronological age']. Also, grey literature was searched through databases and appropriate registers. No restrictions were applied concerning the publication year or the language. Study selection was assessed independently by two independent authors (M.I.M and V.M), who assessed the titles and/or abstracts of retrieved articles. Any study classified as potentially eligible was screened by the reviewers. Any disagreements were verified and resolved by discussion with a third author (A.S.D.) Inter-examiner reproducibility was calculated following full-text assessment via kappa statistics.

2.4. Data extraction process and data items

We used an electronic table to record patient and study characteristics: first author's name, project funding, location of the study, year of publication, design study, records years, X-ray method, patient's characteristics (total number of participants, total number divided by sex and mean chronological age). All data were extracted independently by two authors (M.I.M and V.M), and any disagreements were resolved by discussion with a third author (A.S.D). The authors of the studies were contacted when there was missing information or additional clarifications were required.

2.5. Risk of bias (RoB) in individual studies

Two researchers (M.I.M and V.M) independently assessed the methodological quality of the included studies, following the quality assessment modified from the Strengthening

the Reporting of Observational Studies in Epidemiology (STROBE) (https://www.equator-network.org/reporting-guidelines/strobe/) (Elm et al., 2014), Standards for the Reporting of Diagnostic Accuracy Studies (STARD) (Bossuyt et al., 2003), and (Lagravere et al., 2005). This adaptation of the assessment tool was previously published in a SR (Santiago et al., 2012). The items on the checklist were as follows: "*1) Are the objectives clearly formulated?; 2) Are there key elements of study design early in the paper?; 3) Was the sample size calculated?; 4) Does the study report demographic characteristics of the study population?; 5) Were the sample selection criteria clearly described?; 6) Does the study describe specifications of material and methods involved including how and when measurements were taken?; 7) Was there a reliability assessment, with adequate level of agreement intraexaminer or/and interexaminer?; 8) Were there blinding measurements?; 9) Does the study give details of methods of assessment (measurements) for each variable of interest?; 10) Was there a complete and adequate reporting of results, with self-explanatory tables and figures?; 11) Was there a statistical analysis appropriate for data?; 12) Was the P value stated or confidence intervals provided?"* (Santiago et al., 2012). Each item was scored using a 2-point scale: 0 - *not reported or reported inadequately;* and 1 - *reported and adequate*. Studies with eleven to 11 points were considered to be of high quality, studies with 7 to 10 were of medium quality and studies with 0 to 6 points were of low quality. Discussion resolved the disagreements between the review authors (M.I.M and V.M.) over the quality assessment in any studies, with the involvement of a third review author where necessary (A.S.D.).

On these questions (used to evaluate RoB), different aspects were analysed. On questions number 1 and 2, the answer was considered "yes" when the articles presented the objectives pretended to the study. On question number 3, when the study describes the method used to calculate the sample size (to verify the representative of the population), the answer considered is "yes". On question number 4, the answer was considered "yes" when the description of the location where the study was realized was present. On question 5, the answer was considered "yes" when the selection criteria to include the patients was described. On question 6, when the machines, radiation and other parameters used to evaluate the variables of each study are described, the answer is "yes". On question 7, the answer is "yes" when the agreement between intraexaminator/interexaminator is stated, and the respective values of statistics tests are

also present. On question 8, the answer is "yes" when the examiners of the studies are blinded. On question 9, when the methods used to evaluate the variables of each study are described, the answer is "yes". On question 10, the answer is "yes" when the studies report the results on text or figures/tables. On question 11, the answer is "yes" when the statistics tests used are reported on the study. On the last question, question number 12, the answer is "yes" when the p-value and confidence interval (CI) is reported on the study.

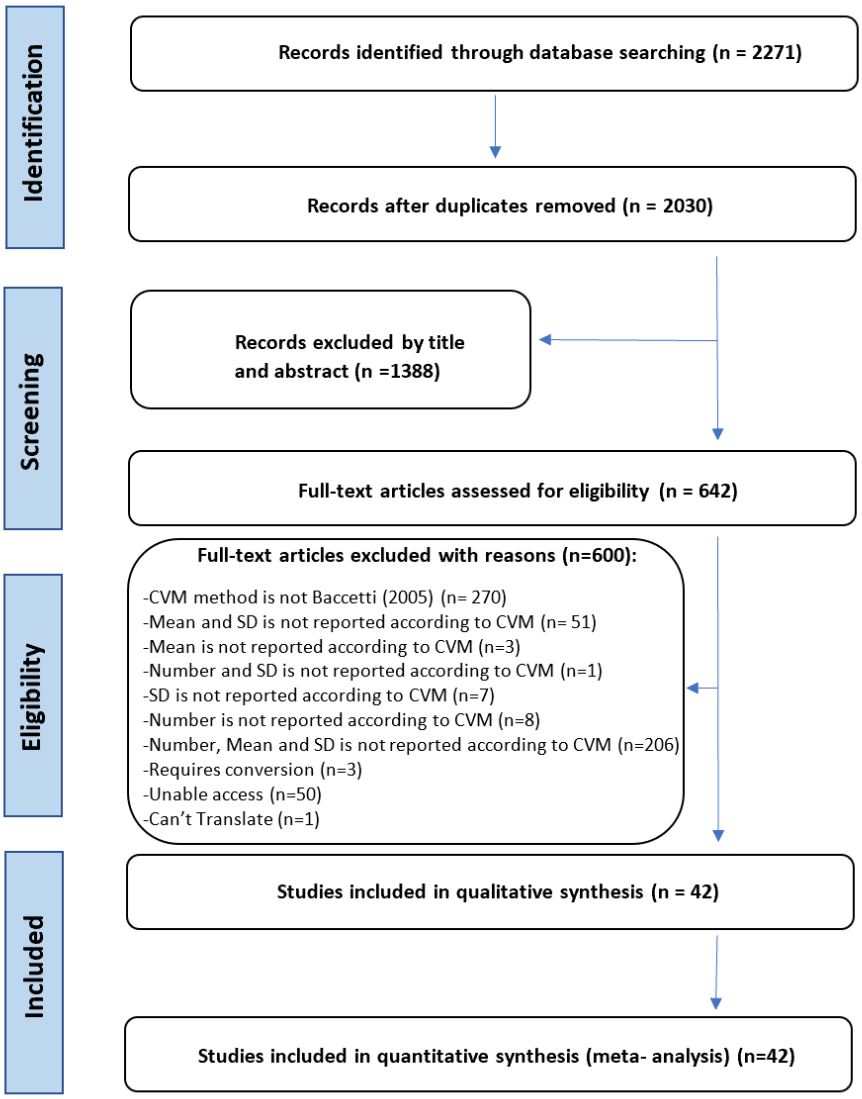
2.6. Summary measures and synthesis of results

For continuous data, mean values and standard deviations (SD) were collected from each article to a predefined table prepared to calculate the quantity of data. Studies that reported median and interquartile range, mean and SD were converted following Hozo's formula (Hozo et al., 2005). The random-effects of single means meta-analysis and forest plots were calculated in R version 3.4.1 (R Studio Team 2018) using the 'meta' package, using DerSimonian-Laird random-effects meta-analysis (Schwarzer, 2007; Schwarzer et al., 2015). To assessed sources of heterogeneity, meta-regression analysis was conducted for each sex. We assessed statistical heterogeneity using I^2 index and Cochrane's Q statistic ($p<0.1$). Chi-square (χ^2) test calculated overall homogeneity (Higgins et al., 2019). All tests were two-tailed with alpha set at 0.05 except for the homogeneity test whose significance level cut off was 0.10. Overall estimates were reported with 95% CI. For meta-analysis including at least 10, we analysed publication bias (Higgins & Green, 2011). Firstly, we started by conducting an *a priori* sensitivity analysis (in the form of subgroup analyses) comparing the impact of studies with low methodological quality with studies with moderate/high quality. If the results in terms of significance were different, only studies with moderate to high quality were included in this specific analysis.

III. RESULTS

3.1. Study selection

The electronic search strategy retrieved a total of 2271 possible relevant articles. After duplicate removal (241 articles), 2030 studies were screened according to the eligibility criteria. Among these, 1388 articles were excluded after title and/or abstract evaluation. After these 600 articles were excluded (reasons for exclusion is referred in PRISMA). A total of 42 studies were included for qualitative synthesis (Figure 6).



CVM - Cervical Vertebral Maturation; SD – Standard Desviation.

Figure 6. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart of studies inclusion.

Some articles (n=270) were excluded due to using another method to evaluate CVM. Some of the articles, around 276 were excluded because they did not report one of the items: the number, average, SD or median and Upper/Lower. Three of the articles (Azevedo et al., 2018; Choudhury et al., 2019, Lajolo et al., 2013) were excluded because it was not possible to convert the values presented. There is one article which is excluded because it is not possible to translate (Abesi et al., 2015). We tried to contact the authors, but it was not possible to obtain additional clarifications. Around 50 articles were excluded due to inability to access.

3.2 Study characteristics

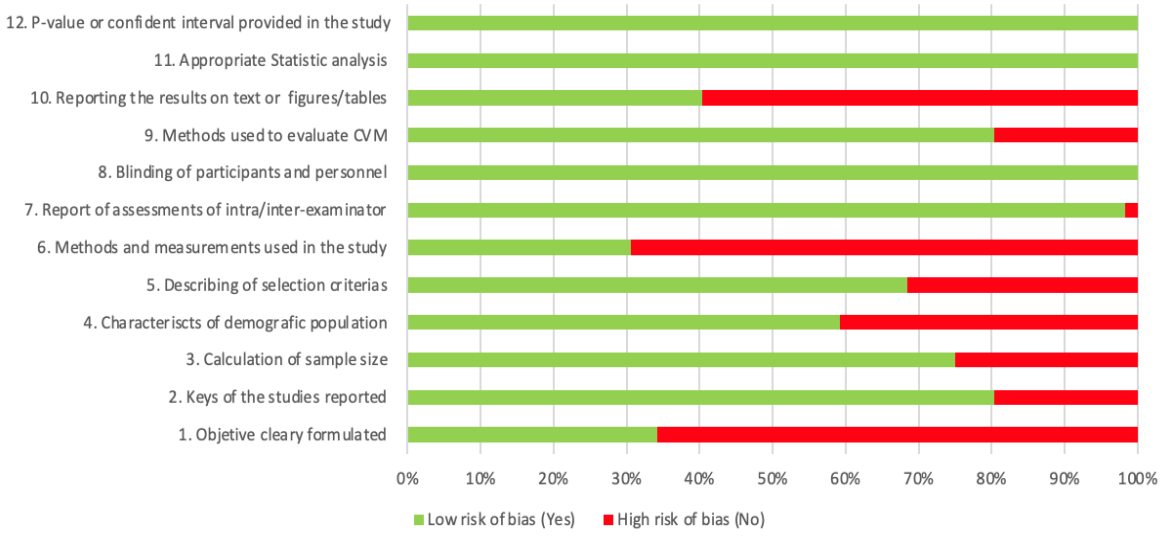
Table 8 summarises the characteristics of the included studies. In total, 10272 participants were included (4301 men, 5971 women). However, eight studies lacked gender information (Flieger et al., 2018; Gu & McNamara, 2007; Hussain et al., 2013; Kuc-Michalska & Baccetti, 2010; Perinetti et al., 2011; Rodríguez et al., 2016; Salazar-Lazo et al., 2014; Wijaya et al., 2017). In addition, thirteen studies were performed in Europe (Flieger et al., 2018; Folmer et al., 2021; Folmer et al., 2021; Hosni et al., 2018; Kalinowska et al., 2011; Kuc-Michalska & Baccetti, 2010; Maló et al., 2014; Moca et al., 2021; Oncan & Akan, 2021; Panainte et al., 2016; Perinetti et al., 2011; Perinetti et al., 2016; Schoretsaniti et al., 2021) and nine articles in America (Carbonel & Reyes, 2013; Flores et al., 2014; Gu & McNamara, 2007; Oyonarte et al., 2020; Perinetti et al., 2017; Rodríguez et al., 2016; Salazar-Lazo et al., 2014; Vilchez et al., 2020; Vuong & Kang, 2021). Only two studies were realized in Africa (El-Bakary & El-Atta, 2018; Hasan & Abuaffan, 2016). Eighteen studies were performed in Asia (Al-Aunhomi et al., 2020; Baidas, 2012; Banda et al., 2020; Chen et al., 2010; Dadgar et al., 2020; Felemban, 2017; Felemban, 2017; Ghaleb et al., 2019; Giri et al., 2016; Hussain et al., 2013; Kumar et al., 2017; Lai et al., 2008; Lai et al., 2008; Mini et al., 2017; Mollabashi, 2019; Vijayashree et al., 2014; Wijaya et al., 2017; Zahid et al., 2021). There aren't any studies performed in Oceania. Only three articles report their funding.

3.3. Risk of bias

Among the included studies, only one was considered as high quality (Folmer et al., 2021). Forty studies (Al-Aunhomi et al., 2020; Baidas, 2012; Banda et al., 2020; Carbonel & Reyes, 2013; Chen et al., 2010; Dadgar et al., 2020; El-Bakary & El-Atta, 2018;

Felemban, 2017; Felemban, 2017; Flieger et al., 2018; Flores et al., 2014; Folmer et al., 2021; Ghaleb et al., 2019; Giri et al., 2016; Gu & McNamara, 2007; Hasan & Abuaffan, 2016; Hosni et al., 2018; Hussain et al., 2013; Kalinowska et al., 2011; Kumar et al., 2017; Lai et al., 2008; Lai et al., 2008; Maló et al., 2014; Mini et al., 2017; Moca et al., 2021; Mollabashi, 2019; Oncan & Akan, 2021; Oyonarte et al., 2020; Panainte et al., 2016; Perinetti et al., 2011; Perinetti et al., 2016; Perinetti et al., 2017; Rodríguez et al., 2016; Salazar-Lazo et al., 2014; Schoretsaniti et al., 2021; Vijayashree et al., 2014; Vilchez et al., 2020; Vuong & Kang, 2021; Wijaya et al., 2017; Zahid et al., 2021) were considered as moderate quality, and one study (Kuc-Michalska & Baccetti, 2010) was considered as low quality.

More specifically, thirty-eight studies reported specifically the location in which these studies were developed. Furthermore, only 9 studies (Dadgar et al., 2020; Folmer et al., 2021; Ghaleb et al., 2019; Giri et al., 2016; Kumar et al., 2017; Mollabashi, 2019; Oyonarte et al., 2020; Salazar-Lazo et al., 2014; Vilchez et al., 2020) report the sample size calculation. Most of the studies did not report strategies to minimize RoB (Figure 7).



CVM – Cervical Vertebral Maturation.

Figure 7. Quality appraisal of included observational studies (based on the points assigned to respective studies).

Table 8. Characteristics of included studies

N articles	Study (Author et al. Year) (Country)	Continent	Type of study	Records year	CBCT	Funding	Total Sample Size	Sample Size, Male/Female	Quality assessment
1	Al-Aunhomi et al., 2020 (Yemen)	Asia	Cross-sectional	2018	No	None	207	85/122	Moderate
2	Baidas, 2012 (Saudi Arabia)	Asia	Cross-sectional	NR	No	NR	214	104/110	Moderate
3	Banda et al., 2020 (Korea)	Asia	Retropective and cross-sectional	NR	No	NR	408	181/227	Moderate
4	Carbonel & Reyes, 2013 (Peru)	America	Retropective and cross-sectional	2011-2012	No	NR	150	74/76	Moderate
5	Chen et al., 2010 (China)	Asia	Retropective	2007-2008	No	Science and Tecnhology Bureau of Sichuan Province	302	134/168	Moderate
6	Dadgar et al., 2020 (Iran)	Asia	Cross-sectional	2019 (Aug-Oct)	No	Self-funded	224	112/112	Moderate
7	El-Bakary & El-Atta, 2018 (Egypt)	Africa	Retropective and cross-sectional	2013-2014	No	NR	148	68/80	Moderate
8	Felemban, 2017 (Saudi Arabia)	Asia	NR	NR	No	NR	405	150/255	Moderate
9	Felemban, 2017 (Saudi Arabia)	Asia	NR	NR	No	NR	405	150/255	Moderate
10	Flieger et al., 2018 (Poland)	Europe	NR	2014-2016	No	None	180	56/124	Moderate
11	Flores et al., 2014 (Peru)	America	Retrospective	NR	No	NR	264	109/155	Moderate
12	Folmer et al., 2021 (Poland)	Europe	Retropective and cross-sectional	2008-2018	No	Medical University of Gdansk	41	12/29	Moderate
13	Folmer et al., 2021 (Poland)	Europe	Retropective and cross-sectional	2008-2019	No	None	213	84/129	High
14	Ghaleb et al., 2019 (Lebanon)	Asia	Retropective and cross-sectional	Till year 2000	No	None	346	131/215	Moderate

15	Giri et al., 2016 (Nepal)	Asia	Cross-sectional	NR	No	NR	84	42/42	Moderate
16	Gu & McNamara, 2007 (USA)	America	Longitudinal	1970	No	NR	118	41/77	Moderate
17	Hasan & Abuaffan, 2016 (Sudan)	Africa	Retropective and cross-sectional	2009-2015	No	NR	112	47/65	Moderate
18	Hosni et al., 2018 (United Kingdom)	Europe	NR	2012-2014	No	NR	22	14/8	Moderate
19	Hussain et al., 2013 (India)	Asia	Cross-sectional	NR	No	NR	90	47/43	Moderate
20	Kalinowska et al., 2011 (Poland)	Europe	Retrospective	1994-2006	No	NR	718	287/431	Moderate
21	Kuc-Michalska & Baccetti, 2010 (Poland)	Europe	Cross-sectional	NR	No	NR	218	125/93	Low
22	Kumar et al., 2017 (India)	Asia	Cross-sectional	2016	No	None	300	137/163	Moderate
23	Lai et al., 2008 (Taiwan)	Asia	Cross-sectional	NR	No	NR	304	0/304	Moderate
24	Lai et al., 2008 (Taiwan)	Asia	Retropective and cross-sectional	1999-2006	No	NR	709	330/379	Moderate
25	Maló et al., 2014 (Portugal)	Europe	Cross-sectional	NR	No	NR	285	114/171	Moderate
26	Mini et al., 2017 (India)	Asia	Cross-sectional	2012-2013	No	None	100	46/54	Moderate
27	Moca et al., 2021 (Romania)	Europe	Retropective and cross-sectional	NR	No	None	252	74/178	Moderate
28	Mollabashi, 2019 (Iran)	Asia	Cross-sectional	NR	No	NR	600	224/376	Moderate
29	Oncan & Akan, 2021 (Turkey)	Europe	Retropective and cross-sectional	2018-2020	No	None	139	57/82	Moderate
30	Oyonarte et al., 2020 (Canada)	America	Retrospective and longitudinal	1952-1970	No	NR	360	180/180	Moderate

31	Panainte et al., 2016 (Romania)	Europe	Cross-sectional	NR	No	NR	221	75/146	Moderate
32	Perinetti et al., 2011 (Italy)	Europe	Prospective and Cross-sectional	NR	No	NR	72	27/45	Moderate
33	Perinetti et al., 2016 (Italy)	Europe	Cross-sectional	2009-2015	No	NR	320	160/160	Moderate
34	Perinetti et al., 2017 (USA)	America	Longitudinal	NR	No	NR	94	49/45	Moderate
35	Rodríguez et al., 2016 (Colombia)	America	Prospective	NR	No	NR	130	58/72	Moderate
36	Salazar-Lazo et al., 2014 (Peru)	America	Cross-sectional	NR	No	NR	154	84/70	Moderate
37	Schoretsaniti et al., 2021 (Greece)	Europe	Retropective and cross-sectional	NR	No	None	474	217/257	Moderate
38	Vijayashree et al., 2014 (India)	Asia	Cross-sectional	NR	No	None	101	47/54	Moderate
39	Vilchez et al., 2020 (Peru)	America	Retropective and cross-sectional	NR	No	NR	200	85/115	Moderate
40	Vuong & Kang, 2021 (USA)	America	Retropective and cross-sectional	NR	Yes	NR	420	210/210	Moderate
41	Wijaya et al., 2017 (Indonesia)	Asia	Cross-sectional	NR	No	NR	136	64/72	Moderate
42	Zahid et al., 2021 (China)	Asia	Cross-sectional	2010-2016	No	NR	32	10/22	Moderate

NR – Not Reported; CBCT – Cone Bean Computerized Tomography.

3.4. Characteristics of the studies

3.4.1. Mean age of cervical vertebrae maturity

Regarding the mean age and respective interval for each CVM stage (Table 9), CS1 stage had an estimated mean age of 9.7 years old (95% CI: 9.4-10.1, p<0.001, I^2=96.8%)(Supplementary Figures 1 and 2), CS2 stage had 10.8 years old (95% CI: 10.6-11.1, p<0.001, I^2=92.1%)(Supplementary Figures 3 and 4), CS3 stage had 12.0 years old (95% CI: 11.8-12.3, p<0.001, I^2=94.4%)(Supplementary Figures 5 and 6), CS4 stage had 13.4 years old (95% CI: 13.2-13.7, p<0.001, I^2=94.3%)(Supplementary Figures 7 and 8), CS5 stage had 14.8 years old (95% CI: 14.4-15.2, p<0.001, I^2=96.7%)(Supplementary Figures 9 and 10), and CS6 stage had 15.9 years old (95% CI: 15.3-16.4, p<0.001, I^2=98.0%)(Supplementary Figures 11 and 12).

Table 9. Estimates for each cervical vertebrae maturation stage.

CS	n	Age Mean (95% CI)	I^2 (%)	p-value	Egger test
1	31	9.7 (9.4-10.1)	96.8	<0.0001	0.2500
2	34	10.8 (10.6-11.1)	92.1		0.9301
3	40	12.0 (11.8-12.3)	94.4		0.1625
4	40	13.4 (13.2-13.7)	94.3		0.5143
5	34	14.8 (14.4-15.2)	96.7		0.1121
6	31	15.9 (15.3-16.4)	98.0		0.0951

CS – Cervical Stage; n – Number of Included Articles; CI – Confidence Interval.

3.4.2 Cervical vertebrae maturity according to sex

In what sex concerns, the mean age and respective interval for each CVM stage is presented for both females and males (Table 10). In the comparison between females and males, the estimates pointed to a significant difference in all stages, with females presenting a cervical maturation earlier than males (Table 11). In females (Table 10), CS1 stage had an estimate age of 9.1 years old (95% CI: 9.1-9.8, p<0.001, I^2=94,9%)(Supplementary Figures 13 and 14), CS2 stage had 10.4 years old (95% CI: 10.2-10.7, p<0.001, I^2=88.3%)(Supplementary Figures 15 and 16), CS3 stage had 11.3 years old (95% CI: 11.3-11.8, p<0.001, I^2=90.1%)(Supplementary Figures 17 and 18), CS4 stage had 13.2 years old (95% CI: 12.9-13.5, p<0.001, I^2=93.1%)(Supplementary Figures 19 and 20), CS5 stage had 14.6 years old (95% CI: 14.2-15.0, p<0.001,

I^2=94.5%)(Supplementary Figures 21 and 22) and CS6 stage had 15.7 years old (95% CI: 15.0-16.3, p<0.001, I^2=97.6%)(Supplementary Figures 23 and 24).

In males (Table 10), CS1 stage had 10.2 years old (95% CI: 9.8-10.6, p<0.001, I^2=94.1%)(Supplementary Figures 25 and 26), CS2 stage had 11.3 years old (95% CI: 10.9-11.6, p<0.001, I^2=91.5%)(Supplementary Figures 27 and 28), CS3 stage had 12.6 years old (95% CI: 12.3-13.0, p<0.001, I^2=94.2%)(Supplementary Figures 29 and 30), CS4 stage had 14.0 years old (95% CI: 13.7-14.3, p<0.001, I^2=90.1%)(Supplementary Figures 31 and 32), CS5 stage had 15.4 years old (95% CI: 15.0-15.8, p<0.001, I^2=92.8%)(Supplementary Figures 33 and 34) and CS6 stage had 16.6 years old (95% CI: 16.2-17.1, p<0.001, I^2=95.6%)(Supplementary Figures 35 and 36).

Table 10. Estimates for each cervical vertebrae maturation stage for females and males.

CS	Females					Males				
	n	**Age Mean (95% CI)**	**I^2 (%)**	**p-value**	**Egger test**	**n**	**Age Mean (95% CI)**	**I^2 (%)**	**p-value**	**Egger test**
1	25	9.1 (9.1-9.8)	94.9	<0.0001	0.6867	25	10.2 (9.8-10.6)	94.1	<0.0001	0.7140
2	27	10.4 (10.2-10.7)	88.3		0.6278	28	11.3 (10.9-11.6)	91.5		0.8350
3	33	11.3 (11.3-11.8)	90.1		0.3022	32	12.6 (12.3-13.0)	94.2		0.7890
4	33	13.2 (12.9-13.5)	93.1		0.0788	32	14.0 (13.7-14.3)	90.1		0.0467
5	29	14.6 (14.2-15.0)	94.5		0.6719	26	15.4 (15.0-15.8)	92.8		0.3678
6	26	15.7 (15.0-16.3)	97.6		0.2379	22	16.6 (16.2-17.1)	95.6		0.0890

CS – Cervical Stage; n – Number of Included Articles; CI – Confidence Interval.

On table 11, the difference between females and males was estimated, CS1 stage had 0.5 years old (95% CI: 0.4-0.7, p<0.001, I^2=40.7%), CS2 stage had 0.5 years old (95% CI: 0.4-0.7, p<0.001, I^2=51.7%), CS3 stage had 0.8 years old (95% CI: 0.8-1.0, p<0.001, I^2=56.0%), CS4 stage had 0.6 years old (95% CI: 0.6-0.7, p<0.001, I^2=70.2%), CS5 stage had 0.6 years old (95% CI: 0.6-0.8, p<0.001, I^2=54.8%) and CS6 stage had 0.5 years old (95% CI: 0.5-0.7, p<0.001, I^2=0%).

Table 11. Estimates comparing cervical vertebrae maturation between females and males.

CS	n	Females vs. Males SMD (95% CI)	I^2 (%)	p-value
1	24	0.5 (0.4-0.7)	40.7	<0.0001
2	26	0.5 (0.4-0.7)	51.7	
3	32	0.8 (0.8-1.0)	56.0	
4	32	0.6 (0.6-0.7)	70.2	
5	25	0.6 (0.6-0.8)	54.8	
6	22	0.5 (0.5-0.7)	0	

SMD - Standardized Mean Difference; CS – Cervical Stage; n – Number of Included Articles; CI – Confidence Interval.

3.4.3. Additional analyses

Publication bias was not noted in data (Table 11). Subgroup analyses accounting for the continent were performed based on the different continents where the articles were performed.

Observing the mean age and respective interval for each CVM stage (Table 12), CS1 stage in Europe had an estimated mean age of 9.7 years old (95% CI: 9.1-10.3, p<0.2321, I^2=94.3%), in America had an estimated mean age of 9.0 years old (95% CI: 8.0-10.0, p<0.2321, I^2=98.3%), in Asia had an estimated mean age of 10.1 years old (95% CI: 9.6-10.7, p<0.2321, I^2=97.1%) and in Africa had an estimated mean age of 9.3 years old (95% CI: 9.3-10.3, p<0.2321, I^2=0%). On the CS2 stage in Europe had an estimated mean age of 10.6 years old (95% CI: 10.0-11.1, p<0.0021, I^2=92.3%), in America had an estimated mean age of 10.2 years old (95% CI: 9.8-10.7, p<0.0021, I^2=81.6%), in Asia had an estimated mean age of 11.3 years old (95% CI: 10.9-11.7, p<0.0021, I^2=93.8%) and in Africa had an estimated mean age of 10.6 years old (95% CI: 10.1-11.0, p<0.0021, I^2=0%). On the CS3 stage in Europe had an estimated mean age of 11.6 years old (95% CI: 11.2-12.0, p<0.0011, I^2=92.7%), in America had an estimated mean age of 11.7 years old (95% CI: 11.2-12.2, p<0.0011, I^2=94.2%), in Asia had an estimated mean age of 12.5 years old (95% CI: 12.2-12.8, p<0.0011, I^2=93.0%) and in Africa had an estimated mean age of 12.2 years old (95% CI: 11.1-13.3, p<0.0011, I^2=74.8%). On the CS4 stage in Europe had an estimated mean age of 12.8 years old (95% CI: 12.5-13.1, p<0.0001, I^2=82.6%), in America had an estimated mean age of 13.3 years old (95% CI: 12.8-13.8, p<0.0001, I^2=93.5%), in Asia had an estimated mean age of 13.9 years old (95% CI: 13.8-

14.2, p<0.0001, I^2=93.6%) and in Africa had an estimated mean age of 13.7 years old (95% CI: 13.3-14.0, p<0.0001, I^2=0%). On the CS5 stage in Europe had an estimated mean age of 13.8 years old (95% CI: 13.2-14.4, p<0.0007, I^2=95.6%), in America had an estimated mean age of 14.7 years old (95% CI: 14.2-15.3, p<0.0007, I^2=93.7%), in Asia had an estimated mean age of 15.5 years old (95% CI: 15.0-15.9, p<0.0007, I^2=94.8%) and in Africa had an estimated mean age of 14.3 years old (95% CI: 12.8-15.8, p<0.0007, I^2=-%). On the CS6 stage in Europe had an estimated mean age of 15.0 years old (95% CI: 14.3-15.7, p<0.0047, I^2=93.6%), in America had an estimated mean age of 15.7 years old (95% CI: 14.8-16.5, p<0.0047, I^2=95.2%), in Asia had an estimated mean age of 16.6 years old (95% CI: 15.9-17.3, p<0.0047, I^2=97.9%) and in Africa had an estimated mean age of 14.9 years old (95% CI: 13.9-15.9, p<0.0047, I^2=22.9%).

Table 12. Estimates comparing cervical vertebrae maturation between continents.

	Europe			America			Asia			Africa			
CS	**n**	**Mean Age (95% CI)**	**I^2 (%)**	**n**	**Mean Age (95% CI)**	**I^2 (%)**	**n**	**Mean Age (95% CI)**	**I^2 (%)**	**n**	**Mean Age (95% CI)**	**I^2 (%)**	**p-value**
1	8	9.7 (9.1-10.3)	94.3	7	9.0 (8.0-10.0)	98.3	14	10.1 (9.6-10.7)	97.1	2	9.3 (9.3-10.3)	0	0.2321
2	9	10.6 (10.0-11.1)	92.3	8	10.2 (9.8-10.7)	81.6	15	11.3 (10.9-11.7)	93.8	2	10.6 (10.1-11.0)	0	0.0021
3	13	11.6 (11.2-12.0)	92.7	9	11.7 (11.2-12.2)	94.2	16	12.5 (12.2-12.8)	93.0	2	12.2 (11.1-13.3)	74.8	0.0011
4	12	12.8 (12.5-13.1)	82.6	9	13.3 (12.8-13.8)	93.5	17	13.9 (13.8-14.2)	93.6	2	13.7 (13.3-14.0)	0	<0.0001
5	9	13.8 (13.2-14.4)	95.6	8	14.7 (14.2-15.3)	93.7	16	15.5 (15.0-15.9)	94.8	1	14.3 (12.8-15.8)	-	0.0007
6	8	15.0 (14.3-15.7)	93.6	7	15.7 (14.8-16.5)	95.2	14	16.6 (15.9-17.3)	97.9	2	14.9 (13.9-15.9)	22.9	0.0047

CS – Cervical Stage; n – Number of Included Articles; CI – Confidence Interval.

According to sex, females verified an earlier CVM on all stages and in all the continents.

In females (Table 13), on CS1 stage in Europe had an estimated mean age of 9.5 years old (95% CI: 8.7-10.2, p<0.5355, I^2=93.3%), in America had an estimated mean age of 8.5 years old (95% CI: 6.9-10.0, p<0.5355, I^2=97.5%), in Asia had an estimated mean age of 9.7 years old (95% CI: 9.2-10.1, p<0.5355, I^2=95.2%) and in Africa had an estimated mean age of 9.5 years old (95% CI: 8.7-10.3, p<0.5355, I^2=0%). On the CS2 stage in Europe had an estimated mean age of 10.3 years old (95% CI: 9.7-10.8, p<0.1169, I^2=86.7%), in America had an estimated mean age of 10.0 years old (95% CI: 9.4-10.6, p<0.1169, I^2=86.2%), in Asia had an estimated mean age of 10.8 years old (95% CI: 10.4-

11.2, p<0.1169, I^2=91.6%) and in Africa had an estimated mean age of 10.1 years old (95% CI: 9.3-10.9, p<0.1169, I^2=52.5%). On the CS3 stage in Europe had an estimated mean age of 11.3 years old (95% CI: 10.9-11.7, p<0.0236, I^2=87.8%), in America had an estimated mean age of 11.0 years old (95% CI: 10.5-11.6, p<0.0236, I^2=85.0%), in Asia had an estimated mean age of 11.9 years old (95% CI: 11.6-12.2, p<0.0236, I^2=91.0%) and in Africa had an estimated mean age of 11.4 years old (95% CI: 10.1-12.7, p<0.0236, I^2=74.1%). On the CS4 stage in Europe had an estimated mean age of 12.5 years old (95% CI: 12.0-13.0, p<0.0057, I^2=90.3%), in America had an estimated mean age of 13.6 years old (95% CI: 13.2-14.0, p<0.0057, I^2=93.7%), in Asia had an estimated mean age of 13.6 years old (95% CI: 13.2-14.0, p<0.0057, I^2=93.6%) and in Africa had an estimated mean age of 13.3 years old (95% CI: 13.0-13.7, p<0.0057, I^2=0%). On the CS5 stage in Europe had an estimated mean age of 13.7 years old (95% CI: 13.0-14.5, p<0.0269, I^2=94.6%), in America had an estimated mean age of 14.6 years old (95% CI: 14.0-15.3, p<0.0269, I^2=91.5%), in Asia had an estimated mean age of 15.1 years old (95% CI: 14.7-15.5, p<0.0269, I^2=90.4%) and in Africa had an estimated mean age of 14.1 years old (95% CI: 11.7-16.5, p<0.0269, I^2=75.7%). On the CS6 stage in Europe had an estimated mean age of 14.7 years old (95% CI: 13.8-15.6, p<0.0429, I^2=93.2%), in America had an estimated mean age of 15.8 years old (95% CI: 14.7-16.9, p<0.0429, I^2=93.0%), in Asia had an estimated mean age of 16.2 years old (95% CI: 15.4-17.0, p<0.0429, I^2=97.1%) and in Africa had an estimated mean age of 14.4 years old (95% CI: 12.7-16.2, p<0.0429, I^2=63.8%).

Table 13. Estimates comparing cervical vertebrae maturation between continents for females.

	Europe			**America**			**Asia**			**Africa**			
CS	**n**	**Mean Age (95% CI)**	**I^2 (%)**	**n**	**Mean Age (95% CI)**	**I^2 (%)**	**n**	**Mean Age (95% CI)**	**I^2 (%)**	**n**	**Mean Age (95% CI)**	**I^2 (%)**	**p-value**
1	6	9.5 (8.7-10.2)	93.3	4	8.5 (6.9-10.0)	97.5	13	9.7 (9.2-10.1)	95.2	2	9.5 (8.7-10.3)	0	0.5355
2	7	10.3 (9.7-10.8)	86.7	6	10.0 (9.4-10.6)	86.2	12	10.8 (10.4-11.2)	91.6	2	10.1 (9.3-10.9)	52.5	0.1169
3	10	11.3 (10.9-11.7)	87.8	6	11.0 (10.5-11.6)	85.0	15	11.9 (11.6-12.2)	91.0	2	11.4 (10.1-12.7)	74.1	0.0236
4	9	12.5 (12.0-13.0)	90.3	6	13.6 (13.2-14.0)	93.7	16	13.6 (13.2-14.0)	93.7	2	13.3 (13.0-13.7)	0	0.0057
5	7	13.7 (13.0-14.5)	94.6	6	14.6 (14.0-15.3)	91.5	14	15.1 (14.7-15.5)	90.4	2	14.1 (11.7-16.5)	75.7	0.0269
6	6	14.7 (13.8-15.6)	93.2	5	15.8 (14.7-16.9)	93.0	13	16.2 (15.4-17.0)	97.1	2	14.4 (12.7-16.2)	63.8	0.0429

CS – Cervical Stage; n – Number of Included Articles; CI – Confidence Interval.

In males (Table 14), CS1 stage in Europe had an estimated mean age of 10.4 years old (95% CI: 9.7-11.1, p<0.1624, I^2=88.8%), in America had an estimated mean age of 9.2 years old (95% CI: 7.9-10.4, p<0.1624, I^2=96.3%), in Asia had an estimated mean age of 10.5 years old (95% CI: 10.0-11.1, p<0.1624, I^2=95.2%) and in Africa had an estimated mean age of 10.0 years old (95% CI: 9.4-10.5, p<0.1624, I^2=0%). CS2 stage in Europe had an estimated mean age of 11.0 years old (95% CI: 10.5-11.5, p<0.0506, I^2=83.5%), in America had an estimated mean age of 10.5 years old (95% CI: 9.8-11.2, p<0.0506, I^2=77.6%), in Asia had an estimated mean age of 11.7 years old (95% CI: 11.2-12.3, p<0.0506, I^2=94.8%) and in Africa had an estimated mean age of 11.0 years old (95% CI: 9.7-12.3, p<0.0506, I^2=62.8%). CS3 stage in Europe had an estimated mean age of 12.1 years old (95% CI: 11.6-12.6, p<0.0008, I^2=88.8%), in America had an estimated mean age of 12.0 years old (95% CI: 11.1-12.9, p<0.0008, I^2=85.2%), in Asia had an estimated mean age of 13.1 years old (95% CI: 12.7-13.5, p<0.0008, I^2=93.0%) and in Africa had an estimated mean age of 13.3 years old (95% CI: 12.9-13.8, p<0.0008, I^2=0%). CS4 stage in Europe had an estimated mean age of 13.2 years old (95% CI: 12.9-13.6, p<0.0001, I^2=52.8%), in America had an estimated mean age of 14.0 years old (95% CI: 13.3-14.8, p<0.0001, I^2=92.6%), in Asia had an estimated mean age of 14.3 years old (95% CI: 14.0-14.7, p<0.0001, I^2=89.4%) and in Africa had an estimated mean age of 14.4 years old (95% CI: 13.6-15.2, p<0.0001, I^2=61.2%). CS5 stage in Europe had an estimated mean age of 14.6 years old (95% CI: 13.9-15.3, p<0.0517, I^2=87.7%), in America had an estimated mean age of 15.3 years old (95% CI: 14.7-15.9, p<0.0517, I^2=91.4%), in Asia had an estimated mean age of 15.9 years old (95% CI: 15.2-16.5, p<0.0517, I^2=92.2%) and in Africa had an estimated mean age of 15.8 years old (95% CI: 14.7-16.8, p<0.0517, I^2=-%). CS6 stage in Europe had an estimated mean age of 16.0 years old (95% CI: 14.8-17.1, p<0.0124, I^2=91.8%), in America had an estimated mean age of 16.6 years old (95% CI: 15.8-17.5, p<0.0124, I^2=93.5%), in Asia had an estimated mean age of 17.0 years old (95% CI: 16.4-17.6, p<0.0124, I^2=95.4%) and in Africa had an estimated mean age of 15.6 years old (95% CI: 14.9-16.2, p<0.0124, I^2=0%).

Table 14. Estimates comparing cervical vertebrae maturation between continents for males.

	Europe			**America**			**Asia**			**Africa**			
CS	**n**	**Mean Age (95% CI)**	**I^2 (%)**	**n**	**Mean Age (95% CI)**	**I^2 (%)**	**n**	**Mean Age (95% CI)**	**I^2 (%)**	**n**	**Mean Age (95% CI)**	**I^2 (%)**	**p-value**
1	6	10.4 (9.7-11.1)	88.8	5	9.2 (7.9-10.4)	96.3	12	10.5 (10.0-11.1)	95.2	2	10.0 (9.4-10.5)	0	0.1624

2	7	11.0 (10.5-11.5)	83.5	6	10.5 (9.8-11.2)	77.6	13	11.7 (11.2-12.3)	94.8	2	11.0 (9.7-12.3)	62.8	0.0506
3	10	12.1 (11.6-12.6)	88.8	6	12.0 (11.1-12.9)	85.2	14	13.1 (12.7-13.5)	93.0	2	13.3 (12.9-13.8)	0	0.0008
4	9	13.2 (12.9-13.6)	52.8	6	14.0 (13.3-14.8)	92.6	15	14.3 (14.0-14.7)	89.4	2	14.4 (13.6-15.2)	61.2	<0.0001
5	7	14.6 (13.9-15.3)	87.7	6	15.3 (14.7-15.9)	91.4	12	15.9 (15.2-16.5)	92.2	1	15.8 (14.7-16.8)	-	0.0517
6	5	16.0 (14.8-17.1)	91.8	4	16.6 (15.8-17.5)	93.5	11	17.0 (16.4-17.6)	95.4	2	15.6 (14.9-16.2)	0	0.0124

CS – Cervical Stage; n – Number of Included Articles; CI – Confidence Interval.

The difference between males and females among the continents was estimated (Table 15). CS1 stage in Europe had an estimated mean age of 0.5 years old (95% CI: 0.2-0.7, p<0.6956, I^2=20.7%), in America had an estimated mean age of 0.5 years old (95% CI: 0.2-0.8, p<0.6956, I^2=0%), in Asia had an estimated mean age of 0.6 years old (95% CI: 0.3-0.9, p<0.6956, I^2=62.5%) and in Africa had an estimated mean age of 0.3 years old (95% CI: -0.2-0.8, p<0.6956, I^2=0%). CS2 stage in Europe had an estimated mean age of 0.5 years old (95% CI: 0.2-0.8, p<0.8716, I^2=29.8%), in America had an estimated mean age of 0.5 years old (95% CI: 0.2-0.8, p<0.8716, I^2=0%), in Asia had an estimated mean age of 0.7 years old (95% CI: 0.3-1.0, p<0.8716, I^2=74.1%) and in Africa had an estimated mean age of 0.4 years old (95% CI: -0.7-1.5, p<0.8716, I^2=56.9%). CS3 stage in Europe had an estimated mean age of 0.6 years old (95% CI: 0.4-0.8, p<0.2059, I^2=22.3%), in America had an estimated mean age of 0.8 years old (95% CI: 0.5-1.0, p<0.2059, I^2=0%), in Asia had an estimated mean age of 0.9 years old (95% CI: 0.7-1.2, p<0.2059, I^2=73.6%) and in Africa had an estimated mean age of 1.0 years old (95% CI: 0.4-1.6, p<0.2059, I^2=0%). On the CS4 stage in Europe had an estimated mean age of 0.4 years old (95% CI: 0.1-0.7, p<0.7821, I^2=69.2%), in America had an estimated mean age of 0.6 years old (95% CI: 0.2-0.9, p<0.7821, I^2=61.7%), in Asia had an estimated mean age of 0.6 years old (95% CI: 0.3-0.9, p<0.7821, I^2=75.3%) and in Africa had an estimated mean age of 0.9 years old (95% CI: -0,2-2.0, p<0.7821, I^2=70.3%). On the CS5 stage in Europe had an estimated mean age of 0.5 years old (95% CI: 0.3-0.8, p<0.6843, I^2=36.8%), in America had an estimated mean age of 0.5 years old (95% CI: 0.2-0.9, p<0.6843, I^2=41.4%), in Asia had an estimated mean age of 0.6 years old (95% CI: 0.2-0.9, p<0.6843, I^2=69.5%) and in Africa had an estimated mean age of 1.3 years old (95% CI: 0.1-2.6, p<0.6843, I^2=-%). CS6 stage in Europe had an estimated mean age of 0.6 years old (95% CI: 0.3-0.9, p<0.9530, I^2=0%), in America had an estimated mean age of 0.4

years old (95% CI: -0.1-0.9, p<0.9530, I^2=0%), in Asia had an estimated mean age of 0.5 years old (95% CI: 0.3-0.7, p<0.9530, I^2=0%) and in Africa had an estimated mean age of 0.7 years old (95% CI: -0.4-1.8, p<0.9530, I^2=8.3%).

Table 15. Estimates comparing cervical vertebrae maturation between females and males by continents.

	Europe			**America**			**Asia**			**Africa**			
CS	**n**	**Females vs. Males SMD (95% CI)**	**I^2 (%)**	**n**	**Females vs. Males SMD (95% CI)**	**I^2 (%)**	**n**	**Females vs. Males SMD (95% CI)**	**I^2 (%)**	**n**	**Females vs. Males SMD (95% CI)**	**I^2 (%)**	**p-value**
1	6	0.5 (0.2-0.7)	20.7	4	0.5 (0.2-0.8)	0	12	0.6 (0.3-0.9)	62.5	2	0.3 (-0.2-0.8)	0	0.6956
2	7	0.5 (0.2-0.8)	29.8	6	0.5 (0.2-0.8)	0	11	0.7 (0.3-1.0)	74.1	2	0.4 (-0.7-1.5)	56.9	0.8716
3	10	0.6 (0.4-0.8)	22.3	6	0.8 (0.5-1.0)	0	14	0.9 (0.7-1.2)	73.6	2	1.0 (0.4-1.6)	0	0.2059
4	9	0.4 (0.1-0.7)	69.2	6	0.6 (0.2-0.9)	61.7	15	0.6 (0.3-0.9)	75.3	2	0.9 (-0.2-2.0)	70.3	0.7821
5	7	0.5 (0.3-0.8)	36.8	6	0.5 (0.2-0.9)	41.4	11	0.6 (0.2-0.9)	69.5	1	1.3 (0.1-2.6)	-	0.6843
6	5	0.6 (0.3-0.9)	0	4	0.4 (-0.1-0.9)	0	11	0.5 (0.3-0.7)	0	2	0.7 (-0.4-1.8)	8.3	0.9530

SMD - Standardized Mean Difference; CS – Cervical Stage; n – Number of Included Articles; CI – Confidence Interval.

IV. DISCUSSION

4.1. Summary of the main results

The aim of this SR was to determine the mean estimated chronological age on each stage of CVM based on Baccetti et al. (2005) method. Through the results obtained, it is possible to verify the estimated values divided by sexes (females and males), and both combined (total population). By comparing the estimated ages obtained from genders, it is possible to claim that females demonstrate an earlier CVM when compared to males on all stages.

To resume, in both sexes, CS1 presented a mean age within an interval of 9-11 years old; CS2 had a mean estimated age between 10-12; CS3 presented a mean age between an interval of 11-13; CS4 has a mean estimated age within 13-15; CS5 presented a mean age between an interval of 14-16 and CS6 had a mean estimated age between 15-17.

We concluded through our analysis that there were significant variations in values between both sexes. On CS1 is 0.5 years old, on CS2 is 0.5 years old, on CS3 is 0.8 years old, on CS4 is 0.6 years old, on CS5 is 0.6 years old and on CS6 is 0.5 years old. The major difference between sexes is on CS3, which corresponds to the interval of 11-13 years old. At this age (11-13 years old) during adolescence, several studies demonstrated that boys and girls have different growth peaks, which could possibly justify the difference on this stage (Litsas & Lucchese, 2016). It is also justifies the fact that girls have an earlier CVM growth peak.

Besides, the estimated ages calculated for each sex, it was also estimated the chronological age according to the continents (Europe, America, Asia, Africa). The differences between sexes are also verified across the continents, so females presented an earlier CVM. Comparing the continents, America is the continent which presented an earlier CVM on CS1, at the estimated age of 9-year-old. However, it is Africa which presents the earlier CVM on CS6, despite demonstrating a later CVM compared to America. At CS1, the difference between America and Africa is just 0,2 years old, but at CS6, the difference is almost 1 year old.

It is possible to verify that the difference between genders across the continents is superior in Africa, mainly in CS3, CS4, CS5 and CS6. In CS1 and CS2, Asia shows a superior difference between genders.

4.2. Quality of the evidence and potential biases in the review process

Almost all studies included on this SR are of moderate quality, just one is low quality (Kuc-Michalska & Baccetti, 2010) and another one high quality (Folmer et al., 2021). The studies included are observational studies, randomized and non-randomized controlled trials.

The majority of the articles included did not report the calculation of sample size and they are not representative of the population. Furthermore, several studies did not describe the methods and measurements of CVM. Some studies also did not present the calibration of intra/inter-examiner. All items mentioned before are fundamental to minimize the RoB, and without this tool, the results of SR would be weak. Just 6 of 42 studies report the blinding of examiners, and this bias should be considered on future investigations.

The heterogeneity between studies reports the different conclusions between them and should be considered. This factor could have different reasons such as the different chronological age, the genetic factor, individual gender and region. The studies require a lateral cephalometric X-ray to evaluate the CVM, and one study also uses CBCT (Vuong & Kang, 2021). Determining the CVM is essential in an orthodontic treatment, to determine the biological age and consequently the correct interval time to intervene.

In the future, CBCT may be the best exam to analyse the CVM due to being a tridimensional exam, compared to cephalometric lateral X-ray, a bidimensional exam.

This SR presents some limitations due to the variables which may influence the CVM. Genetic factors, the regular activities of the children or adolescents, some alteration on column curvature, the gender, the different normal growth peak between persons of the same age, are some variables which may influence the results.

A way to improve this area is to further investigate and develop new studies in the future. Beyond cervical vertebrae, there are other ways to determine biological age such as teeth. A SR which considers the correlation between CVM and dental maturation may be useful. However, the method considered to evaluate dental teeth has to be evaluated. Another interesting perspective would be to study the correlation between CVM and biological markers on the way to innovate the technology.

4.3. Agreements and disagreements with other reviews or studies

Previous SR were based on the comparison of hand-wrist exams to CVM (Cericato et al., 2015; Ferrillo et al., 2021; Szemraj et al., 2018). As time progressed investigators started to evaluate the efficacy of CMV with the objective of replacing the hand-wrist exams entirely to avoid extra radiation (O'Reilly & Yanniello, 1988). In addition to this, there were no references as to the fact that CVM occurs earlier on females than does on male subjects (a result that this SR intends to analyse).

Although the majority of the studies report the reliability of the method, to my knowledge, none analysed the mean estimated age on each CVM stage based on Baccetti et al. (2005) and distinguished between genders and continents. These are the three main goals that my SR pretends to achieve.

Skeletal growth varies during puberty, so it could be influenced by several external factors (Lourenço & Queiroz, 2010). As mentioned before, each person has his individual development, and it is variable according to diverse factors such as genetic variants, nutrition, physical activity, health, and other points (Schumacher, 1999). This can be separated into two categories, the primary and secondary growing factors. Some primary factors are the sex of the person and their ethnicity (Nanda, 2000). As for secondary factors, nutrition is a good example. It is evident that children with better nutrition have a faster maturation (Schumacher, 1999). Africa is a continent with nutritional deficit (International Food Policy Research Institute, 2016) , and according to our results Africa presents a later CVM when compared to other continents.

The relation between growth and nutrition is interactive and influenced by multiple illnesses and different historical periods. In general, by improving the life quality of an individual, his nutrition improves as well. Anamneses is important to identify disturbances in nutrition such as anorexia and bulimia. Through the growth, it is possible to evaluate if the children had a correct nutrition (Eisenstein et al., 2000).

Another factor which could influence the CVM is race (García-Fernandez et al., 1998; Uysal et al., 2006). In 1999, a study was realized to evaluate the differences between white race and black race on CVM. The results show a precocious CVM on black race females (Chaves et al., 1999). However, in our results, Africa (black race) has shown a later CVM compared to other continents where white race prevails. Our results have been

in accordance with the importance of nutritional factors, and in Africa there is a nutritional deficit, so a later CVM (International Food Policy Research Institute, 2016).

As mentioned before and confirmed in our results, the sex influences CVM. There are several differences between the sexes especially during puberty. Some studies have demonstrated that endocrine disruptors have distinctively influenced each sex during puberty. Thus, it would be interesting to evaluate the impact of them in CVM directly (Castro-Correia & Fontoura, 2015).

Another important factor which influences maturation is sexual hormones. Since sexual hormones enhance some variations during the development, they could also be the cause of differences found between CVM in individuals of the opposite sex. Hassel and Farman (1995) refer that sexual maturation has more influence in CVM than other factors such as stature.

Büken et al. (2009) and Nanda (2000) also refers to the importance of genetic factors (hereditary) in the development of each individual person.

The methods developed to evaluate CVM nowadays are all of them, the visual evaluation through the shape of vertebras (C2, C3, C4), and the presence of a lower concavity. It would be a huge improvement to develop a more effective method to evaluate CVM and this allows a more precise determination of biological age. Nowadays there is not a standardized method, however in the future should be developed a method which considers the differences between sexes and the distinct skeletal patterns. Therefore, a future perspective to have in consideration, is to develop and evaluate more objective methods, so that studies do not rely on subjective methods, as the ones mentioned before.

Finally, as referred before, this SR presents innovative contents about CVM, and the actual methods used to evaluate it. This one is based on searches made until July 2021.

V. CONCLUSION

Skeletal maturation through CVM method does not always occur at the exact same time in children and adolescents, and, therefore, each patients present a different maturation pace.

We successfully estimated the age ranges for each CVM stage, allowing a better understanding on the patient's growth timing. Girls presented an earlier skeletal maturation compared to boys.

When we compare the CVM through different continents, there is also a significant difference between genders in all of them. Asia is the continent where CS6 takes more time to reach, so Asian subjects have a late CVM when compared to other continents.

VI. FUTURE PERSPECTIVES

Nowadays, determining the biological age is fundamental in several areas as it was mentioned. In a clinical orthodontic context, using CVM is useful because the exams required to evaluate CVM are the same used to evaluate other orthodontic parameters. However, the methods developed to evaluate CVM today are still very subjective, since they consist of two visual exams: the evaluation through the shape of vertebrae (C2, C3, C4), and the presence of lower concavity. To develop a more effective method to evaluate CVM, consequently allowing to determine a more precise biological age, would be a huge progress in the field.

There are several studies which evaluate biological age through CVM using different methods. It would be useful to develop a universal method, making it easier to compare the reproducibility of the method in a larger population. Nowadays there are lots of studies evaluating CVM, however these studies are based at least in three different methods (Baccetti et al., 2002; Baccetti et al., 2005; Hassel & Farman, 1995).

Using the CVM method to determine biological age requires a cephalometric lateral X-ray. Despite the low radiation, developing an exam which does not require any exposure radiation to evaluate biological age and orthodontic parameters would be the best option. Another suggestion to evaluate CVM could be through CBCT (tridimensional exam) on the way to be more precise in the visual evaluation, however it is more expensive. There is only one study that requires the CBCT exam to evaluate CVM.

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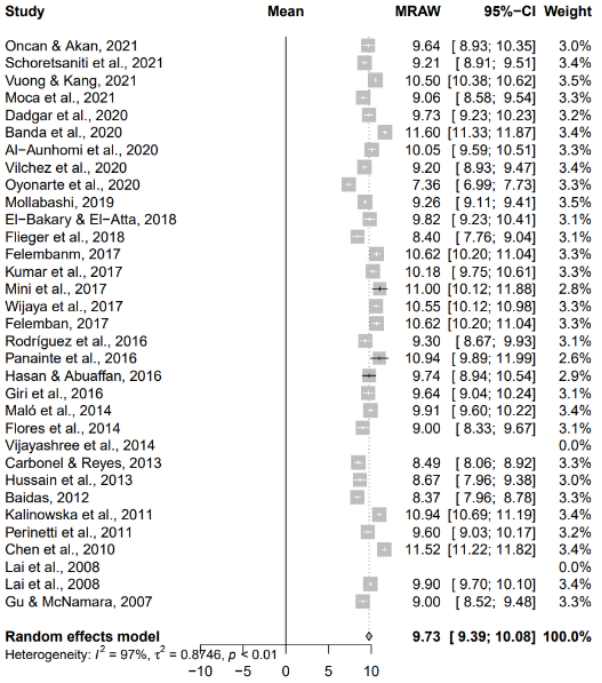
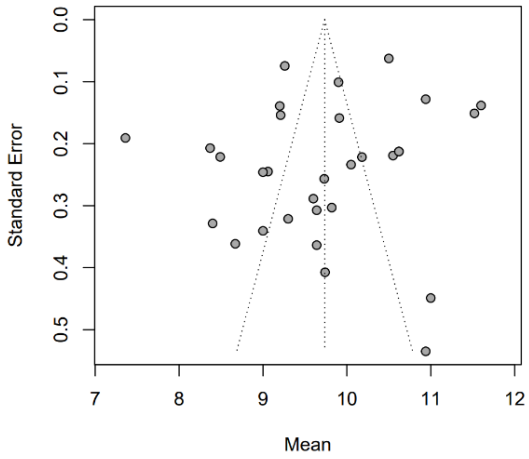
VIII. APPENDICES

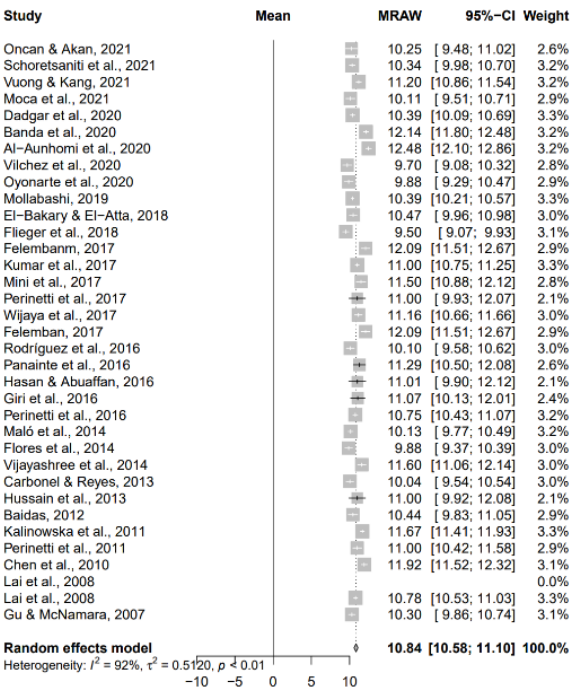
Supplementary Figure 1 – Cervical vertebral maturation of both sexes in CS1. Subgroup analysis according to the study type.



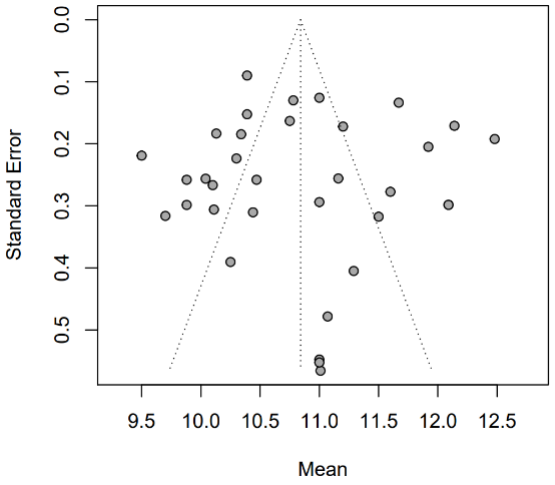
Supplementary Figure 2 – Funnel plot and Egger's test of cervical vertebral maturation in both sexes in CS1.



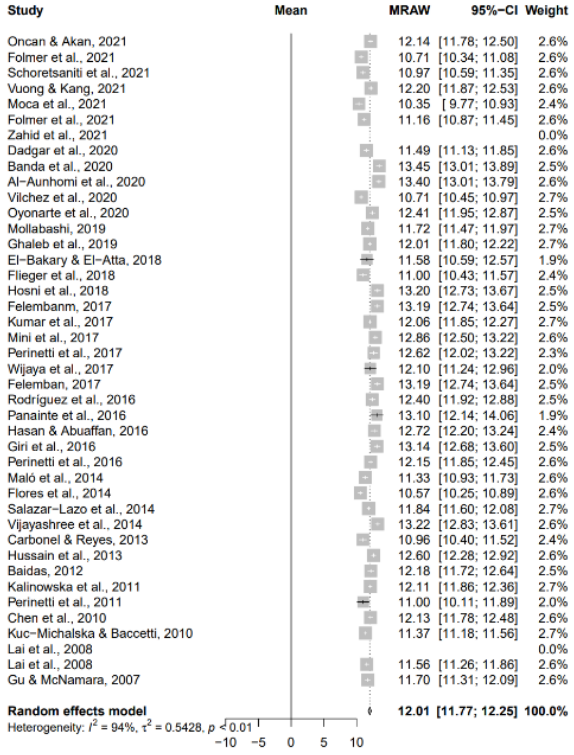
Supplementary Figure 3 – Cervical vertebral maturation of both sexes in CS2. Subgroup analysis according to the study type.



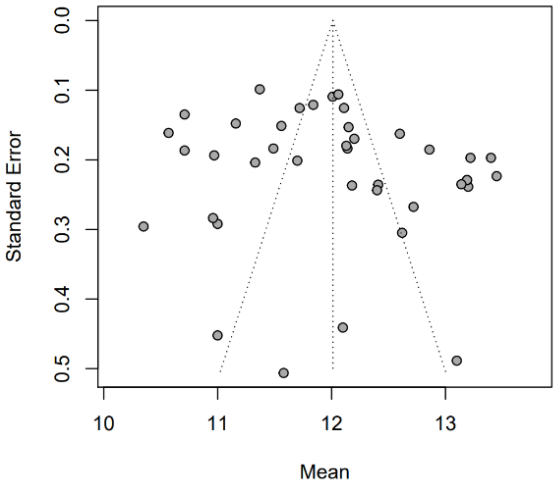
Supplementary Figure 4 – Funnel plot and Egger's test of cervical vertebral maturation in both sexes in CS2.



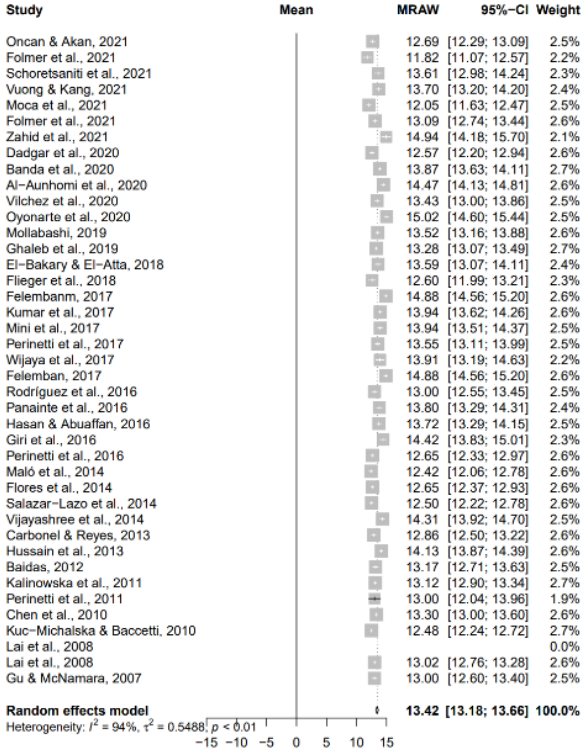
Supplementary Figure 5 – Cervical vertebral maturation of both sexes in CS3. Subgroup analysis according to the study type.



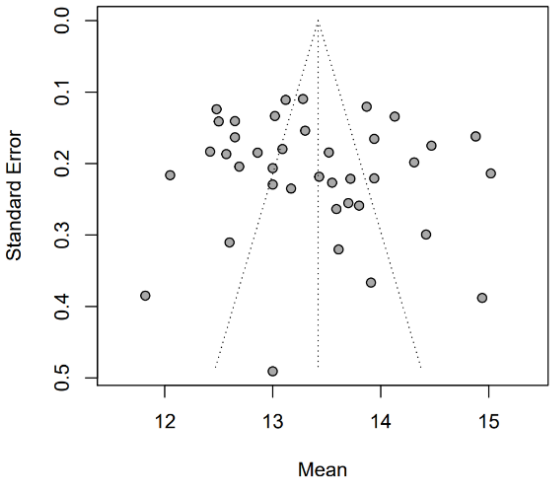
Supplementary Figure 6 – Funnel plot and Egger's test of cervical vertebral maturation in both sexes in CS3.



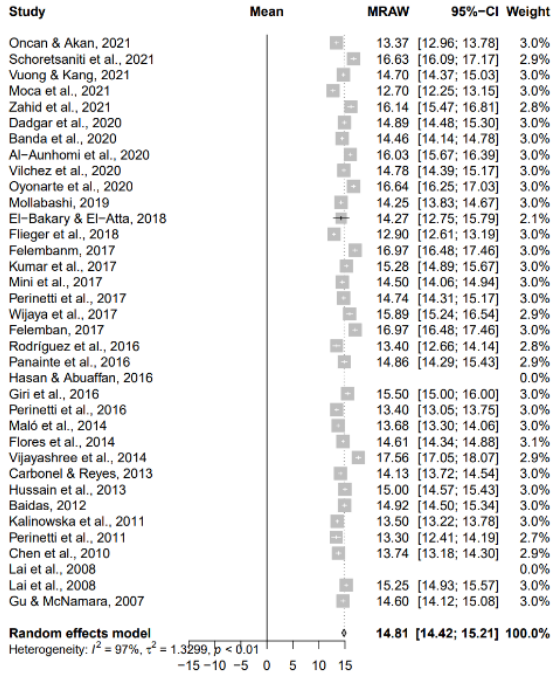
Supplementary Figure 7 – Cervical vertebral maturation of both sexes in CS4. Subgroup analysis according to the study type.



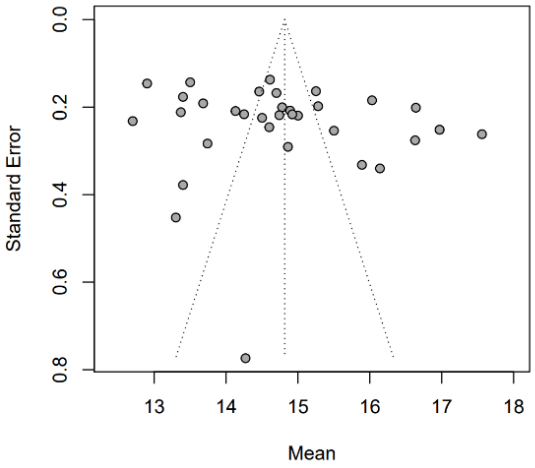
Supplementary Figure 8 – Funnel plot and Egger's test of cervical vertebral maturation of both sexes in CS4.



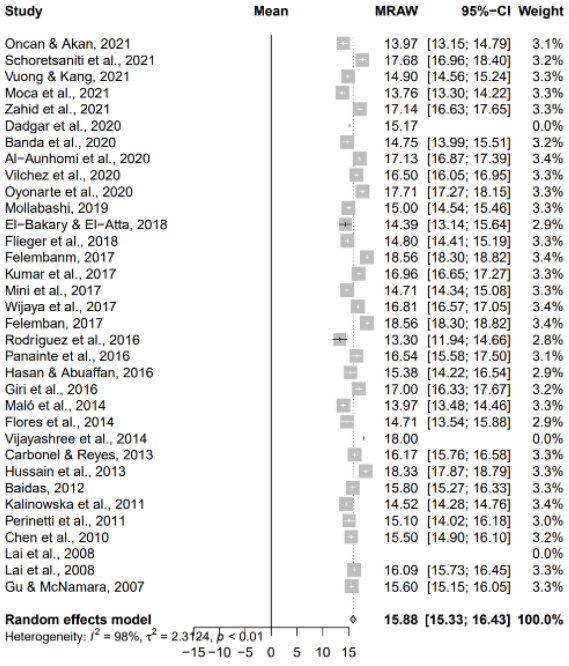
Supplementary Figure 9 – Cervical vertebral maturation of both sexes in CS5. Subgroup analysis according to the study type.



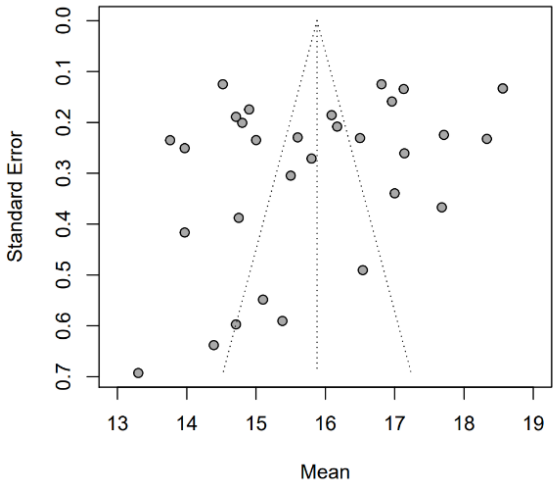
Supplementary Figure 10 – Funnel plot and Egger's test of cervical vertebral maturation of both sexes in CS5.



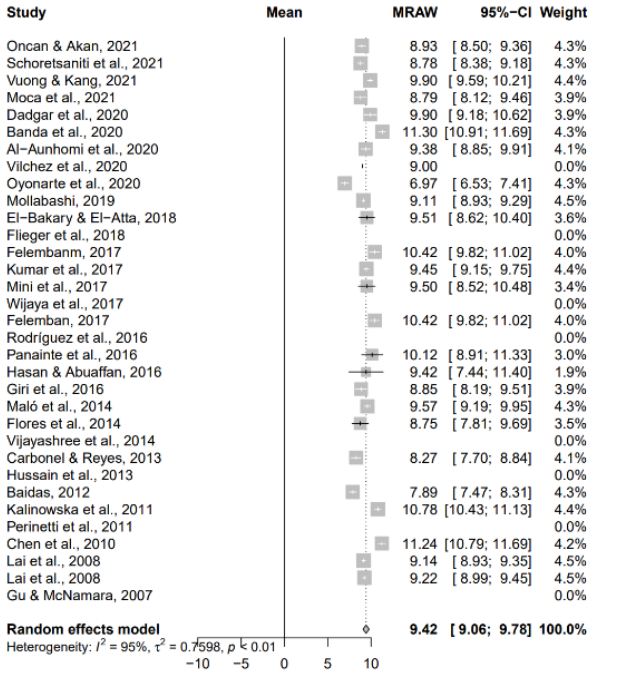
Supplementary Figure 11 – Cervical vertebral maturation of both sexes in CS6. Subgroup analysis according to the study type.



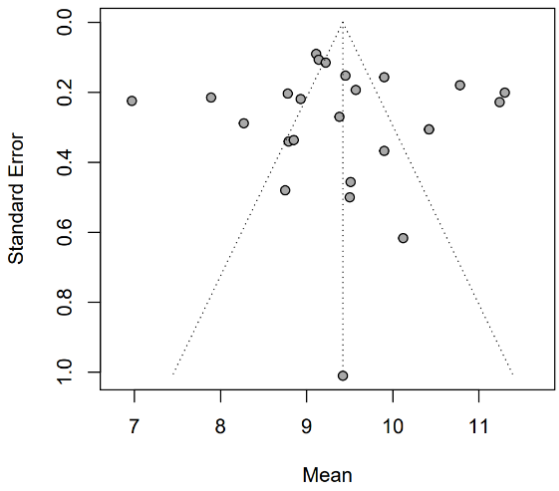
Supplementary Figure 12 – Funnel plot and Egger's test of cervical vertebral maturation of both sexes in CS6.



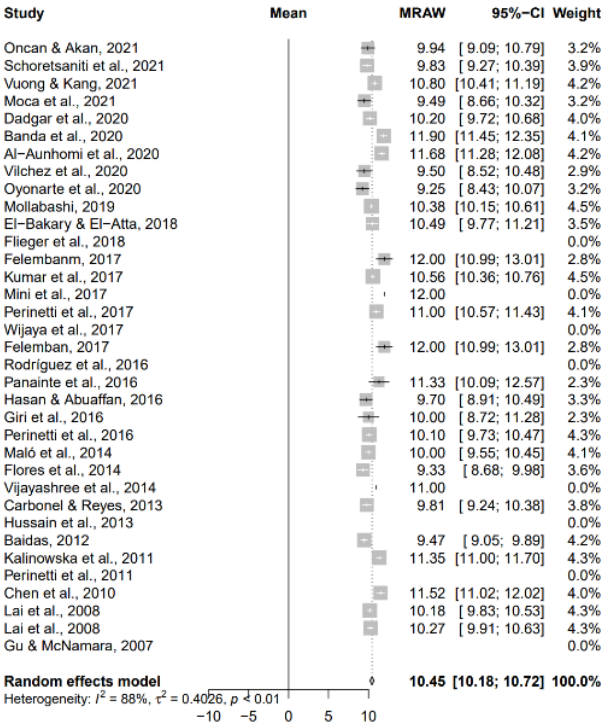
Supplementary Figure 13 – Cervical vertebral maturation of females in CS1. Subgroup analysis according to the study type.



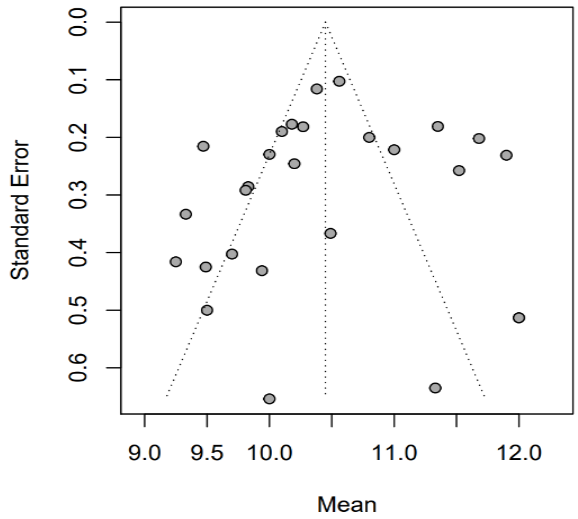
Supplementary Figure 14 – Funnel plot and Eggers's test of cervical vertebral maturation in females in CS1.



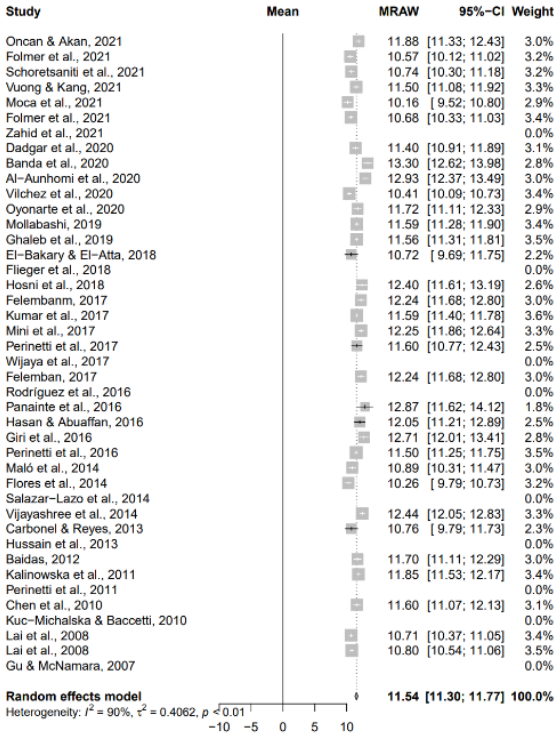
Supplementary Figure 15 – Cervical vertebral maturation of females in CS2. Subgroup analysis according to the study type.



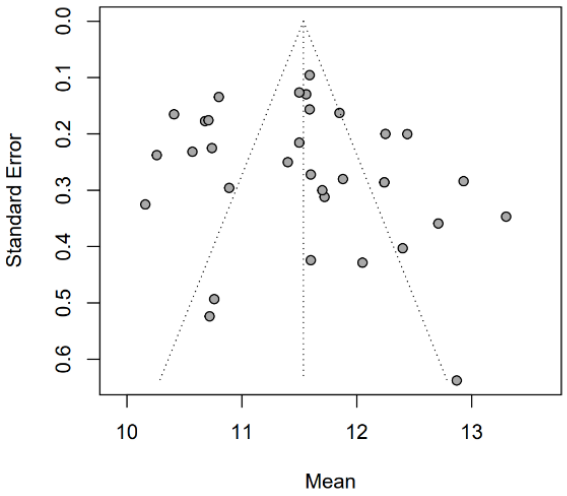
Supplementary Figure 16 – Funnel plot and Egger's test of cervical vertebral maturation in females in CS2.



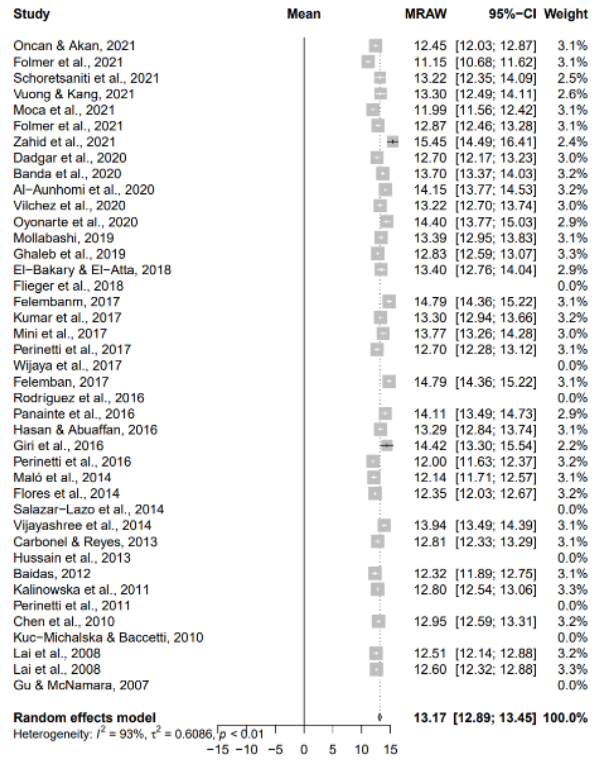
Supplementary Figure 17 – Cervical vertebral maturation of females in CS3. Subgroup analysis according to the study type.



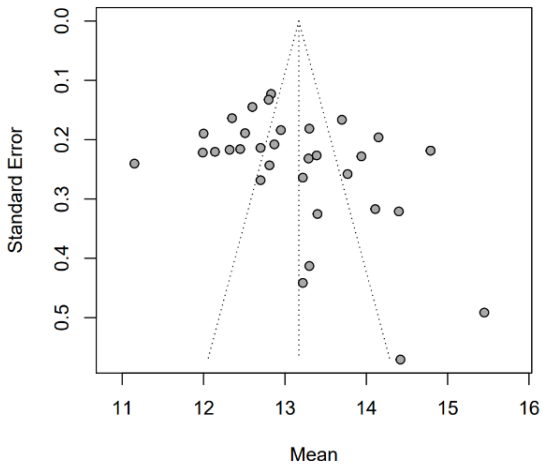
Supplementary Figure 18 – Funnel plot and Egger's test of cervical vertebral maturation in females in CS3.



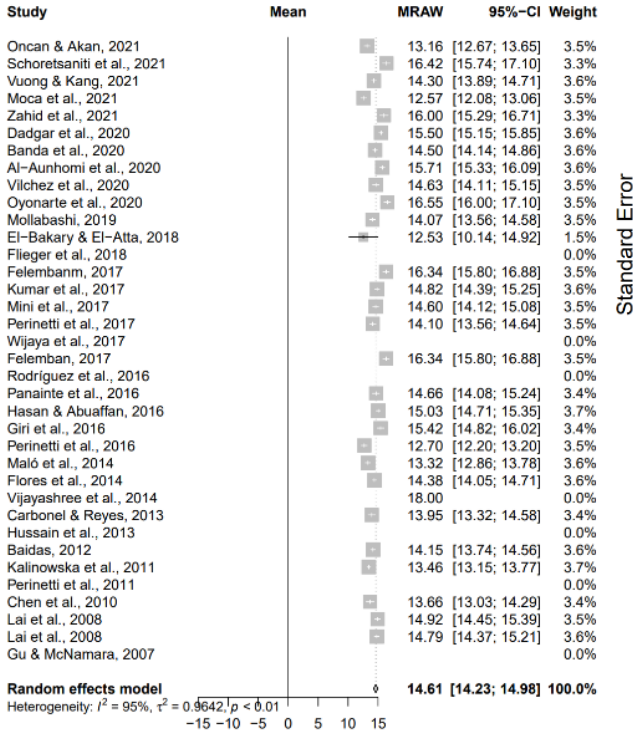
Supplementary Figure 19 – Cervical vertebral maturation of females in CS4. Subgroup analysis according to the study.



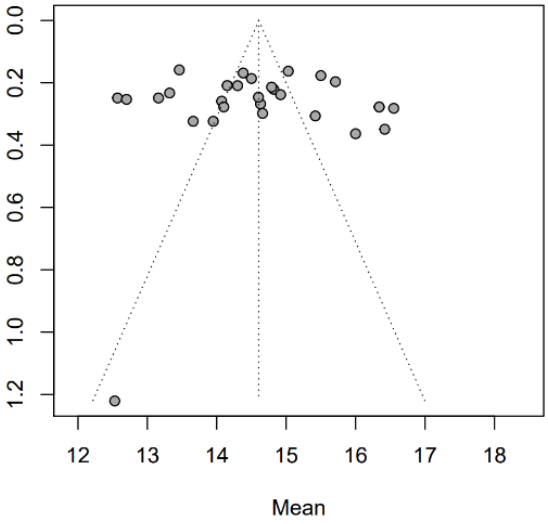
Supplementary Figure 20 – Funnel plot and Egger's test of cervical vertebral maturation in females in CS4.



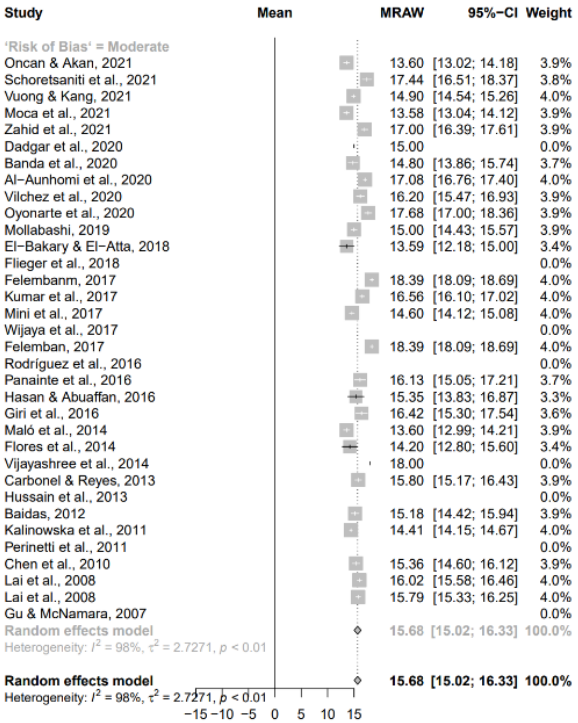
Supplementary Figure 21 – Cervical vertebral maturation of females in CS5. Subgroup analysis according to the study.



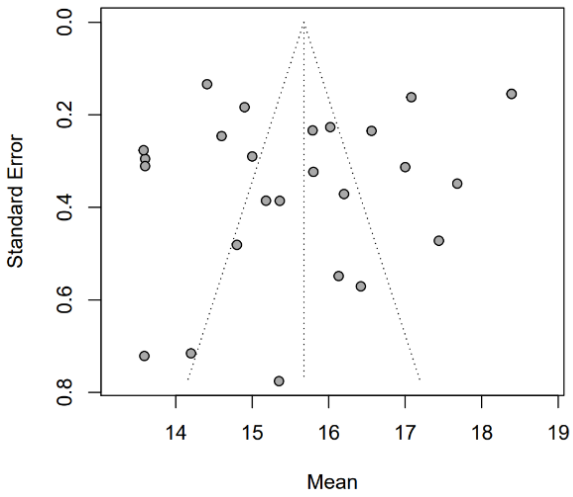
Supplementary Figure 22 – Funnel plot and Egger's test of cervical vertebral maturation in females in CS5.



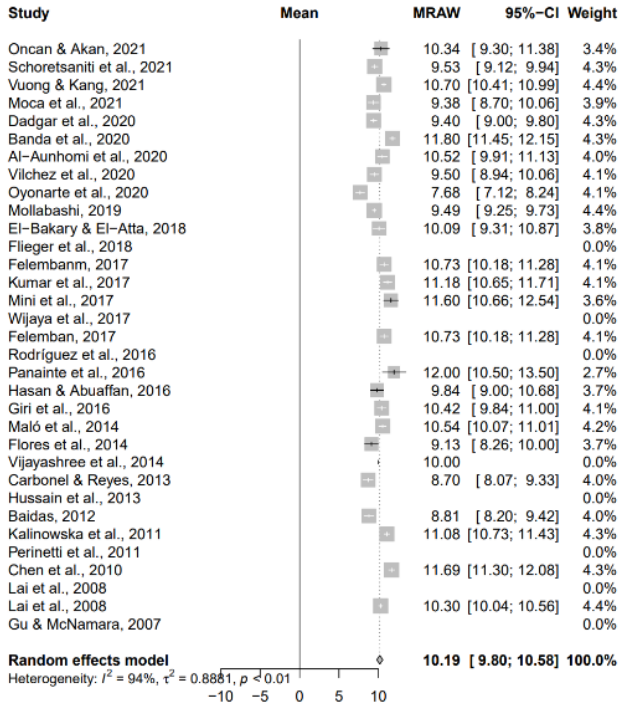
Supplementary Figure 23 – Cervical vertebral maturation of females in CS6. Subgroup analysis according to the study type.



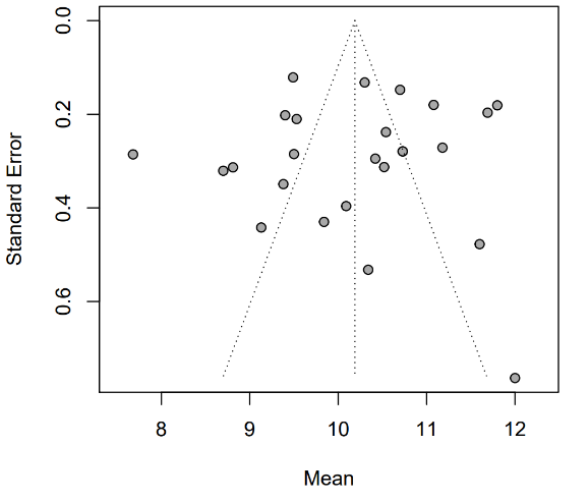
Supplementary Figure 24 – Funnel plot and Egger's test of cervical vertebral maturation in females in CS6.



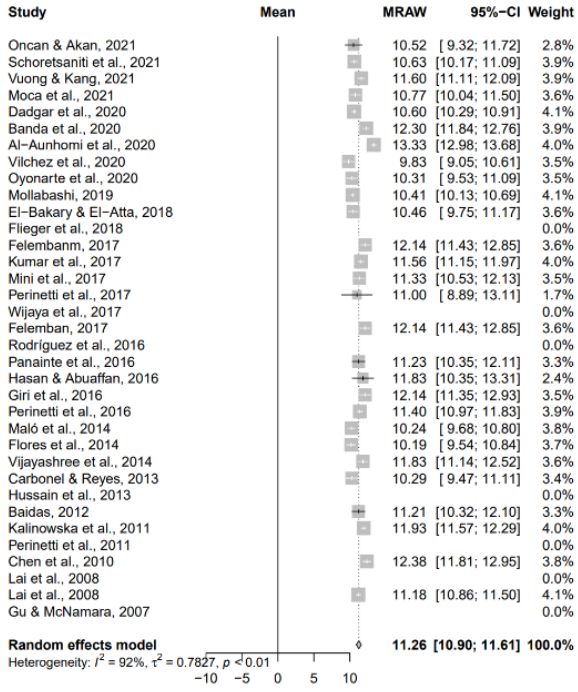
Supplementary Figure 25 – Cervical vertebral maturation of males in CS1. Subgroup analysis according to the study type.



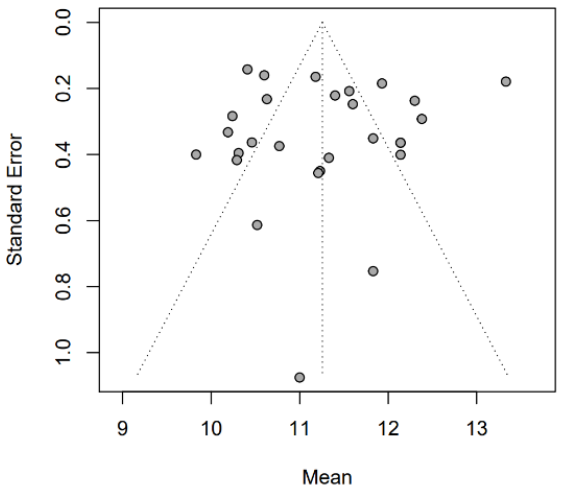
Supplementary Figure 26 – Funnel plot and Egger's test of cervical vertebral maturation in males in CS1.



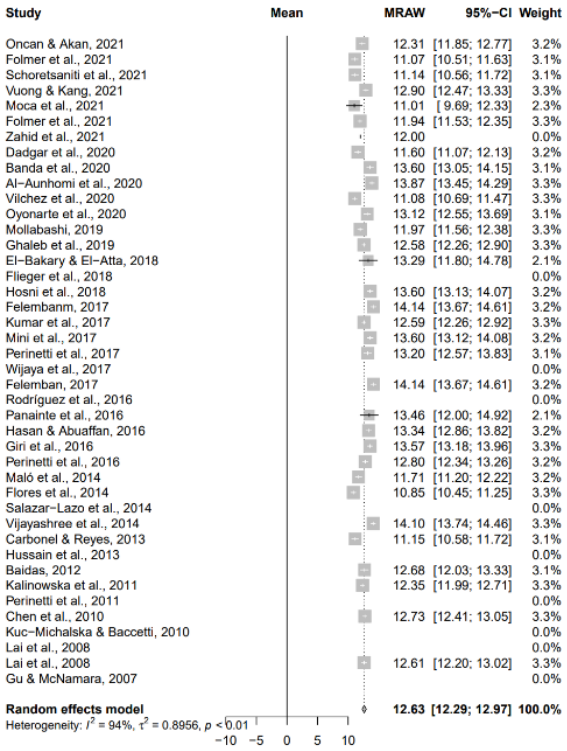
Supplementary Figure 27 – Cervical vertebral maturation of males in CS2. Subgroup analysis according to the study type.



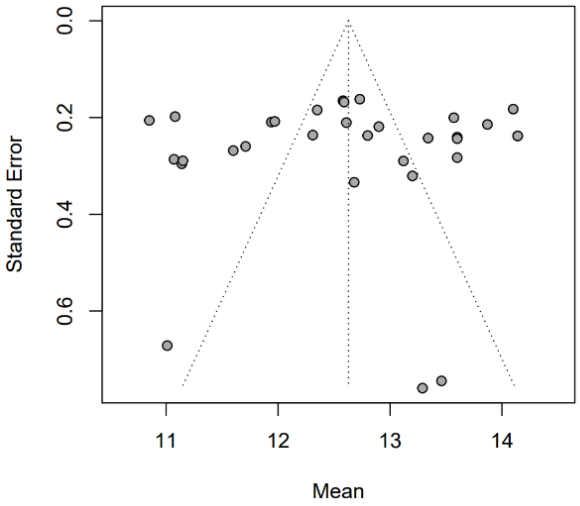
Supplementary Figure 28 – Funnel plot and Egger's test of cervical vertebral maturation in males in CS2.



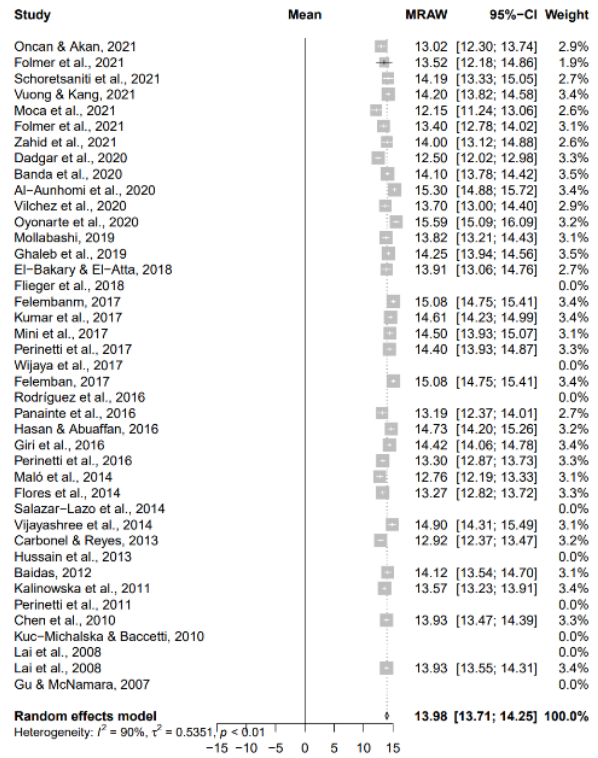
Supplementary Figure 29 – Cervical vertebral maturation of males in CS3. Subgroup analysis according to the study type.



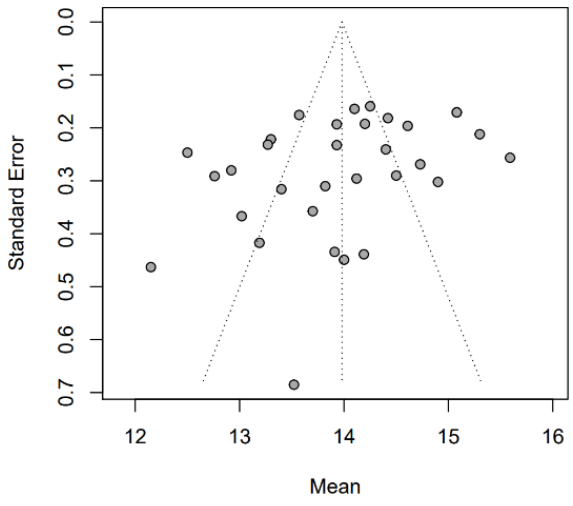
Supplementary Figure 30 – Funnel plot and Egger's test of cervical vertebral maturation in males in CS3.



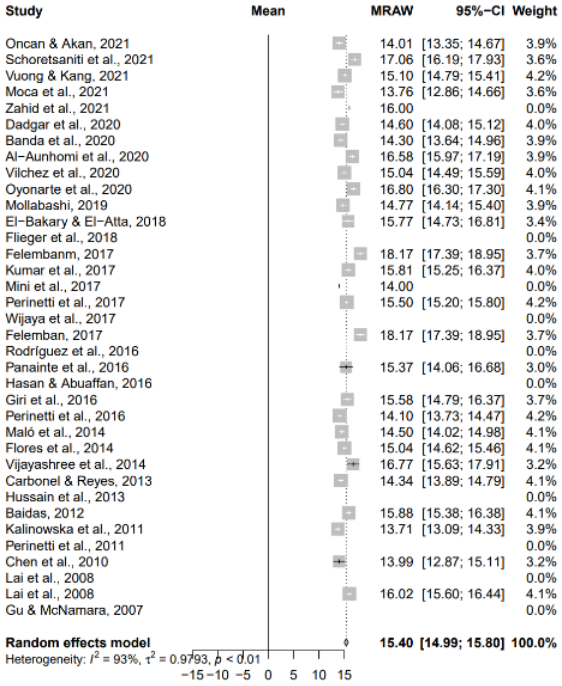
Supplementary Figure 31 – Cervical vertebral maturation of males in CS4. Subgroup analysis according to the study type.



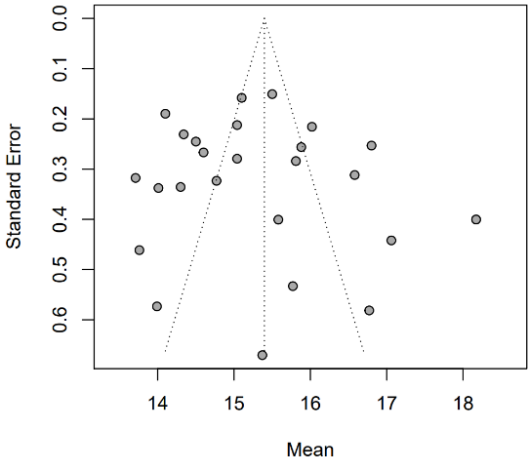
Supplementary Figure 32 – Funnel plot and Eggers's test of cervical vertebral maturation in males in CS4.



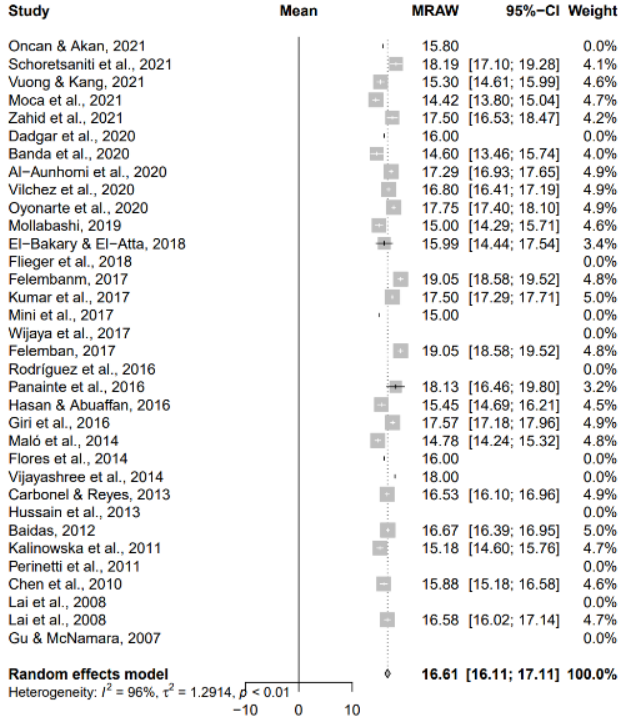
Supplementary Figure 33 – Cervical vertebral maturation of males in CS5. Subgroup analysis according to the study type.



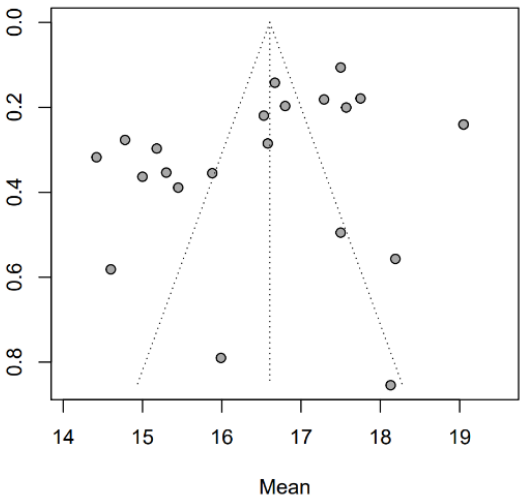
Supplementary Figure 34 – Funnel plot and Egger's test of cervical vertebral maturation in males in CS5.



Supplementary Figure 35 – Cervical vertebral maturation of males in CS6. Subgroup analysis according



Supplementary Figure 36 – Funnel plot and Egger's test of cervical vertebral maturation in males in CS6.



Supplementary Document – Authorization to use clinical images.

Solicitação para uso de dados clínicos

Clínica Universitária Egas Moniz

INSTITUTO UNIVERSITÁRIO EGAS MONIZ

Sou aluna do 5º ano de medicina dentária, e como tal estou a realizar a tese de mestrado no ano 2020/2021. Solicito à direção clínica se me é permitido o uso de dados clínicos, mais especificamente uma ortopantomografia e uma telerradiografia lateral de perfil, de modo que as possa analisar e usar como exemplos práticos de imagens na minha tese de mestrado no Instituto Universitário Egas Moniz.

Ano: 2020/2021

Aluna: Maria Inês Magalhães, 112259 – 5º ano de Medicina Dentária

Assinatura:

12/03/21