Norwegian Institute of Public Health

REPORT

2018

SYSTEMATIC REVIEW:

Age estimation by ossification stages of the medial clavicular epiphysis

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Authors	Kristoffer Yunpeng Ding, project leader, *Norwegian Institute of Public Health* Veslemøy Rolseth, *Oslo University Hospital* Pål Skage Dahlberg, *Oslo University Hospital* Annhild Mosdøl, *Norwegian Institute of Public Health* Gyri Hval Straumann, *Norwegian Institute of Public Health* Øyvind Bleka, *Oslo University Hospital* Gunn Elisabeth Vist, *Norwegian Institute of Public Health*
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Key messages

This systematic review summarizes the evidence on the distribution of chronological age from pre-defined stages of clavicular ossification studied by MRI or CT in living individuals.

We included ten observational studies, all published within the last five years. The studies were conducted in five different countries, involving 4190 participants. Nine studies used CT and one used MRI. The QUADAS-2 checklist was used to assess risk of bias. The mean chronological age and its 95 % confidence interval (95% CI) were presented for males and females separately in each stage and substage of medial clavicle epiphysis.

Most of the studies showed a high risk of selection bias due to age mimicry, which could influence the distribution of age from each clavicular stage. Due to the limitations, we are unable to provide a reliable distribution of chronological age from each stage of medial clavicular development.

Title: Age estimation by ossification stages of the medial clavicular epiphysis: a systematic review

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Type of publication:

Systematic review

A review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyse data from the studies that are included in the review. Statistical methods (meta-analysis) may or may not be used to analyse and summarise the results of the included studies.

Doesn’t answer everything:

- Excluded studies are not evaluated
- No recommendation
- No cost-effectiveness evaluation

Publisher:

Norwegian Institute of Public Health

Updated:

Last search for studies: April 2017

Peer review:

- Signe Agnes Flottorp (internal)
- Kjetil Gundro Brurberg (internal)
- Andreas Schmeling (Professor, Dr. Med and Director of the Institute of Legal Medicine, University of Munster)

Executive summary

Introduction

Every year, young asylum seekers come to Norway without legal documentation of their chronological age. To ensure that children receive their entitled rights and that adults are not treated as children, it is necessary to estimate their chronological age. Assessments of hand skeleton and third molar teeth using X-ray have been used for age estimation in Norway for years. We have previously published systematic reviews assessing age distribution using radiographs based on the Greulich & Pyle atlas for hand-wrist skeleton and the Demirjian's stages for the third molar teeth. Here we present a systematic review to evaluate the use of computed tomography (CT) and magnetic resonance imaging (MRI) on the medial clavicle epiphysis for age estimation in the living.

Method

We searched for studies in the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase and Google Scholar. This was a joint search conducted for studies using X-ray of teeth and hand, CT and MRI of the clavicle, knee and ankle in both males and females. An update search was conducted in April 2017 for clavicle, knee and ankle only. Two people screened the literature independently and assessed the risk of the included studies based on the QUADAS-2 checklist. The mean chronological age and the standard deviation in the included studies were extracted for each stage and substage for each sex separately.

Results

We found 10059 abstracts in the first search and 663 in the second search. In total 63 potentially relevant publications were forwarded for full-text screening. Eventually ten studies were included, all published within the last five years. Nine studies used CT and one study used MRI. The sample sizes in the included studies ranged from 152 to 752 participants. Six studies were from Turkey, and one from Australia, China, Germany and Thailand, respectively.

The age distribution for each clavicular stage varied largely in and between the included studies. According to the QUADAS-2 checklist, all the included studies were associated with high risk of age mimicry bias. This particular bias lead to unreliable estimates of chronological age within each stage of medial clavicular ossification. In addition, we summarized information on the developmental asymmetry of right and left clavicles. Five relevant studies were found and 11% of included cases showed different epiphysis stages of clavicular ossification.

Discussion

These findings are consistent with our previous systematic reviews regarding estimation of chronological age by development of the hand-wrist skeleton and third molar teeth, which also revealed high risks of age mimicry bias. Our findings raise concern about the study design and sample selection process used in age estimation research. When studying the direct probability of chronological age from stage we highlight the need to include populations with uniform distribution and sufficiently wide spectrum of chronological age, or using statistical techniques like transition analysis to overcome the age mimicry bias. Another suggested possibility is to observe the minimum age for each stage (minimum age concept), which is data that is not affected by the age mimicry bias. However, this cannot give an estimate of the individual's probable age (which is centred on the mean value).

Conclusion

We are unable to assess the validity of using CT or MRI as a method to show the distribution of chronological age from each clavicular stage due to the high risk of age mimicry bias in the included studies and the observed high heterogeneity among included studies. None of the studies included a study population with a uniform distribution of chronological age, which leads to potential age mimicry bias of the results (the distribution of chronological age from each clavicular stage). Studies avoiding the age mimicry selection bias are warranted for a better description of the age distribution of the medial clavicular epiphysis development stages.

Hovedbudskap (norsk)

Denne systematiske oversikten oppsummerer den forskningsbaserte dokumentasjonen på fordelingen av kronologisk alder fra forhåndsdefinerte stadier av den mediale kragebeinsutviklingen hos levende personer med CT eller MR.

Ti studier oppfylte inklusjonskriteriene våre, alle publisert de siste fem årene. Studiene var fra fem land og omfattet totalt 4190 deltakere. Ni studier brukte CT og én MR. QUADAS-2 sjekklisten ble brukt for å vurdere risikoen for systematiske skjevheter. Gjennomsnittlig kronologisk alder og 95 % konfidensintervall (95 % CI) ble presentert separat for menn og kvinner for hvert stadium av den mediale kragebeinsutviklingen.

Alle de inkluderte studiene viste høy risiko for seleksjonsskjevhet knyttet til aldersmimikering, som kan påvirke presisjonen og påliteligheten av den estimerte aldersfordelingen. Vi kan derfor ikke angi pålitelige fordelinger av kronologisk alder fra hvert stadium av den mediale kragebeinsutviklingen.

Tittel:
Estimering av alder ved hjelp av utviklingsstadier av det mediale kragebeinet: en systematisk oversikt

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Publikasjonstype:
Systematisk oversikt
En systematisk oversikt er resultatet av å
- innhente, kritisk vurdere og
- sammenfatte

relevante forskningsresultater ved hjelp av forhåndsdefinerte og eksplisitte metoder.

Svarer ikke på alt:
- Ingen studier utenfor de eksplisitte inklusjonskriteriene
- Ingen helseøkonomisk evaluering
- Ingen anbefalinger

Hvem står bak denne publikasjonen?
Folkehelseinstituttet

Når ble litteratursøket utført?
Siste søket: April 2017

Fagfeller:
- Signe Agnes Flottorp (internal)
- Kjetil Gundro Brurberg (internal)
- Andreas Schmeling ((Professor, Dr. Med og Direktør ved Rettsmedisinsk institutt, Universitet i Munster))

Sammendrag (norsk)

Innledning
Hvert år kommer unge asylsøkere til Norge uten juridisk dokumentasjon på kronologisk alder. Det er nødvendig å fastsette kronologisk alder for å sikre at barn får de rettighetene de har krav på, og for ikke å behandle voksne som barn. I Norge har alder på asylsøkere blitt estimert ved å evaluere modningen av skjelettet i hånd-håndrot og tannutviklingen. Vi har tidligere publisert systematiske oversikter som vurderte aldersfordelingen basert på håndrøntgen med Greulich & Pyle atlaset og Demirjians gradering av visdomstenner (tredje molar). Her presenterer vi en systematisk oversikt for å vurdere validiteten av å bruke computertomografi (CT) og magnetresonanstomografi (MR) av den mediale kragebeinsutviklingen for aldersestimering i levende individer.

Metode
Vi søkte etter studier i Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase og Google Scholar. Et felles søk ble gjort for å finne studier som benyttet røntgen av tenner og hånd, CT og MR av kragebein, kne og ankel, hos både menn og kvinner mellom 10 og 25 år. Et oppdatert søk ble gjennomført i april 2017 kun for CT og MR av kragebein, kne og ankel. To personer vurderte uavhengig av hverandre referansene og risiko for systematiske skjevheter i de inkluderte studiene basert på QUADAS-2 sjekklisten. Gjennomsnittlig kronologisk alder og standardavviket ble ekstrahert for hvert stadium, separat for menn og kvinner fra alle inkluderte studier.

Resultat
Vi fant 10059 referanser i det første søket og 663 i det andre søket. Totalt 63 potensielt relevante publikasjoner ble vurdert i fulltekst. Vi inkluderte 10 artikler, alle publisert de siste fem årene. Ni studier brukte CT og én brukte MR. Studiene inkluderte mellom 152 og 752 personer med kjent kronologisk alder. Totalt var det seks studier fra Tyrkia, og én studie fra hvert av landene: Australia, Kina, Tyskland og Thailand.

Aldersspennet i studiene og antallet i hver aldersgruppe varierte i stor grad. Basert på QUADAS-2 sjekklisten hadde alle de inkluderte studiene høy risiko for seleksjonsskjevheten aldersmimikering. Denne formen for seleksjonsskjevhet kan påvirke estimatene av gjennomsnittlig kronologisk alder fra hvert utviklingsstadium av kragebeinet. Det ble også observert stor heterogenitet mellom de inkluderte studiene. I tillegg har vi oppsummert informasjon om forskjeller i utvikling mellom høyre og venstre kragebein. Fem relevante studier ble funnet og 11 % av de inkluderte deltakerne viste forskjellige epifysestadier.

Diskusjon
Disse resultatene er i samsvar med funnene fra våre tidligere systematiske oversikter om estimering av kronologisk alder ved hjelp av røntgenbilder av håndskjelettet og visdomstenner. Funnene våre viser problemer knyttet til studiedesign og utvelgelse av deltakere til aldersestimeringsstudier. Når man studerer den direkte sannsynligheten av alder fra stadium er det viktig å fordele antall deltakere jevnt mellom hver aldersgruppe og inkludere en populasjon med tilstrekkelig bredt aldersspenn, eller å benytte statistiske teknikker slik som transisjonsanalyse for å redusere konsekvensen av aldersmimikering. En annen mulighet er å observere den laveste observerte alder for hvert stadium («minimum age concept»), som vil være upåvirket av aldersmimikeringen i studiene. Ulempen er at en slik bruk av dataene ikke vil gi et estimat av personens sannsynlige alder (som gjenspeiles i gjennomsnittsverdiene av kronologisk alder fra hvert stadium).

Konklusjon
Vi kan ikke vurdere validiteten knyttet til å bruke CT og MR som metode for å angi fordelingen av kronologisk alder for hvert stadium av kragebeinsutviklingen på grunn av aldersmimikering i studiene og høy heterogenitet mellom studiene. Ingen av studiene inkluderte en studiepopulasjon med jevn aldersfordeling, noe som fører til potensielle systematiske skjevheter i de ekstraherte resultatene (fordelingen av kronologisk alder for hvert steg av kragebeinsutviklingen). Studier som unngår seleksjonsskjevheten aldersmimikering er nødvendig for å få bedre mål på aldersfordelingen for hvert stadium av kragebeinsutviklingen.

Preface

This systematic review summarizes evidence of age distribution according to the ossification stages of medial clavicular epiphysis using CT or MRI. We have previously published two systematic reviews on age assessment by skeletal hand-wrist maturation using the Greulich & Pyle atlas and wisdom teeth formation using Demirjian's grading. In parallel with the current study, we have carried out another systematic review on age assessment of knee and ankle by CT and MRI. We have chosen to write these systematic reviews as separate documents, but we use consistent texts throughout the documents where relevant.

The project group consisted of:

- Kristoffer Y. Ding, project leader, Norwegian Institute of Public Health
- Veslemøy Rolseth, Oslo University Hospital
- Pål Skage Dahlberg, Oslo University Hospital
- Annhild Mosdøl, Norwegian Institute of Public Health
- Gyri H. Straumann, Norwegian Institute of Public Health
- Øyvind Bleka, Oslo University Hospital
- Gunn E. Vist, Norwegian Institute of Public Health

We thank Signe Agnes Flottorp and Kjetil Gundro Brurberg for being the internal reviewers, and Professor Dr. Med. and Director of the Institute of Legal Medicine at University of Munster, Andreas Schmeling for conducting the external review of our research protocol and final report. We also want to thank Marit Johansen as peer reviewer for our literature search.

Notably, Figure 1 is reprinted from "The value of sub-stages and thin slices for the assessment of the medial clavicular epiphysis: a prospective multi-center CT study", 2013, Daniel Wittschieber, Ronald Schulz, Volker Vieth et al, with permission from Springer Nature [Forensic Science, Medicine, and Pathology]. License no: 4382961293227.

Signe Flottorp	Gunn E. Vist	Kristoffer Y. Ding
Department director	*Unit leader*	*Project leader*

Introduction

Age estimation of individuals with unknown age has been of considerable interest in forensic practice and research, especially for young, unaccompanied asylum-seekers (1). From 1 January 2016, the Division of Forensic Sciences at the Norwegian Institute of Public Health, now at the Oslo University Hospital, received the national assignment to take the scientific responsibility for medical age assessment. It was decided to conduct systematic reviews of various methods used for medical age assessment.

There are a number of biological changes as a person grows and develops. The assessment of specific developmental stages constitutes the basis for medical age assessments. Currently, the most widely used methods (2) are based on evaluation of radiographs of hand-wrist and teeth, of which we recently reviewed the methods based on the Greulich and Pyle atlas (3) and Demirjian's development stages of third molar tooth (4). In the latter review, we observed high heterogeneity in results between studies. Part of the variation may be due to the study characteristics, particularly uneven number of participants in each age group or the age range in the studies. This is known to introduce "age mimicry" bias in this type of studies. This particular form of selection bias in forensic age assessment has been discussed in detail elsewhere (4). In short, age mimicry occurs when the results are given as age from stage, and the numbers of enrolled participants in each age group are uneven, or the age range do not cover all ages that can fall into the stages analyzed. Hence, the results "mimic" the distribution of age in the reference sample (study population) (5).

Since the skeleton of hand and wrist is fully developed close to 18 years of age, it has been suggested to use regions of interest that mature at later ages, such as the clavicle or third molar teeth. Assessment of medial clavicular bone can e.g. be performed by X-ray, computed tomography (CT), magnetic resonance imaging (MRI) or sonography. We chose to review the CT and MRI method as CT is recommended over conventional radiography due to superimposition of anatomy (6). MRI is the most advanced radiation-free method and we also chose to review this method.

The purpose of this systematic review is to get an overview of how chronological age is distributed within different medial clavicular epiphysis stages, and to explore, if possible, variations between different populations. The current study, together with others, constitutes part of a basis for further discussion and recommendation on how medical age assessments should be conducted in Norway.

Description of clavicular developmental stages

There is 4 common staging systems for ossification of the clavicle: A 4-stage classification system (7, 8), Schmeling et al. 5-stage classification (9), Kellinghaus et al. 9-stage classification (10) and Ufuk et al. modified 5-stage classification (11). The studies often use one of these staging systems or a combination of these. The classification methods of the medial clavicular epiphysis defined by Schmeling et al. and Kellinghaus et al. is shown in Figure 1. The stages 1-5 illustrate the classification system by Schmeling et al. (9), while stages followed by a letter (from a to c) are the Kellinghaus substages.

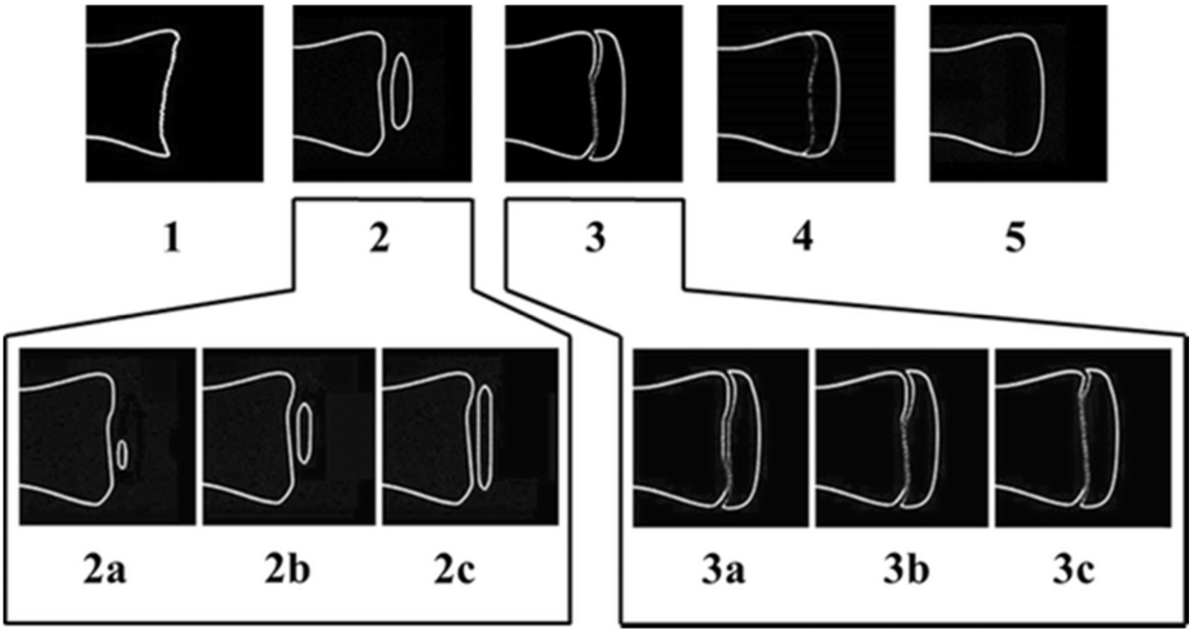


Figure 1. Assessment of the medial clavicular epiphysis. Stage 1, Ossification center has not ossified yet; Stage 2, Ossification center has ossified. Epiphyseal cartilage has not ossified; Stage 3, Epiphyseal cartilage has partially ossified; Stage 4, Epiphyseal cartilage has completely ossified. Epiphyseal scar is visible; Stage 5, Epiphyseal cartilage has completely ossified. Epiphyseal scar is not visible any more. The figure is reprinted with permission from Springer Nature (12).

For further sub-classification of the stages 2 and 3 (2a-3c), the sub-staging scheme by Kellinghaus et al. (10) is often applied. In stage 2a, the lengthwise epiphyseal measurement is one third or less compared to the widthwise measurement of the metaphyseal ending. In stage 2b, the lengthwise epiphyseal measurement is over one third to two thirds compared to the widthwise measurement of the metaphyseal ending. In stage 2c, the lengthwise epiphyseal measurement is over two thirds compared to the widthwise measurement of the metaphyseal ending. In stage 3a, the epiphyseal-metaphyseal fusion completes one third or less of the former gap between epiphysis and metaphysis. In stage 3b, the epiphyseal-metaphyseal fusion completes over one third to two thirds of the former gap between epiphysis and metaphysis. In stage 3c, the epiphyseal-metaphyseal fusion completes over two thirds of the former gap between epiphysis and metaphysis (12). The 4-stage system has a stage 4 that is a combination of the 4 and 5 in the Schmeling et al. staging system. The Ufuk et al. staging system (11) is a modified version of Schmeling et al. 5 stages.

Method

The current project included systematic literature searches on studies focusing on age estimation of the clavicle using computed tomography (CT) or magnetic resonance imaging (MRI) techniques. This systematic review is conducted following the guideline "*Slik oppsummerer vi forskning*" published by the former Norwegian Knowledge Center (13). We used the following specifications:

Inclusion criteria

Study design:	Studies that summarized data on age estimation from clavicular development stages using CT or MRI techniques
Population:	Living persons between 10 and 25 years old with no pathological clavicular findings
Index test:	Maturity stages of medial clavicular epiphysis
Reference:	Chronological age
Outcome:	Chronological age summary in each stage
Language:	Language limits was not applied to the searches. However, project members only read Chinese, Danish, English, German, Japanese, Norwegian, and Swedish. Relevant publications that we could not read due to language limitation is listed in a separate table

Exclusion Criteria:

- Studies without full-text (conference abstracts)
- Studies that is not an empirical study
- Studies using techniques other than CT or MRI
- Studies that have included remains instead of living human beings
- Studies that focused on osteometric parameters instead of age estimation
- Studies with less than 50 participants between 10 and 25 years old

Separate list

After reading full-text articles, we made a separate list for future reference to track studies that might have relevant data, but did not present the data in a way that we could utilize.

Literature search

Research librarian Gyri Hval Straumann created and conducted the literature searches and Marit Johansen peer-reviewed the search strategies. We searched for primary studies with no limit on study design, publication time, or language in the following databases:

- Cochrane Central Register of Controlled Trials (CENTRAL)
- MEDLINE (Ovid) and Pubmed [sb]
- Embase (Ovid)
- Google Scholar

The first search was carried out on 19 May 2016. This was a joint search conducted for studies using X-ray of teeth and hand, CT and MRI of the clavicle, knee and ankle in both males and females. An update search was conducted in April 2017 only for clavicle, knee and ankle. The search strategies are presented in Appendix 1.

Article selection and assessment

For the first search, six review authors (AH, GEV, GHS, KYD, PSD and VR) independently screened abstracts identified by the searches; for the second search, two review authors screened abstracts independently (GEV and KYD). All abstracts were screened in duplicates via the systematic reviews web-application Rayyan (14).

Articles were excluded if the title and/or abstract did not meet the inclusion criteria. For potentially relevant studies, the full-text articles were obtained and screened by two reviewers independently, with discrepancies resolved by consensus of reviewers. Studies that were considered as relevant to the review topic but did not meet all the inclusion criteria for the review were listed in the 'Characteristics of excluded studies' table, with the reason for their exclusion described. We recorded the selection process in sufficient detail to complete a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Risk of bias and data extraction

To evaluate the risk of bias (methodical quality) of included studies, we adopted a revised QUADAS-2 checklist (15) that has been described in detail in the previous age estimation projects on hands and teeth. KYD extracted the following information from articles, and GEV double-checked the data accordingly:

- Where and when the study was carried out (country and year)
- Scoring method (e.g. Schmeling's stages and/or Kellinghaus' substages)
- Age range, sex, and sample size
- Study design

- Sample selection method
- Age estimation method

In addition, we extracted the following data for analysis

- Mean age and its standard deviation (SD) of chronological age for each stage
- Total number of participants in each stage
- Left and right clavicle epiphysis asymmetry

Analyses

Our primary outcome is the mean age and its 95% confidence interval (95 % CI) distributed from each stage and substage of clavicular epiphysis for both genders. We illustrated the results with forest plots, which also include information about heterogeneity. In detail, we first summarized the results according to Schmeling's stage system (stage 1-5), then summarized the results according to Kellinghaus' substage system (substage 2a-3c). Specifically, for studies with only Kellinghaus substage data, in order to combine the data for the analysis of Schmeling's stage system, we first combined the substage results and then estimated the pooled mean chronological age and corresponding standard deviation with the following formula:

For the combined mean,

$$\bar{x} = \frac{\sum_{i=1}^{n} x_i}{n}$$

where x_i is the sample mean for substages, and n is the number of substages.

For the combined standard deviation,

$$s = \sqrt{\frac{\sum_{i=1}^{n} {x_i}^2 - (\sum_{i=1}^{n} x_i)^2/n}{n-1}}$$

where x_i is the sample mean for substages, and n is the number of substages.

Information on the maturation asymmetry of right and left clavicles was also collected from relevant studies and presented as a secondary outcome.

We planned to conduct meta-analysis with random effects model. Heterogeneity between included studies was evaluated by Cochran's Q test, P value of 0.10 is used to determine statistical significance. In addition, I^2 was calculated for quantifying inconsistency of results between studies. Notably, summarized results with high heterogeneity need to be interpreted with caution. The 95% confidence intervals (95% CI) of the population means and inference of heterogeneity between studies were calculated by the statistical software R (version 3.3.2) with the R- package "metafor".

GRADE framework

Notably, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool (16) is often used in systematic reviews to rate the quality and certainty of the included evidence. However, the current systematic review is not a typical diagnostic accuracy assessment study, where one presents positive/negative results with sensitivity and specificity analysis. Therefore, evaluating evidence quality by GRADE could not be conducted in the current systematic review.

Results

Results of literature search

We initially searched electronic databases and registries in May 2016 (search I), and found 10059 potential relevant publications on age estimation with hands, teeth, clavicles, knees and ankles after removing duplicates. Among those publications, we found 52 potential relevant articles on age estimation using the medial clavicle epiphysis. In addition, we carried out an update search in April 2017 (search II) and found 663 articles, in which 11 articles were of interest and were read in full-text. We eventually included ten studies. Process in detail is described below in Figure 2.

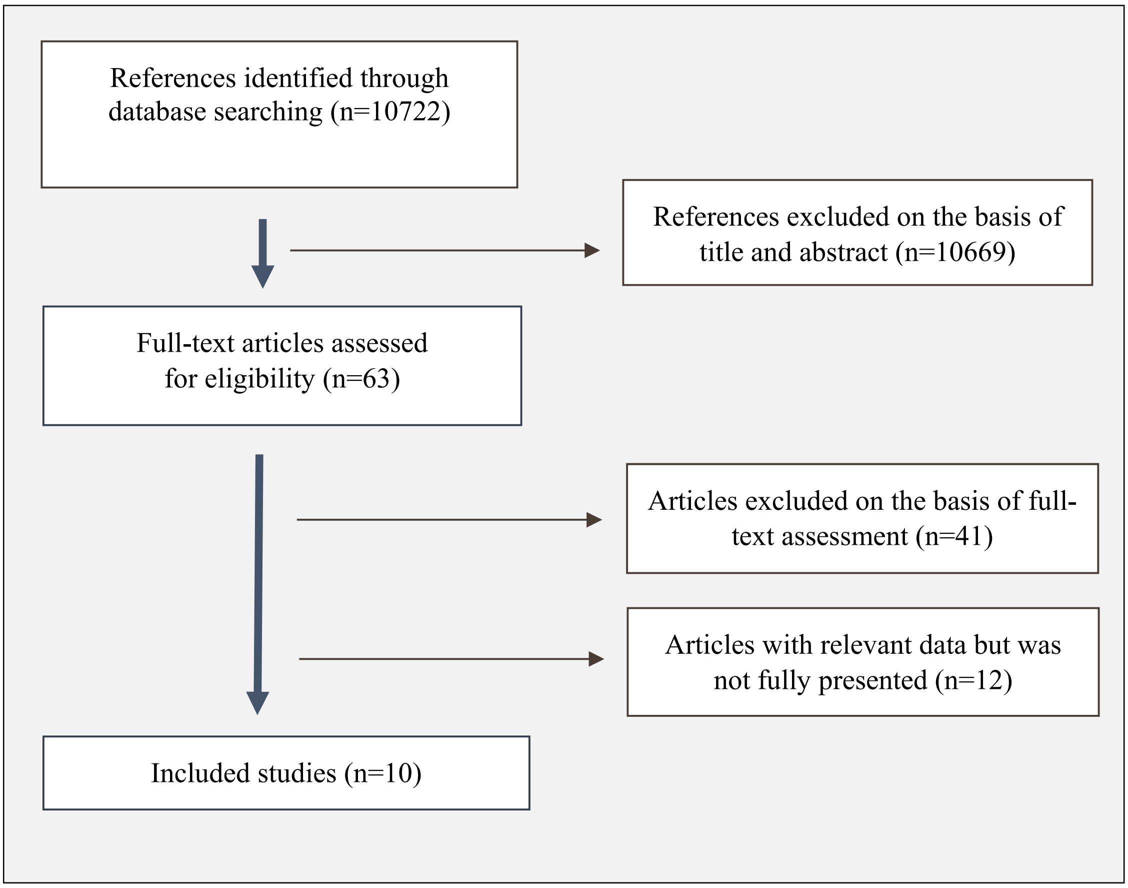


Figure 2. Flow chart of literature selection

Separate list

After reading the full-text publications, we put 12 studies on the separate list, which included nine studies using CT, two studies using MRI, and one study using both. Those studies appeared to have data that we could use, but the design or the format of the presented results could not be incorporated into our current analysis. The characteristics of the studies on this separate list are presented in Appendix 4.

Excluded studies

Of the 63 references obtained in full text, we excluded 41 due to conflicts against the inclusion criteria. See Appendix 5 for a list of excluded studies with reasons for exclusion.

Description of included studies

Of the ten studies that we included in this systematic review, eight have adopted Schmeling's 5-stage system and/or Kellinghaus' substage method on medial clavicular epiphysis. Only one study used the 4-stage classification system (Zhang et al. 2015) and Ufuk et al. 2016 has its own modification of Schmeling's 5 stages, dividing the stage 3 into 2 separate stages. The characteristics of the included studies are summarized in Table 1.

Table 1. Characteristics of included studies

Author	Year	Country	Slice thickness	Stages	Size	Age range
CT						
Ekizoglu (a) (17)	2015	Turkey	1 mm	2-3	193	13-28
Ekizoglu (b) (18)	2015	Turkey	1 mm	1-5	503	10-35
Franklin (19)	2015	Australia	< 2 mm	1-5	388	10-35
Gurses (a) (20)	2016	Turkey	0.6 - 1 mm	1-5	725	10-35
Gurses (b) (21)	2017	Turkey	0.6 - 1 mm	2-3	254	13-28
Pattamapaspong (22)	2015	Thailand	0.6 - 1 mm	1-5	409	11-29
Uysal Ramadan (23)	2017	Turkey	0.6 mm	1-5	601	10-35
Ufuk (11)	2016	Turkey	1-3 mm	1-5*	354	10-30
Zhang (24)	2015	China	1 mm	1-4#	752	15-25
MRI						
Vieth (25)	2014	Germany	Not applicable	2-4	152	18-22

**A modification of Schmeling 5-stage classification# The 4-stage classification where stage 4 is a combination of 4 and 5 in the Schmeling 5-stages system*

Studies included in the project were published during the last five years. There was one study from Germany, China, Thailand and Australia, and six studies from Turkey. Among those studies, there were nine studies using CT and one study using MRI. Most CT studies were conducted using slice thickness of 1 mm or less, which is recommended by Kellinghaus (10). The complete sample size for the CT studies was 4179 individuals, covering both genders from 10-35 years old. The MRI study was comprised of 152 male football players from 18-22 years old.

Risk of bias assessment of included studies according to QUADAS-2

Table 2 shows our risk of bias assessment of the included studies based on the QUADAS-2 checklist (15).

Table 2. Risk of bias assessment of the included studies based on QUADAS-2 checklist, with additional consideration of age mimicry.

	Domains for quality evaluation based on QUADAS-2				
	Selection bias		Index test interpretation	Reference standard	Patient flow and timing bias
Author, year	Patient selection	Age mimicry			
Ekizoglu (a) 2015	+	−	?	+	+
Ekizoglu (b) 2015	+	−	?	+	+
Franklin 2015	+	−	?	+	+
Gurses (a) 2016	+	−	+	+	+
Gurses (b) 2017	+	−	+	+	+
Pattamapaspong 2015	+	−	+	+	+
Uysal Ramadan 2017	+	−	+	+	+
Ufuk 2016	+	−	+	+	+
Vieth 2014	?	−	+	+	+
Zhang 2015	+	−	+	+	+

+ *Low risk,* ? *unclear risk and* − *high risk for systematic bias in the included study.*

Most of the included studies showed low risk of bias on Patient selection, Reference standard, and Patient flow and timing bias domain. Three studies (Ekizoglu 2015 (a), Ekizoglu 2015 (b), and Franklin 2015) showed unclear risk on Index test interpretation domain. In addition, because all the included studies presented the age ranges and corresponding sizes in each age group of the reference sample, we could assess whether the distribution of chronological age for given developmental stages are prone to the influence of age mimicry. Number of participants in eight studies showed distinguishable uneven sizes in each age group, and we therefore marked them as having high risk of age mimicry bias. Although Zhang et al. (24) and Vieth et al. (25) included similar number of participants in each age group, the age span of the reference sample did not cover all possible ages for the analysed stages. We therefore marked these two studies as high risk of age mimicry bias due to narrow age range.

Chronological age distribution and clavicular epiphysis stages using CT

Nine studies that used CT were included. We first assessed whether it was appropriate to summarize the results of these studies in meta-analyses. QUADAS-2 checklist showed that all the included studies were at high risk of being affected by age mimicry. We believe that the effect of age mimicry is so large that it could severely bias the pooled results and lead to inaccurate and unreliable estimates of chronological age in each clavicular stage. Therefore, we concluded that it is not appropriate to combine and utilize the results in meta-analyses. However, we present the findings for each study and stage graphically with estimated heterogeneity. Figures 3-7 show the results for each development stage 1-5 using Schmeling's stages for males, while figures 8-12 show the results for females. We have included the stages 1-3 from Zhang et al. 2015 using the 4-stage system as these stages corresponds to Schmeling's stages 1-3.

Figure 3. Age distribution of clavicular ossification stage 1 in males

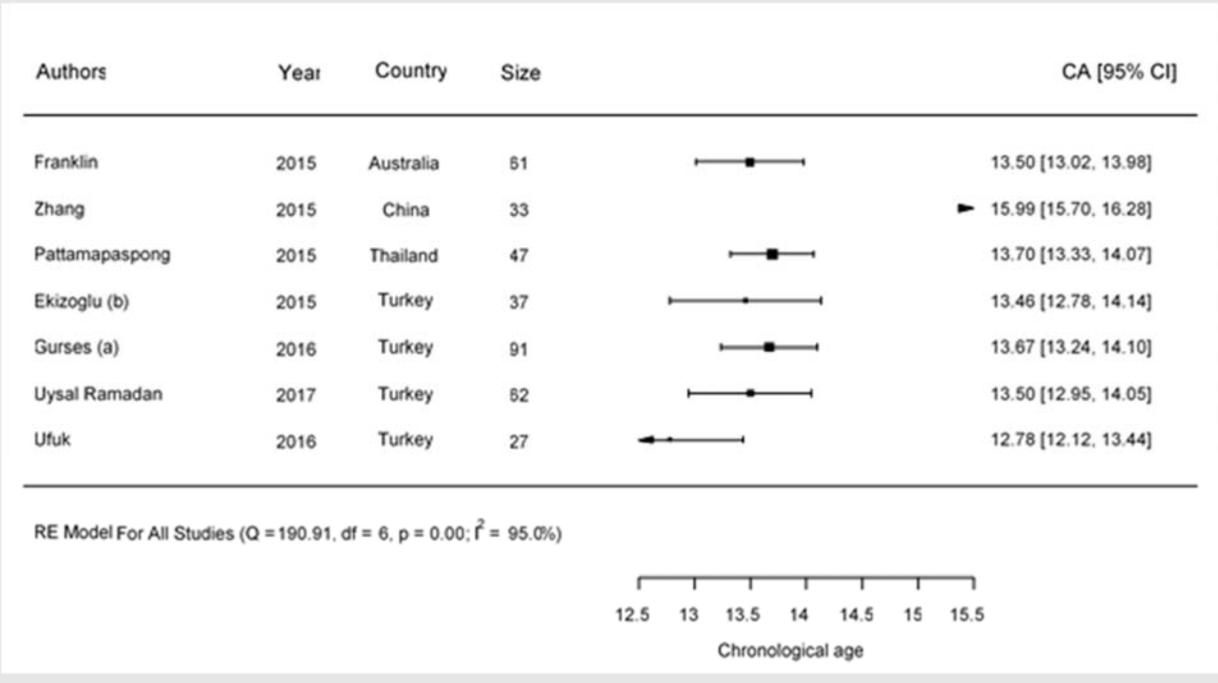


Figure 4. Age distribution of clavicular ossification stage 2 in males

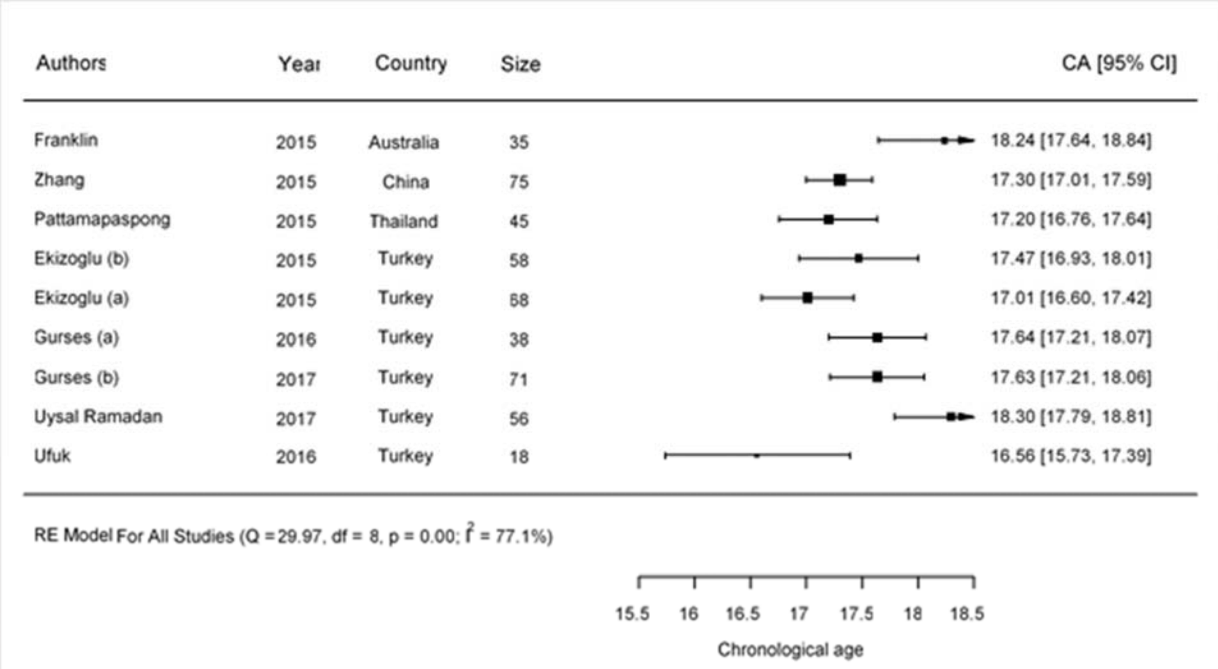


Figure 5. Age distribution of clavicular ossification stage 3 in males

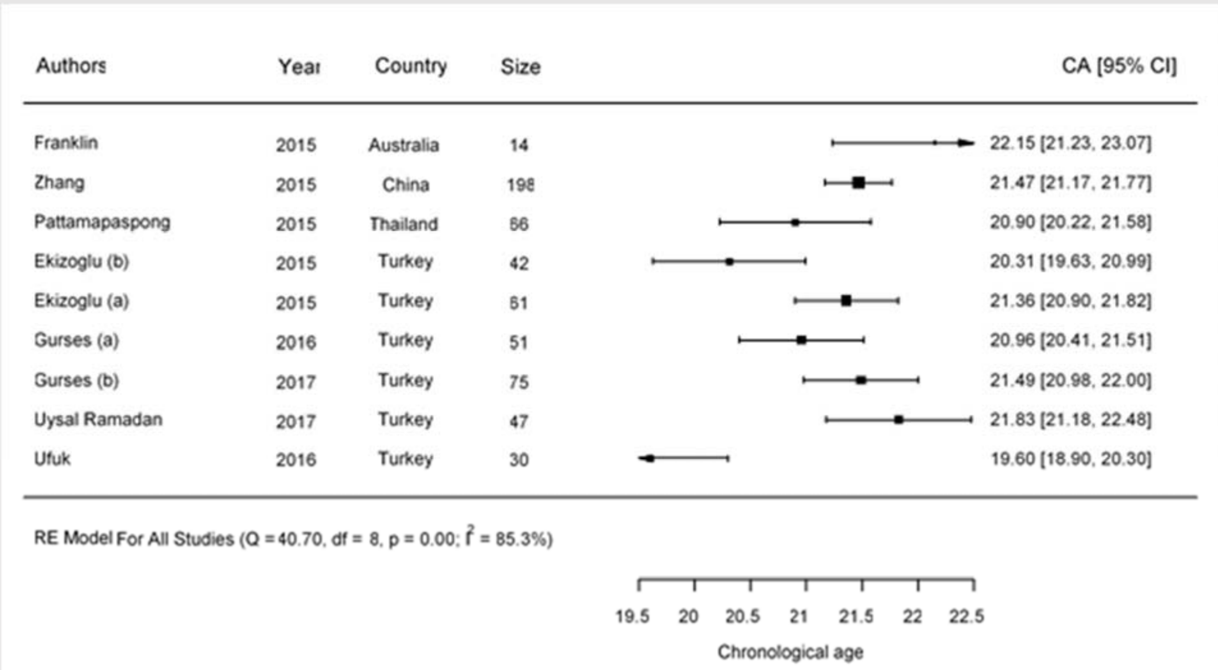


Figure 6. Age distribution of clavicular ossification stage 4 in males

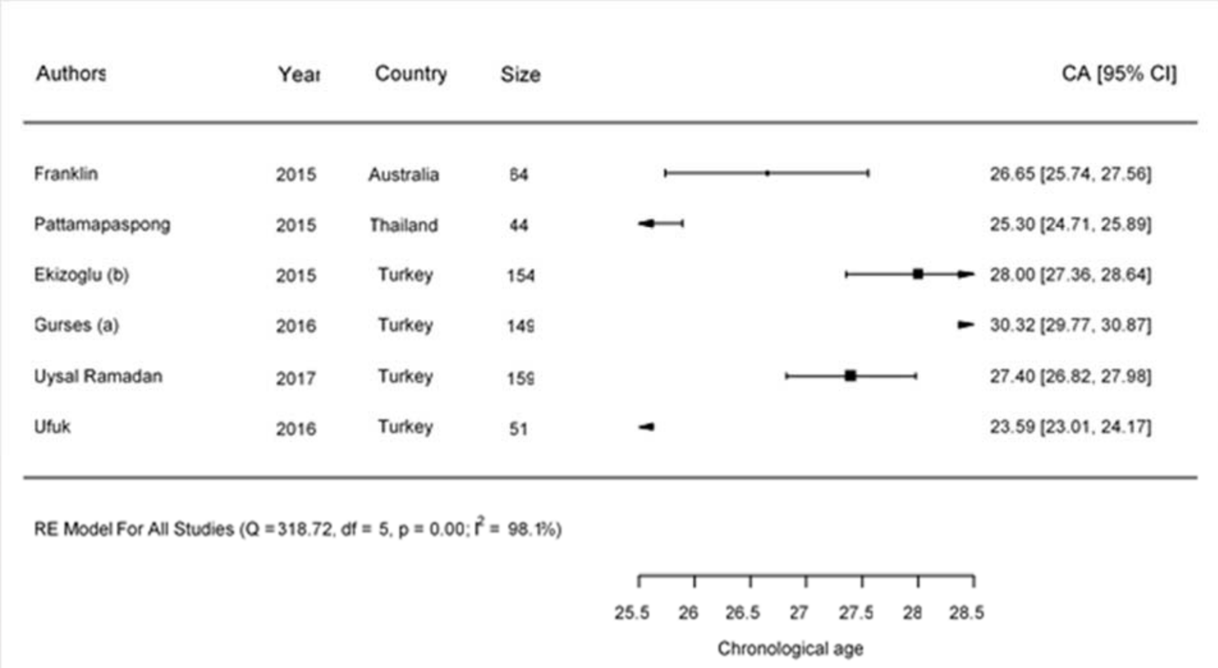


Figure 7. Age distribution of clavicular ossification stage 5 in males

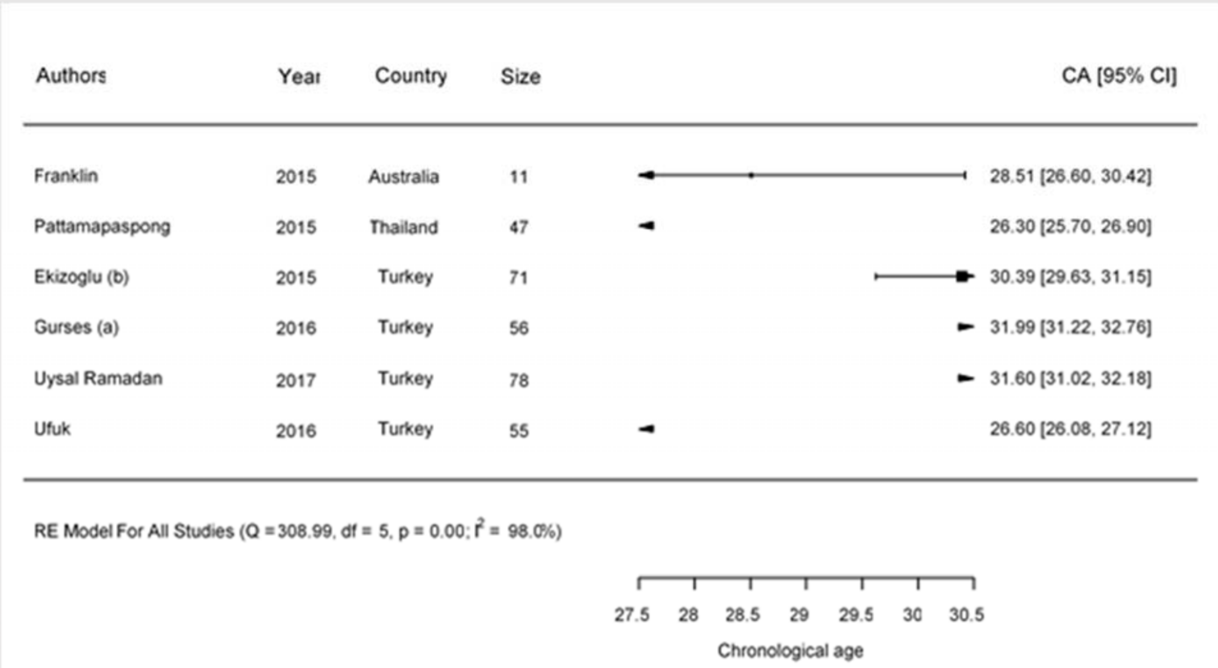


Figure 8. Age distribution of clavicular ossification stage 1 in females

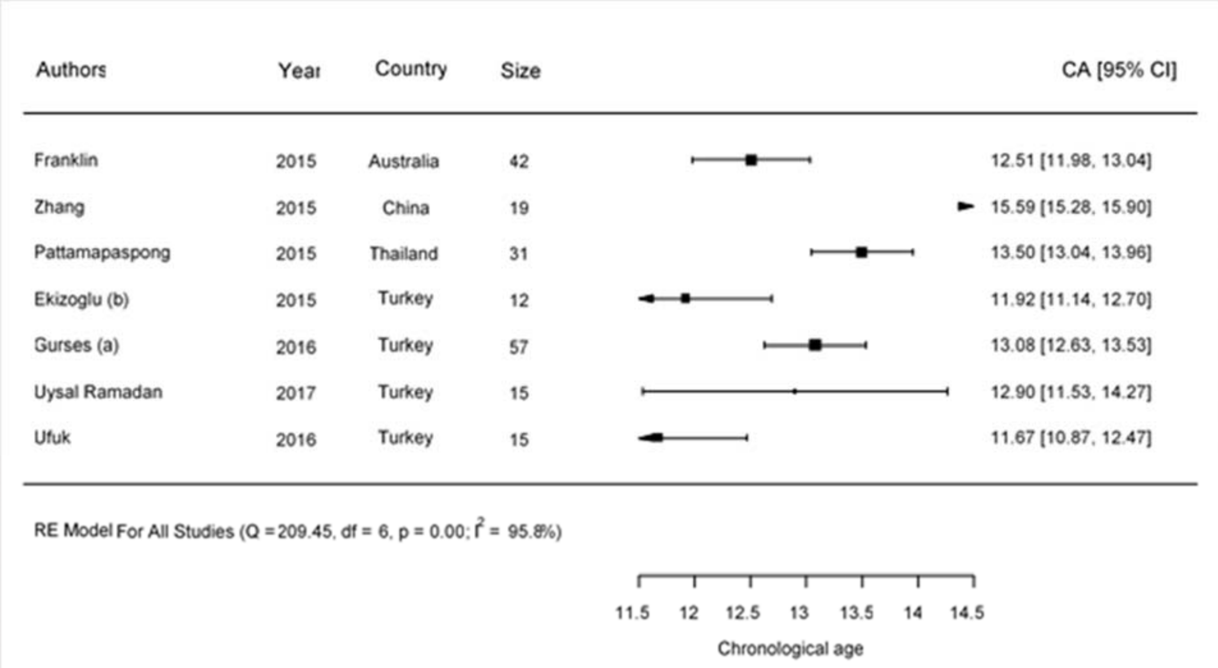


Figure 9. Age distribution of clavicular ossification stage 2 in females

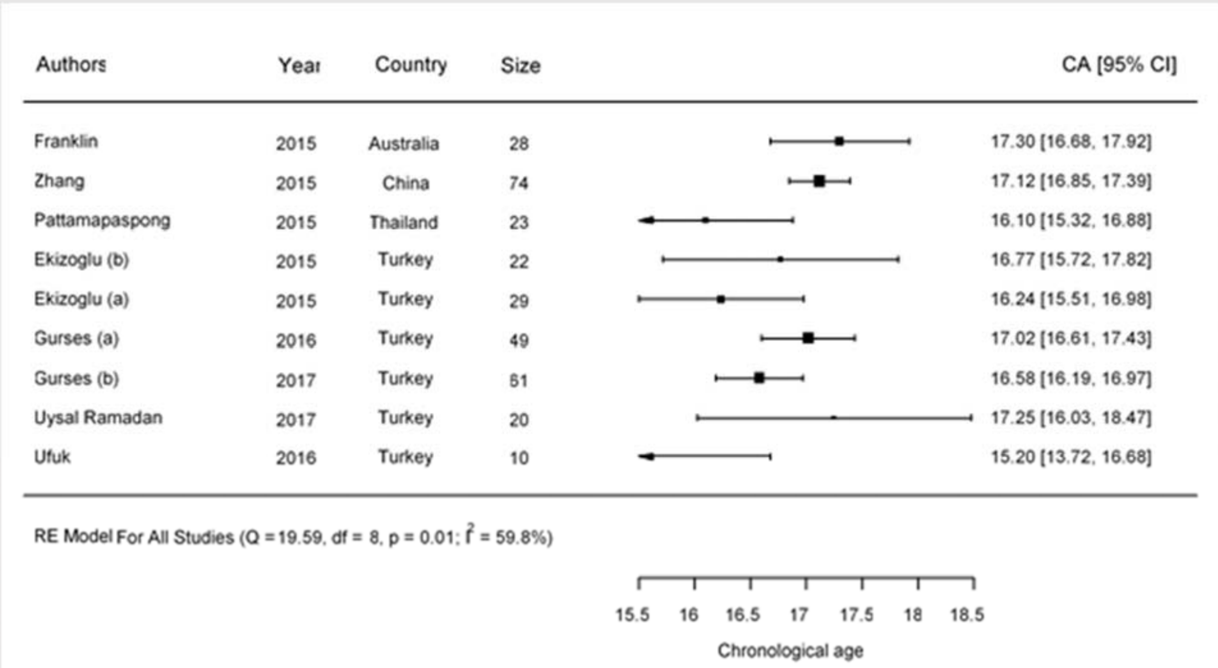


Figure 10. Age distribution of clavicular ossification stage 3 in females

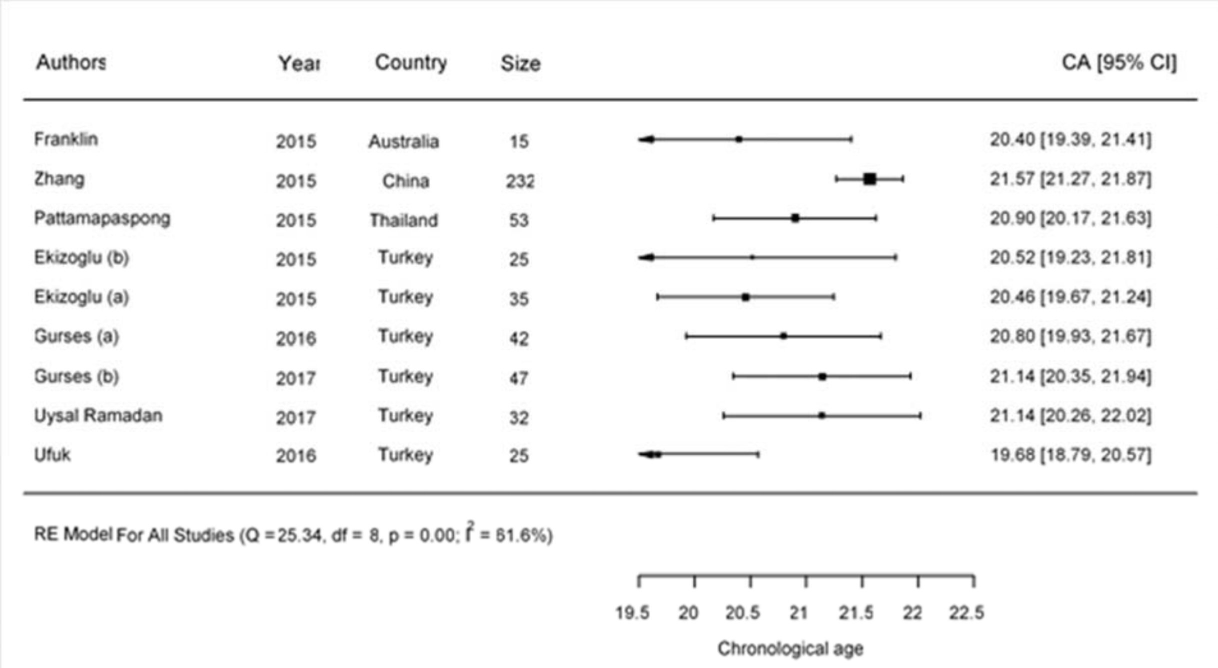


Figure 11. Age distribution of clavicular ossification stage 4 in females

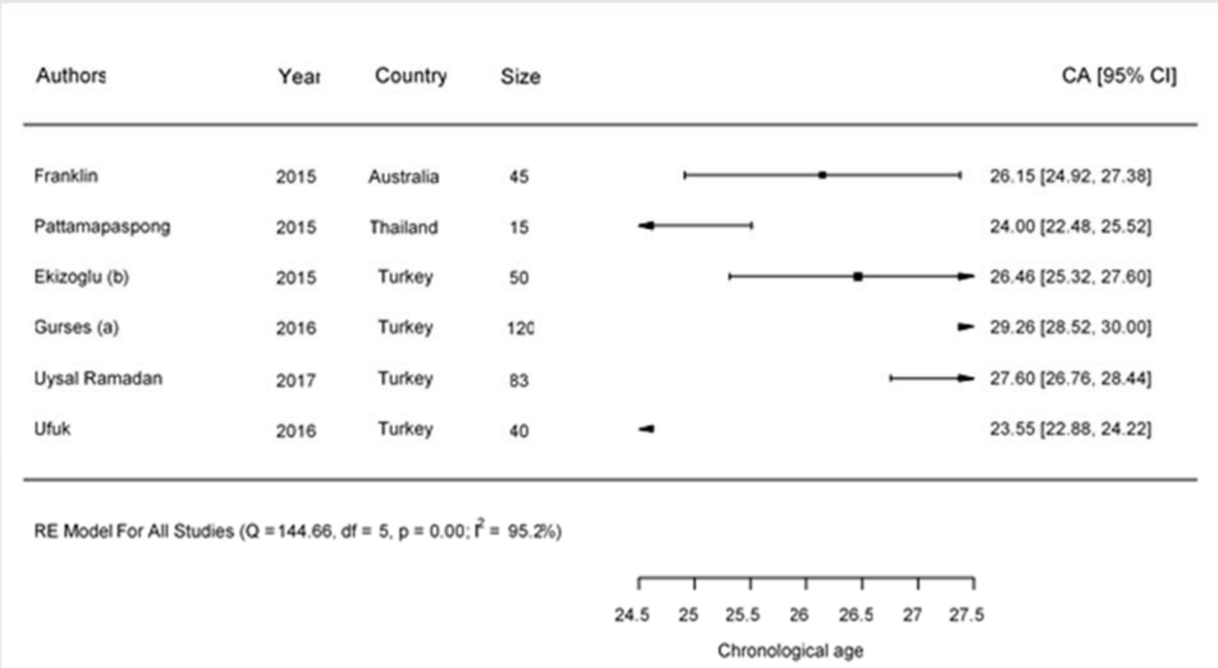
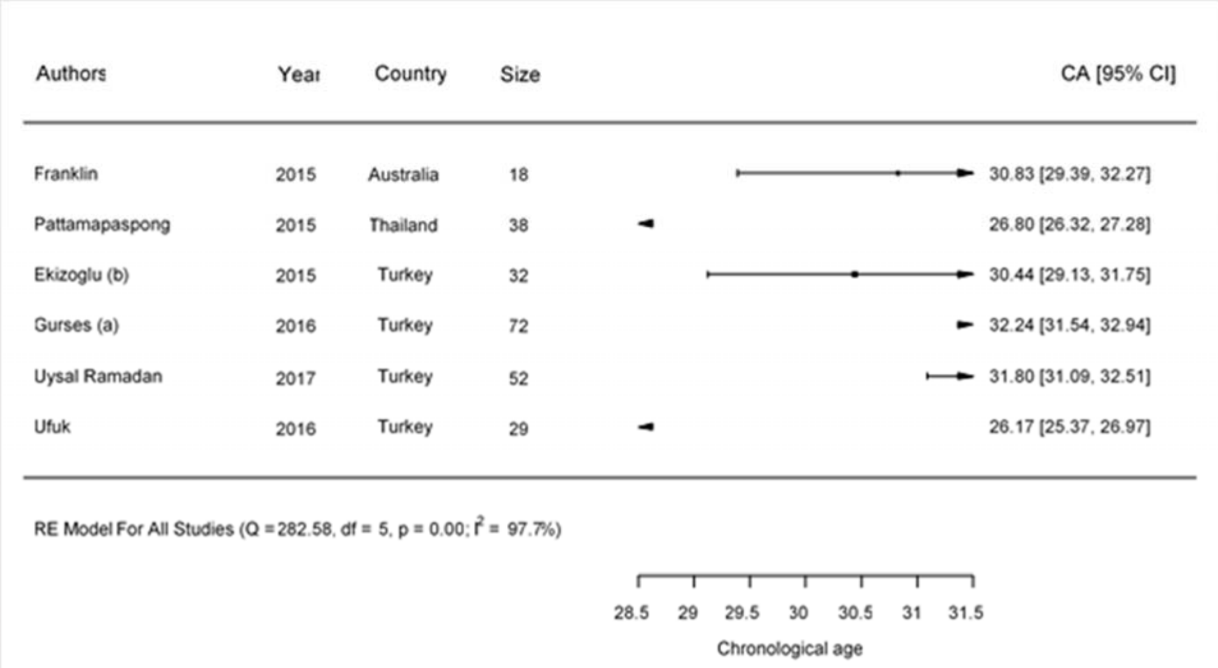


Figure 12. Age distribution of clavicular ossification stage 5 in females



We found five studies presenting results of Kellinghaus' substage. Below we present the results of age distribution in each substage in males (Figures 13-18) and females (Figures 19-24), respectively.

Figure 13. Age distribution of clavicular ossification substage 2a in males

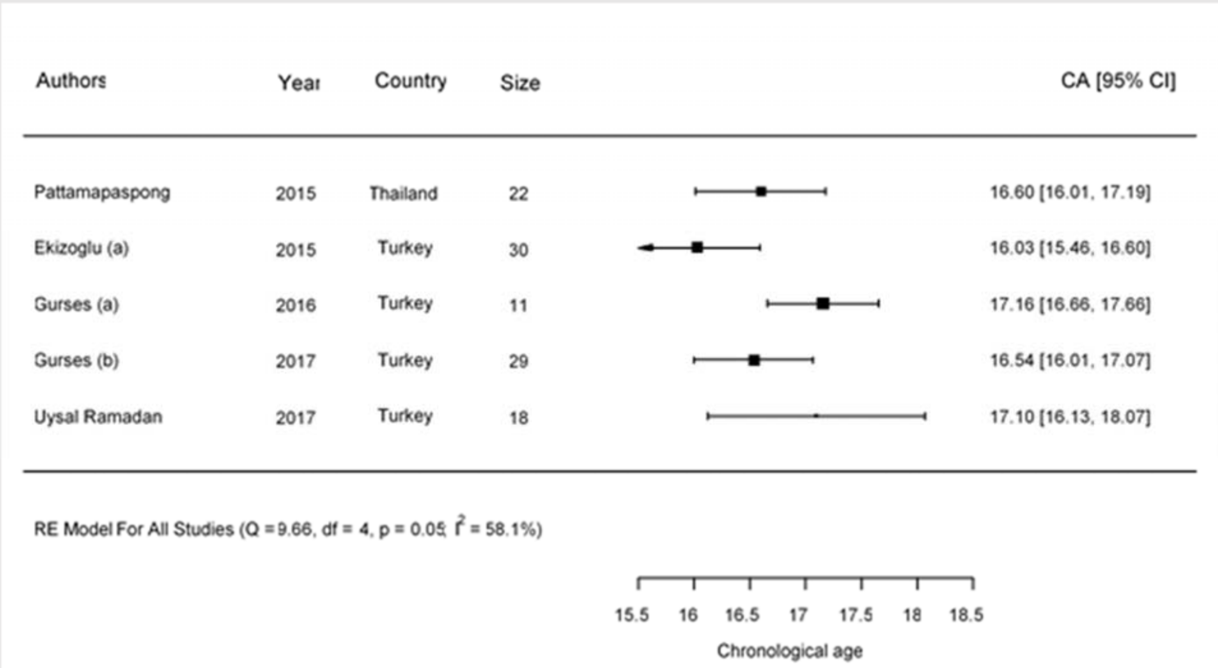


Figure 14. Age distribution of clavicular ossification substage 2b in males

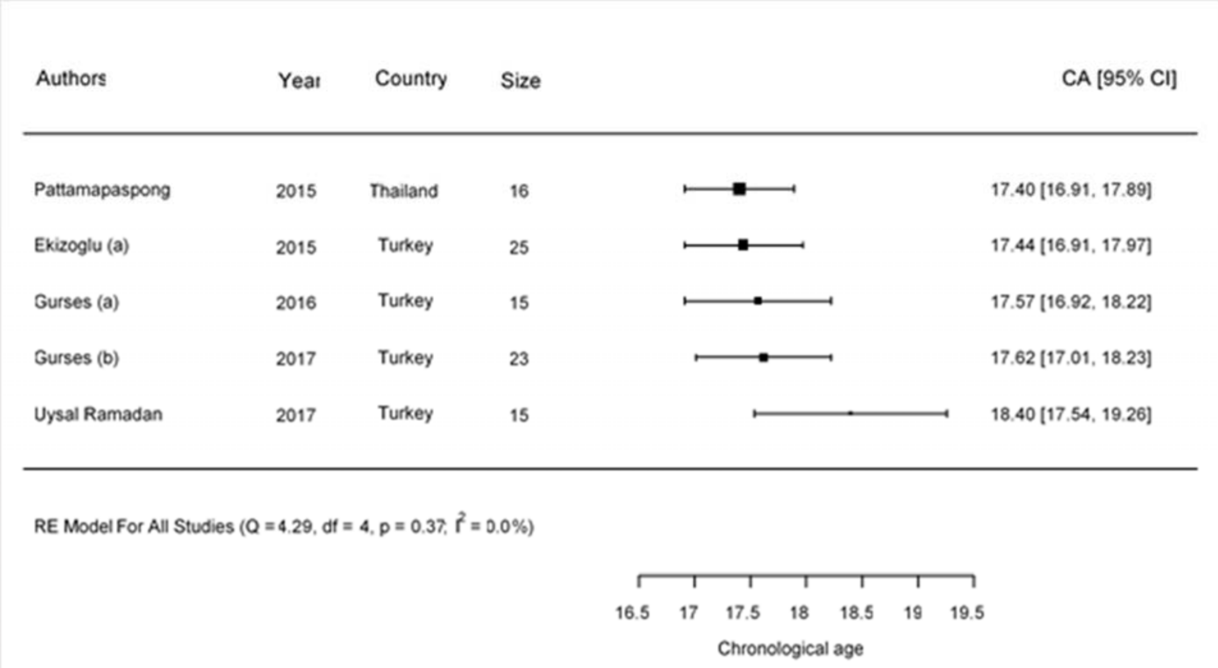


Figure 15. Age distribution of clavicular ossification substage 2c in males

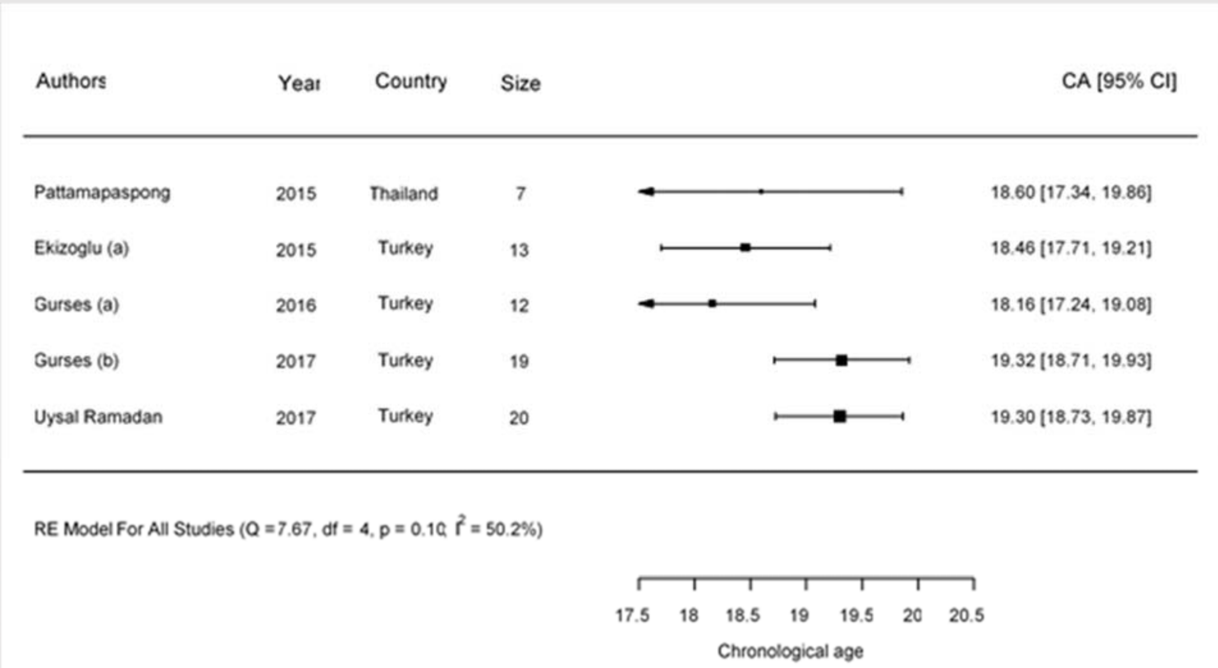


Figure 16. Age distribution of clavicular ossification substage 3a in males

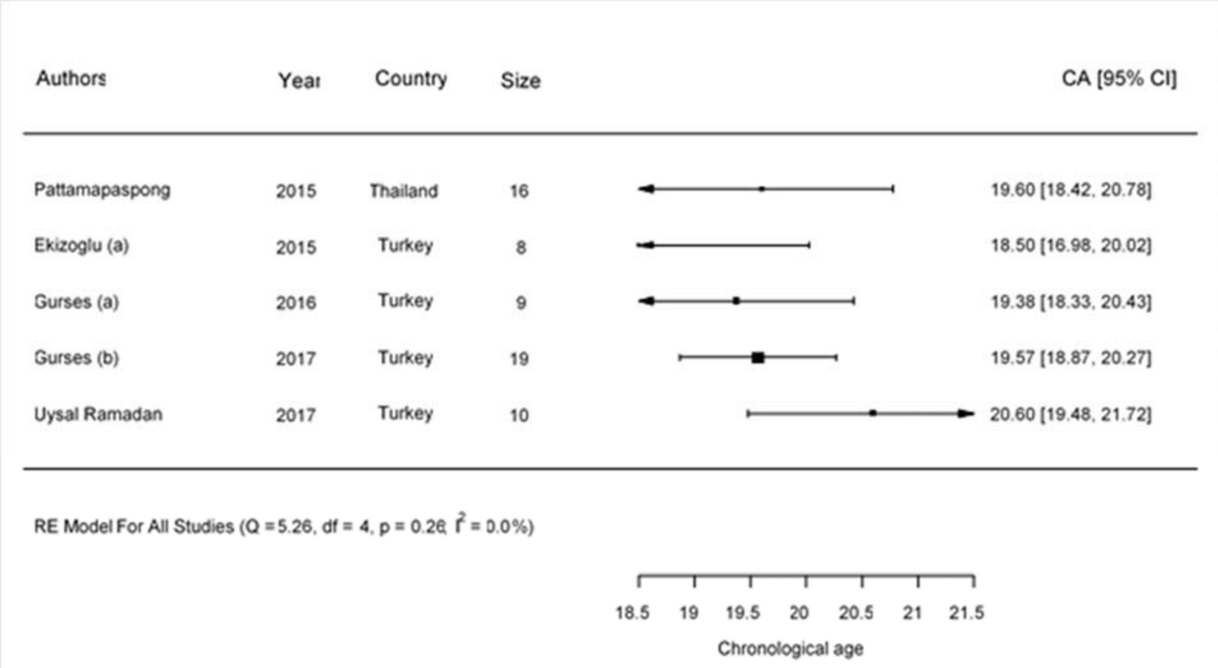


Figure 17. Age distribution of clavicular ossification substage 3b in males

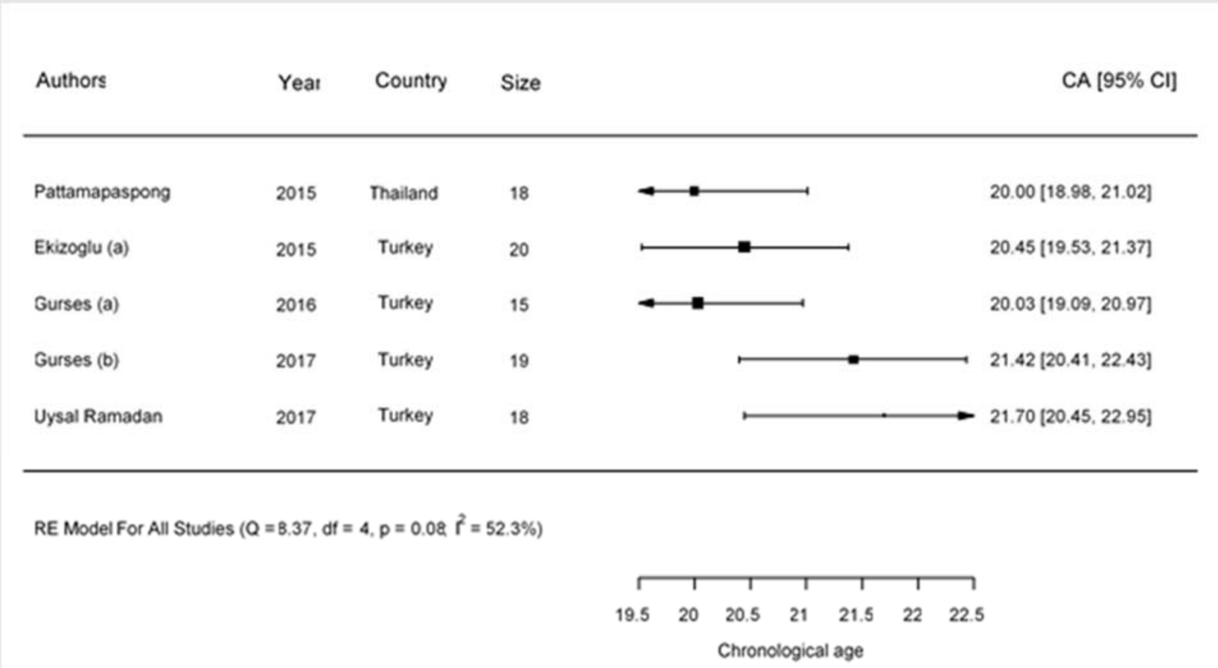


Figure 18. Age distribution of clavicular ossification substage 3c in males

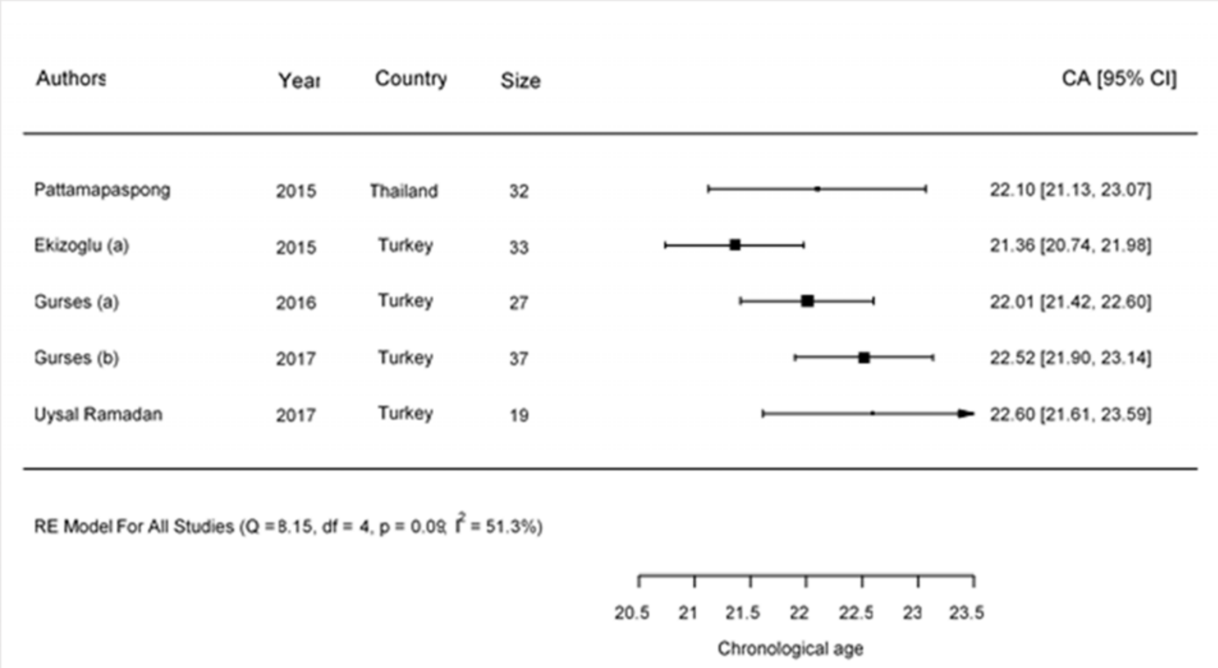


Figure 19. Age distribution of clavicular ossification substage 2a in females

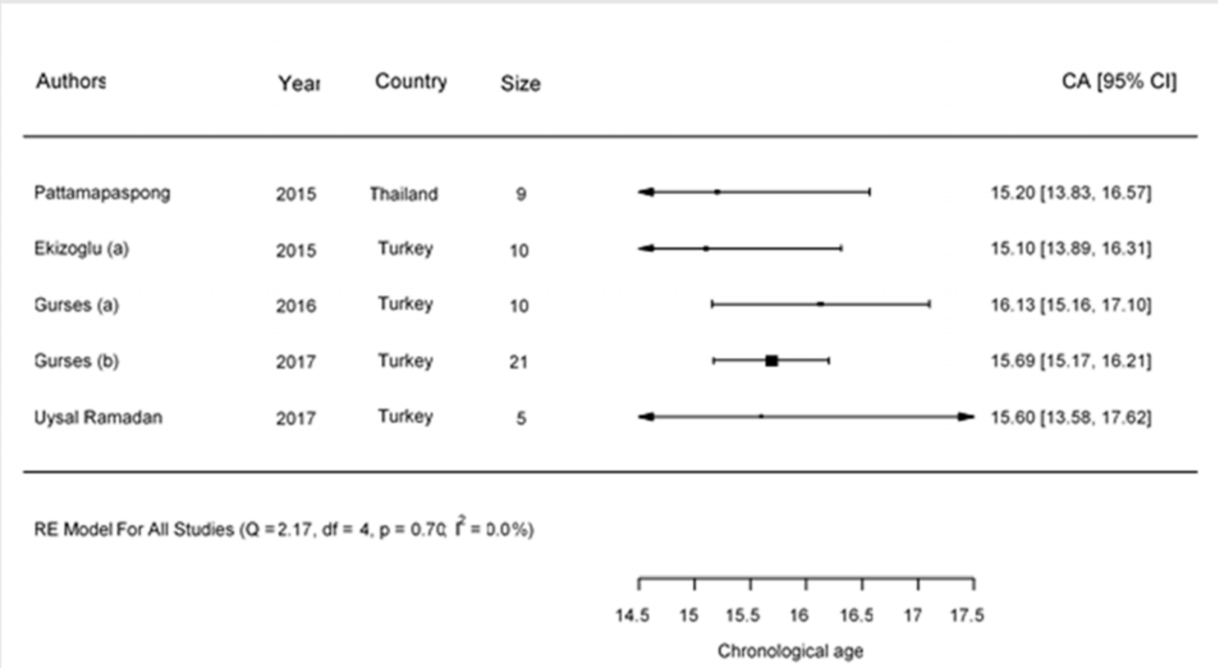


Figure 20. Age distribution of clavicular ossification substage 2b in females

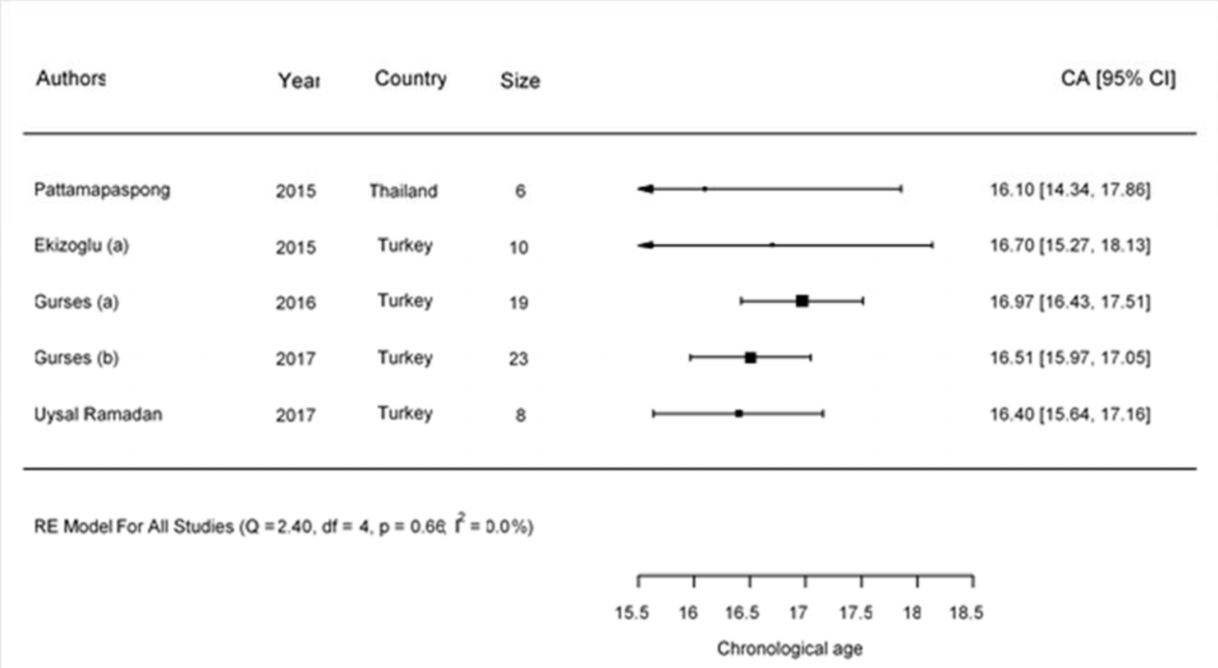


Figure 21. Age distribution of clavicular ossification substage 2c in females

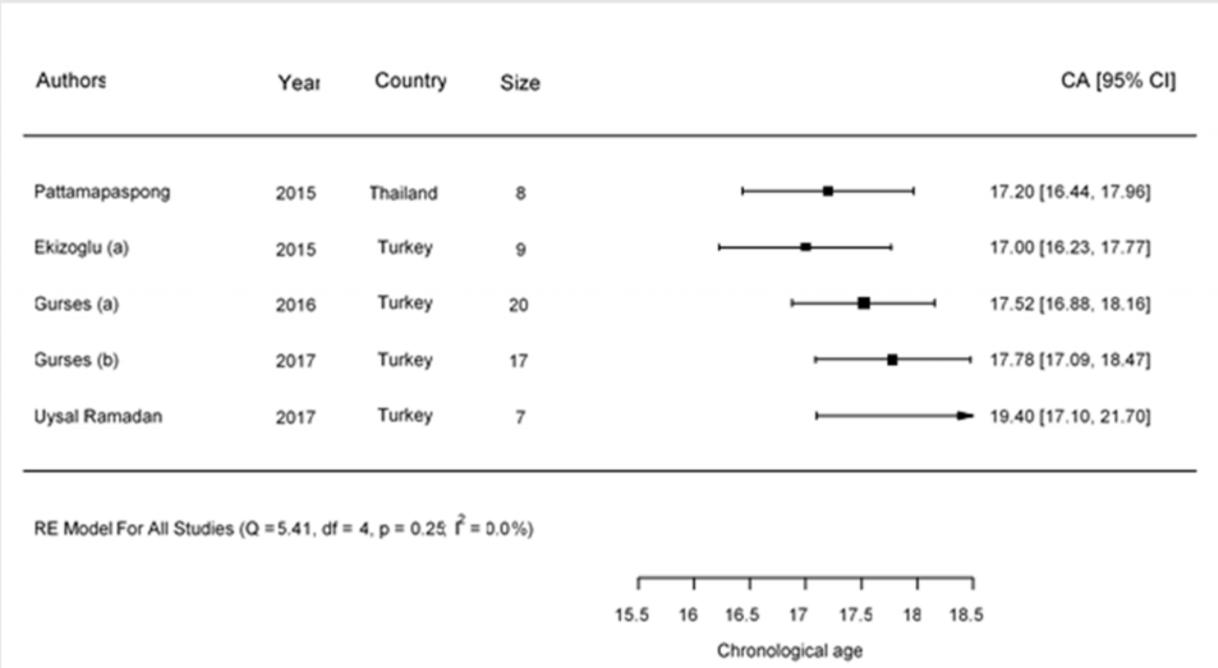


Figure 22. Age distribution of clavicular ossification substage 3a in females

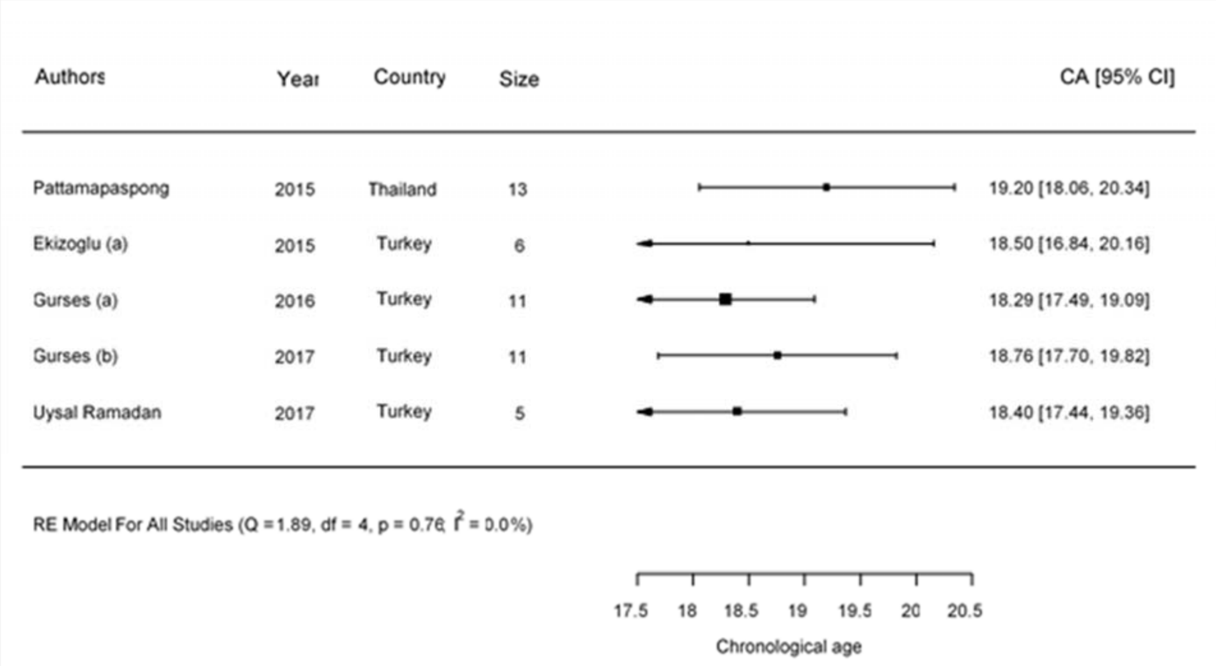


Figure 23. Age distribution of clavicular ossification substage 3b in females

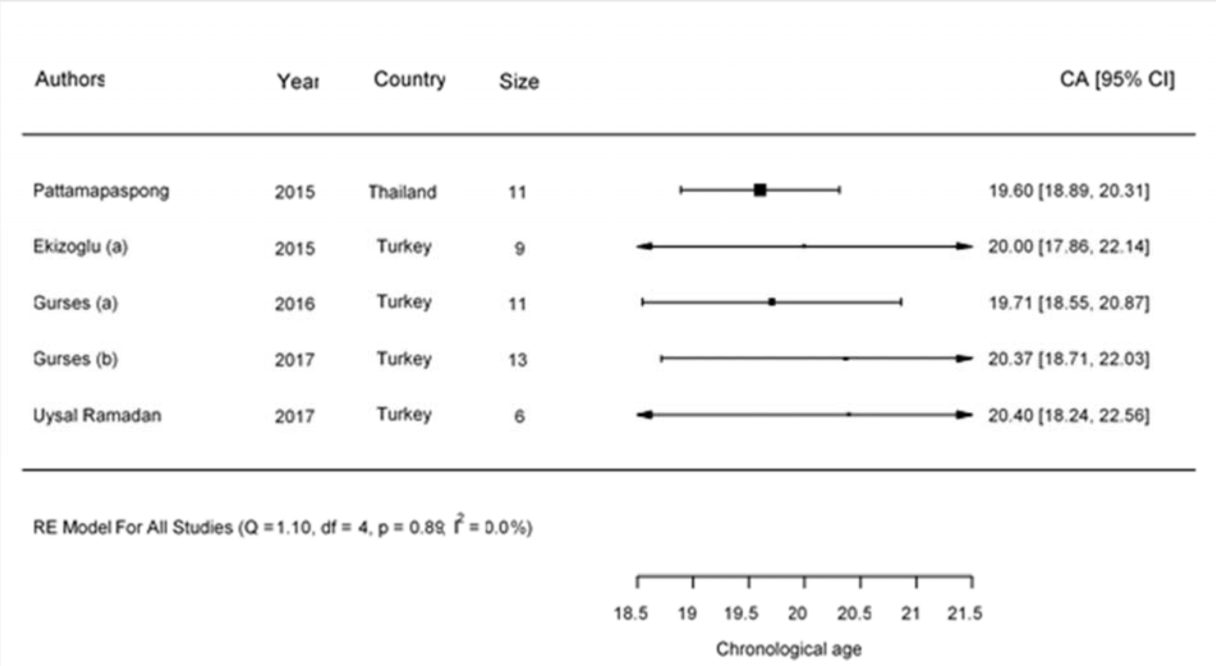
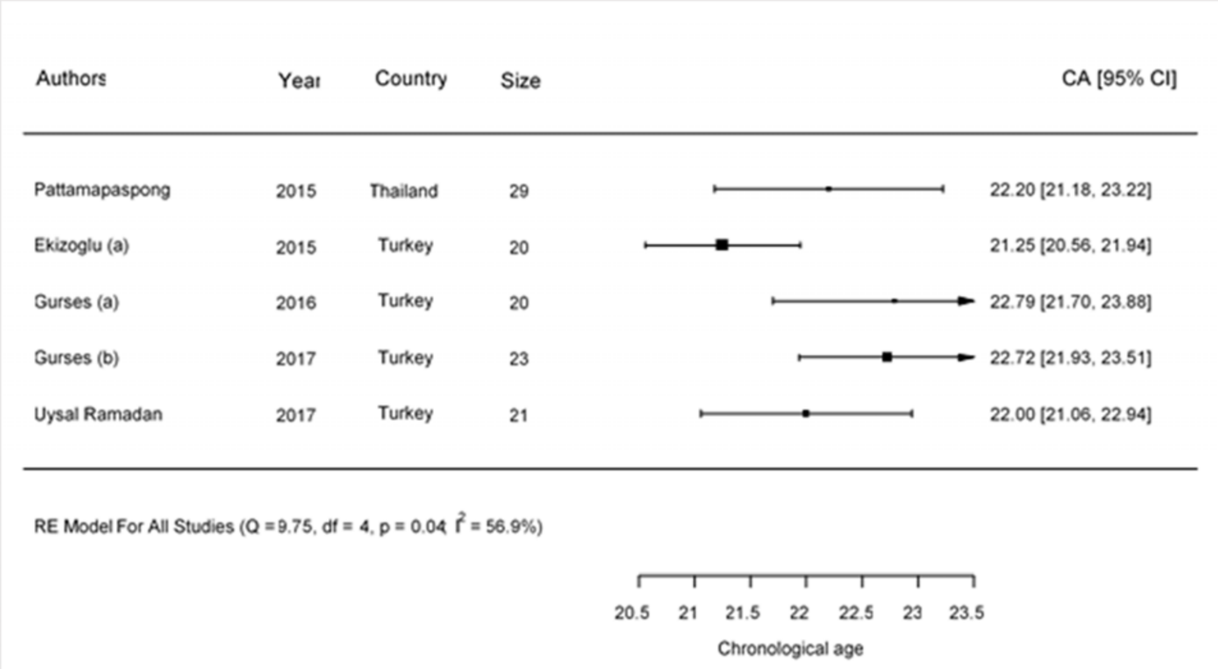


Figure 24. Age distribution of clavicular ossification substage 3c in females



Epiphysis asymmetry of right-left clavicles

Bilateral clavicle asymmetry is the difference in the fusion timing of the medial epiphysis between the two clavicular bones of the same individual. Several studies (Franklin 2015, Gurses 2016, Pattamapaspong 2015, Uysal Ramadan 2017 and Ufuk 2016) presented information on the right-left asymmetry of clavicular epiphysis development (Table 4).

Table 4. Epiphysis asymmetry of right-left clavicles

Study	Size	Differed [1]	Percentage
Franklin 2015	332	27	8.1%
Gurses 2016	725	94	13.0%
Pattamapaspong 2015	409	62	15.2%
Uysal Ramadan 2017	601	64	10.7%
Ufuk 2016	300	18	6.0%
Total	**2367**	**265**	**11.2%**

[1] Differed indicates the number of participants who appeared to have bilateral clavicle asymmetry in the assessment of medial clavicular epiphysis.

The asymmetry rate varied from 6.0% to 15.2%, the weighted average is 11.2%, suggesting a possible developmental difference between left and right clavicles in the included populations. However, it is not clear if this difference is systematic for left/right orientation and by gender.

Clavicular stages and chronological age with MRI

Only one study (25) fulfilling the inclusion criteria has explored the age distribution within clavicular stages using MRI. This study included 152 German football players from 18 to 22 years (30 men in each of the 18-20 age groups, and 31 men in the 21 and 22 age groups). The detailed age distribution is presented in Table 5.

Table 5. Statistical parameters for Schmeling stages from Vieth et al. (25)

Stage	Size	Mean±SD	Min	Max
2	15	20.4±1.1	18.4	22.3
3	111	20.6±1.5	18.1	23.0
4	1	21.2	21.2	21.2

In stage 2, there were 15 participants, with a mean age of 20.4 years (SD=1.1). The majority of participants were in stage 3, with a mean age of 20.6 years (SD=1.5). There was only one participant in stage 4, aged 21.2 years.

Discussion

Summary and key findings

In this systematic review, we have summarized evidence on the distribution of chronological age from pre-defined stages of medial clavicular ossification measured by CT or MRI in living individuals. We included ten studies (nine using CT and one using MRI) that met the inclusion criteria.

Most of the CT studies covered a relatively wide age spectrum, but included uneven numbers of participants in each age group, leading to an inaccurate estimation of age distribution due to age mimicry bias. The right-left asymmetry analysis revealed a possible developmental difference of right and left clavicles in around 11% of the included populations.

Only one MRI study was included, which included a relatively uniform sample size in each age group, but the age spectrum was too narrow, which is also associated with high risk of age mimicry bias.

Taken together, our pooled results suggested high risk of age mimicry bias in the data we extracted from all of the included studies, which is characterized by uneven number of participants in each age group or an age range not covering all ages that can fall into the analyzed ossification stages. This bias could lead to skewed and inaccurate estimates of age distribution. Future studies need to take into account the potential age mimicry bias in study design when presenting the probability of age from stage.

Quality of the results

The results of age distribution within Schmeling's stages 1-5 in both males and females showed considerable heterogeneity. This is caused by large variation in mean age between the included studies. Part of the heterogeneity might be caused by age mimicry, which is a special type of selection bias found in the data we extracted from all included studies. In addition, there might be other sources for the observed heterogeneity.

There has been an extensive debate on the causes of the observed heterogeneity between studies of skeletal maturation over the last decades. Obviously, the critical lack of well-conducted studies we have pointed at in this systematic review makes it even more difficult to identify what is truly causing the heterogeneity between studies on the ossification of the medial clavicle.

Several studies point at socio-economic status as an important variable affecting skeletal maturation (reviewed by Buckley and Clark (6)). However, the number of studies supporting this is small and the results are conflicting (6). Also, age assessment studies only occasionally report the socio-economic level of the included individuals. Buckley and Clark summarized all methods used for medial clavicle ossification in both living and remains, and conclude with CT as the method of choice for forensic age estimation. They also point to multiple factors that may influence the age assessment. These are interpreters experience, socio-economic class/regional differences and limitations of the methods applied (6).

According to the QUADAS-2 checklist, extracted data from all the included studies showed high risk of age mimicry. Among those studies, eight out of ten showed uneven numbers of participants in each age group. In addition, the other source of age mimicry bias is caused by different age range in the reference sample. Several studies included populations from 10 to 35 years old, while others used a narrower range. This systematic difference also leads to skewness when pooling the mean age from included studies according to the ossification stages, and appears to be more obvious at both the early and the late stages in both genders. As an example, Figure 3 shows the mean chronological age of clavicular ossification stage 1 in men among included studies. The mean age of Zhang et al. (24) was 1 year older than the rest of studies, most likely due to a minimum inclusion age of 15 years. Another example is shown in Figure 12 (results for stage 5 for females), in which Pattamapaspong et al. (22) and Ufuk et al. (11) only included participants younger than 30 years, while other studies included participants up to 35 years. This latter example is what is called the “end stage problem”, as the last stage of all skeletal development measurements is everlasting. The mean age within the last stage is highly dependent on the highest included ages in the reference sample. The pooled mean age (95% CI) in Figure 12 is 29.7 (27.6 – 31.8) years old (results not shown). If the included studies extended the upper boundary of age range by including more participants older than 35 years old, the pooled mean age of this stage would be driven up. In fact, this issue has also been observed in several studies (26-28) and is discussed in our consortium papers on age estimation by hand-wrist and teeth development (3, 4). The end stage problem is avoided when using the minimum age concept (29), since this is not a probability distribution of age. However, it is equally important to include a reference sample that is able to reflect a population’s true minimum age of a stage (in terms of size and age range).

The analysis of the Kellinghaus’ substages (2a-3c) revealed relatively lower heterogeneity in our analysis. The age span of the relevant substages was from 15 to 23 years, which was similar in all the included studies. This may explain the relatively lower level of heterogeneity. However, we need to keep in mind that the sample size in each substage was relatively small, resulting in larger variation in each study and hence wider confidence intervals. Therefore, the substantial within-study error in each study probably masked the heterogeneity between studies.

Regarding the right-left asymmetry of medial clavicular epiphysis, the results are relatively consistent and showed that approximately 10% of the population in the analysis might have different development stages between the right and left medial clavicle. However, it is not clear if this difference is systematic for left/right orientation and by gender, or at random. The difference in ossification of the right and left medial clavicle is not a problem as long as the same procedure is used when the method is applied in practical age assessment work as in the reference study.

Future perspective

In our opinion, age mimicry is an important source of selection bias in age estimation studies when mean age within stage is used as outcome, which also makes it less sensible to summarize individual studies that did not take this issue into account. Future studies are warranted to use uniform number of participants in each age group to estimate the age distribution, and also covering a wide age range with large sample size. An alternative approach is to collect the original research data from current studies, re-distribute and analyze them, which can yield more reliable results.

In practice, to determine age from developmental stages of skeleton or teeth a reference sample from a selected age estimation study is often applied. Therefore, to assess the most probable age interval it is crucial to have a reliable and representative reference age distribution for each stage for the individuals tested. Several age estimation studies (16, 29) have proposed transition analysis as an analytical technique to obtain reference samples. This approach estimates probability-based age of a population according to Bayes' theorem, which is known to be less sensitive to age mimicry bias. The detailed explanation of transition analysis can be found elsewhere (5).

The minimum age concept is proposed as a measurement to avoid assessing children as adults (29). As ossification of the medial clavicle is suggested as an additional method when skeletal hand is fully matured, the age prediction is focused on the question if the individual is under or over 18 years. In this matter the minimum age concept may be a preferred measurement compared to probability of an age range within a stage. Several studies indicate that ossification stage 3c and 4 represent an age over 18 years (6, 12). However, further studies assessing chronological age by clavicle ossification from several populations are warranted.

Strengths and limitations

The strength of this systematic review is the systematic and transparent approach that we have used to review the question. We have implemented systematic literature search in many electronic databases, with clear inclusion and exclusion criteria. Two people have independently considered each reference according to these criteria, and assessed the risk of bias in the included studies. These independent assessments are one of the strengths of this systematic review. Although we have conducted a thorough literature search, potential relevant studies might not have been identified. A built-in weakness with systematic review is that they may become outdated when new studies are published. This systematic review is up-to-date as of April 2017.

As the purpose of this systematic review was to evaluate age assessment by the medial clavicle ossification in the living, we excluded studies of corpses. Several reviews (6, 12) have chosen to include studies on corpses as well, and this might be regarded as a limitation of our systematic review. However, we argue that the differences between the two groups are not fully understood (e.g. movement artifacts in the study of living persons), which is the reason for our choice.

The current systematic review was undertaken to evaluate different age estimation methods in order to improve the Norwegian system for age assessment of minor asylum seekers. The assignment given was to estimate a probable age, as well as prediction values at threshold ages of 16 and 18 years. Hence, we chose to focus on the most probable age range (mean values) given the observed development stages. A different approach is to focus on the minimum age (ever observed for an individual with a certain observed development stage of e.g. the clavicle). With this approach, one may reach a high degree of certainty as to whether the individual is above eighteen. One concern with this method is that it often relies on single or few observations instead of the trend of the whole reference sample (as for the mean age of stage).

In the end-phase of the writing of this paper another systematic review on age estimation by CT of the medial clavicle epiphysis was published (30). This review included 13 papers, of which 7 overlap with our systematic review. The papers included in this study and excluded in ours do not contain numbers of individuals in each stage, which is necessary for calculation of 95 % CI. Hermetet et al. 2018 present box plots for the stages from each of the studies and focus on whether the participants are under or over 18 years old. They conclude that all individuals from all studies in stage 4 and 5 are over the age of 18 years. This is also the case for the stage 3c, except for some females in one study (22). The systematic review from Hermetet et al. (30) provides an interesting alternative way to portray results compared to ours. The minimum age concept avoids the pitfall of age mimicry bias that haunts the probability distributions of age from stage.

Conclusion

In this systematic review, we have summarized evidence that describes the use of CT and MRI to assess the distribution of chronological age from pre-defined stages of medial clavicular epiphysis. In all of the ten studies, the age estimates are likely to be influenced by a specific selection bias called age mimicry.

To get more reliable results of mean age within ossification stages, studies need to have an evenly distributed number of participants in each age group of the reference population covering a sufficiently wide age spectrum, or using statistical techniques like transition analysis to overcome the age mimicry bias. In addition, 11% of the population included in the analysis showed right-left asymmetry of medial clavicular development, which also needs to be considered when carrying out age estimation based on clavicular development stages. Nevertheless, future studies with particular consideration of age mimicry and a large reference sample are warranted for forensic age estimation. Alternatively, the studies can be used to determine the minimum age observed for a certain stage, and apply this principle to the 18 years threshold. Although those data are not subjected to the age mimicry bias, they answer a somewhat different question.

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26. Lee S-H, Lee J-Y, Park H-K, Kim Y-K. Development of third molars in Korean juveniles and adolescents. Forensic science international. 2009;188:107-11.
27. Olze A, Pynn BR, Kraul V, Schulz R, Heinecke A, Pfeiffer H, Schmeling A. Studies on the chronology of third molar mineralization in First Nations people of Canada. International journal of legal medicine. 2010;124:433-7.

28. Roberts GJ, McDonald F, Andiappan M, Lucas VS. Dental Age Estimation (DAE): Data management for tooth development stages including the third molar. Appropriate censoring of Stage H, the final stage of tooth development. Journal of forensic and legal medicine. 2015;36:177-84.
29. Schmeling A, Dettmeyer R, Rudolf E, Vieth V, Geserick G. Forensic Age Estimation: Methods, Certainty, and the Law. Deutsches Ärzteblatt International. 2016;113:44-50.
30. Hermetet C, Saint-Martin P, Gambier A, Ribier L, Sautenet B, Rérolle C. Forensic age estimation using computed tomography of the medial clavicular epiphysis: a systematic review. International journal of legal medicine. 2018.

Appendices

Appendix 1. Literature search strategy

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Search date: 2016-05-19

1. Age Determination by Teeth/ (1422)
2. Age Determination by Skeleton/ (3937)
3. (age adj3 (determinat* or estimat* or assess*)).ti. (2851)
4. ((forensic or radiological) adj age).ti,ab. (158)
5. ((age or maturation or mature or ossification) adj5 (determinat* or estimat* or assess* or examinat*)).ti,ab. (41703)
6. (hand$1 or wrist$ or carpal or metacarpal or metacarpus or dental or teeth or tooth or third molar* or clavicle* clavicula* or collar bone* or femur or tibia* or fibula* or knee or knees or foot or feet or ankle or ankles).ti,ab. (904235)
7. (MRI or MR imag* or magnetic resonance imag* or ct scan* or cat scan* or (comput* adj2 tomograp*) or roentgen or x-ray* or xray* or radiolog* or radiograp*).ti,ab. (1032026)
8. 5 and 6 and 7 (1297)
9. 1 or 2 or 3 or 4 or 8 (7491)
10. exp Animals/ (20185560)
11. Humans/ (15941900)
12. 10 not (10 and 11) (4243660)
13. 9 not 12 (7007)
14. (greulich adj2 pyle).ti,ab. (238)
15. (tanner adj2 whitehouse).ti,ab. (246)
16. demirjian.ti,ab. (218)
17. haavikko.ti,ab. (20)
18. kullman.ti,ab. (6)
19. nortje.ti,ab. (5)

20. liversidge.ti,ab. (10)
21. kvaal.ti,ab. (13)
22. or/14-21 (674)
23. 13 or 22 (7178)

Database: Embase 1974 to 2016 May 18
Search date: 2016-05-19
1. age determination/ (5176)
2. (age adj3 (determinat* or estimat* or assess*)).ti. (3291)
3. ((forensic or radiological) adj age).ti,ab. (199)
4. ((age or maturation or mature or ossification) adj5 (determinat* or estimat* or assess* or examinat*)).ti,ab. (57474)
5. (hand$1 or wrist$ or carpal or metacarpal or metacarpus or dental or teeth or tooth or third molar* or clavicle* clavicula* or collar bone* or femur or tibia* or fibula* or knee or knees or foot or feet or ankle or ankles).ti,ab. (1087091)
6. (MRI or MR imag* or magnetic resonance imag* or ct scan* or cat scan* or (comput* adj2 tomograp*) or roentgen or x-ray* or xray* or radiolog* or radiograp*).ti,ab. (1334461)
7. 4 and 5 and 6 (1656)
8. 1 or 2 or 3 or 7 (8121)
9. exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/ (23089391)
10. human/ or normal human/ or human cell/ (17222575)
11. 9 not (9 and 10) (5913580)
12. 8 not 11 (7315)
13. (greulich adj2 pyle).ti,ab. (338)
14. (tanner adj2 whitehouse).ti,ab. (279)
15. demirjian.ti,ab. (208)
16. haavikko.ti,ab. (19)
17. kullman.ti,ab. (7)
18. nortje.ti,ab. (4)
19. liversidge.ti,ab. (18)
20. kvaal.ti,ab. (11)
21. or/13-20 (794)
22. 12 or 21 (7692)

Database: Central
Search date: 2016-05-19
#1 MeSH descriptor: [Age Determination by Skeleton] explode all trees (99)

#2 MeSH descriptor: [Age Determination by Teeth] explode all trees (5)
#3 (age near/3 (determinat* or estimat* or assess*)):ti (30)
#4 ((forensic or radiological) next age) (0)
#5 ((age or maturation or mature or ossification) near/5 (determinat* or estimat* or assess* or examinat*)) (3474)
#6 (hand or hands or wrist or wrists or carpal or metacarpal or metacarpus or dental or teeth or tooth or third molar* or clavicle* clavicula* or collar bone* or femur or tibia* or fibula* or knee or knees or foot or feet or ankle or ankles) (78361)
#7 (MRI or (MR next imag*) or (magnetic next resonance next imag*) or ct-scan* or cat-scan* or (comput* near/2 tomograp*) or roentgen or x-ray* or xray* or radiolog* or radiograp*) (52159)
#8 #5 and #6 and #7 (236)
#9 (greulich near/2 pyle) (6)
#10 (tanner near/2 whitehouse) (12)
#11 demirjian (11)
#12 haavikko (1)
#13 kullman (17)
#14 nortje (9)
#15 liversidge (9)
#16 kvaal (5)
#17 #1 or #2 or #3 or #4 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 in Trials (197)

Database: PubMed

Search date: 2016-03-14

Search (((publisher [sb]) OR pubstatusaheadofprint)) AND (((age determinat*[Title/Abstract]) OR age estimat*[Title/Abstract]) OR age assess*[Title/Abstract])	46

Database: Google Scholar

Search date: 2016-03-23

"age estimation" OR "estimation of age" OR "estimating age" OR "age determination" OR "determination of age" OR "determining age" OR "age assessment" OR "assessing age" OR "assessment of age"	We screened the first 100 references

Database: Clinicaltrials.gov

Dato for søk: 2016-03-15

"age estimation" OR "estimation of age" OR "estimating age" OR "age determination" OR "determination of age" OR "determining age" OR "age assessment" OR "assessing age"	16

OR "assessment of age"	
greulich OR pyle OR demirjian OR haavikko OR kullman OR nortje OR liversidge OR kvaal	14

Database: WHO - International Clinical Trials Registry Platform (ICTRP)

Dato for søk: 2016-03-15

age estimation OR estimation of age OR estimating age OR age determination OR determination of age OR determining age OR age assessment OR assessing age OR assessment of age	20
greulich OR pyle OR demirjian OR haavikko OR kullman OR nortje OR liversidge OR kvaal	2

Appendix 2. Description of included studies with quality assessment

Ekizoglu O, Hocaoglu E, Inci E, Can IO, Aksoy S, Sayin I. Estimation of forensic age using substages of ossification of the medial clavicle in living individuals. Int J Legal Med. 2015;129(6):1259-64.		
Population: Country, ethnicity, place and year	Turkish patients who presented for trauma and other conditions at Istanbul between January 2014 and August 2014	
Age and sex, sample	193 patients, 13-28 years, 64 (33.2%) females	
Design of the study	Retrospective	
Index test	Kellinghaus stage 2a-3c, slice thickness 1 mm	
Aim of the study	"we explored the utility of the subclassification of Kellinghaus et al. in such a population and compared our data to those of previous studies"	
QUADAS-2 assessment		
Patient selection method:	Consecutive	
	Rating	**Comment**
- Consecutive or random sample of patients?	Yes	
- Avoid inappropriate exclusions?	Yes	"Patients with a history of any surgery or pathological bone conditions were also excluded"
DOMAIN 1: Patient selection	Low risk	
DOMAIN 1: Extra questions on age cohorts and age range	High risk	
- Index test interpreted without knowledge of CA?	Unclear	No relevant description
DOMAIN 2: Index test interpretation	Unclear risk	
- CA interpreted without knowledge of SA?	Yes	"Age was concealed from observers using a blind data feature of the software from the hospital"
DOMAIN 3: Reference standard	Low risk	
- All patients included in analysis?	Yes	
DOMAIN 4: Patient flow and timing bias	Low risk	

Ekizoglu O, Hocaoglu E, Inci E, Sayin I, Solmaz D, Bilgili MG, Can IO. Forensic age estimation by the Schmeling method: computed tomography analysis of the medial clavicular epiphysis. Int J Legal Med. 2015;129(1):203-10.	
Population: Country, ethnicity, place and year	Turkish patients who presented for trauma and other conditions at Istanbul between January 2013 and November 2013
Age and sex, sample	503 patients, 10-35 years, 141 (28.0%) females

Design of the study	Retrospective	
Index test	Schmeling stage 1-5, slice thickness 1 mm	
Aim of the study	"to enlarge the database by studying and reporting the results of staging the degree of ossification of the medial clavicle."	
QUADAS-2 assessment		
Patient selection method:	Consecutive	
	Rating	**Comment**
- Consecutive or random sample of patients?	Yes	
- Avoid inappropriate exclusions?	Yes	"Patients with a history of craniofacial or thoracic surgery were excluded from the study. CT scans that demonstrated clavicular fractures (45 cases) or developmental abnormalities (2 cases of clavicular aplasia) were also excluded."
DOMAIN 1: Patient selection	Low risk	
DOMAIN 1: Extra questions on age cohorts and age range	High risk	
- Index test interpreted without knowledge of CA?	Unclear	No relevant description
DOMAIN 2: Index test interpretation	Unclear risk	
- CA interpreted without knowledge of SA?	Yes	We assume age was recorded in the medical records when patients went to the hospital prior to this study
DOMAIN 3: Reference standard	Low risk	
- All patients included in analysis?	Yes	
DOMAIN 4: Patient flow and timing bias	Low risk	

Franklin D, Flavel A. CT evaluation of timing for ossification of the medial clavicular epiphysis in a contemporary Western Australian population. Int J Legal Med. 2015;129(3):583-94.	
Population: Country, ethnicity, place and year	The sample comprises individuals who presented for clinical thoracic evaluation in the Western Australian hospital system between 2006 and 2013, 80 % of those patients were admitted between 2010 and 2013
Age and sex, sample	388 patients, 10-35 years, 178 (45.9%) females
Design of the study	Retrospective
Index test	Schmeling stage 1-5, slice thickness < 2 mm
Aim of the study	"The primary objective of the study is to statistically quantify ossification and fusion timing in the medial clavicle epiphysis as visualized in high-resolution multislice CT scans"

QUADAS-2 assessment		
Patient selection method:	Consecutive	
	Rating	**Comment**
- Consecutive or random sample of patients?	Yes	
- Avoid inappropriate exclusions?	Yes	"those presenting obvious abnormal morphologies were accordingly removed; exclusions were most commonly made on the basis of anatomical shape variants associated with the medial end"
DOMAIN 1: Patient selection	Low risk	
DOMAIN 1: Extra questions on age cohorts and age range	High risk	
- Index test interpreted without knowledge of CA?	Unclear	No relevant description
DOMAIN 2: Index test interpretation	Unclear risk	
- CA interpreted without knowledge of SA?	Yes	We assume age was recorded in the medical records when patients went to the hospital prior to this study
DOMAIN 3: Reference standard	Low risk	
- All patients included in analysis?	Yes	
DOMAIN 4: Patient flow and timing bias	Low risk	

Gurses MS, Inanir NT, Gokalp G, Fedakar R, Tobcu E, Ocakoglu G. Evaluation of age estimation in forensic medicine by examination of medial clavicular ossification from thin-slice computed tomography images. Int J Legal Med. 2016;130(5):1343-52.		
Population: Country, ethnicity, place and year	CT scans were taken from patients between January 2012 and February 2014 at the Uludag University, Turkey	
Age and sex, sample	725 patients, 10-35 years, 340 (46.9%) females	
Design of the study	Retrospective	
Index test	Schmeling stage 1-5 and Kellinghaus 2a-3c, slice thickness 0.6 - 1 mm	
Aim of the study	"The aim of our study was to use CT scans with 0.6 mm thick and 1 mm thick slices to assess the stage of clavicle ossification in the Turkish population"	
QUADAS-2 assessment		
Patient selection method:	Consecutive	
	Rating	**Comment**
- Consecutive or random sample of patients?	Yes	

- Avoid inappropriate exclusions?	Yes	Patients with endocrine disorders (36 cases), constitutional growth retardation or cerebral palsy (41 cases), clavicular fracture (17 cases), chronic illness (43 cases), developmental abnormalities (20 cases), artifacts due to motion or contrast medium (21 cases), missing or doubtful data on chronological age (7 cases), and anatomic shape variants (131 cases) were excluded from the study.
DOMAIN 1: Patient selection	Low risk	
DOMAIN 1: Extra questions on age cohorts and age range	High risk	
- Index test interpreted without knowledge of CA?	Yes	"Prior to and during the image assessments, neither of the examiners knew the age of the patients."
DOMAIN 2: Index test interpretation	Low risk	
- CA interpreted without knowledge of SA?	Yes	We assume age was recorded in the medical records when patients went to the hospital prior to this study
DOMAIN 3: Reference standard	Low risk	
- All patients included in analysis?	Yes	
DOMAIN 4: Patient flow and timing bias	Low risk	

Gurses MS, Inanir NT, Soylu E, Gokalp G, Kir E, Fedakar R. Evaluation of the ossification of the medial clavicle according to the Kellinghaus substage system in identifying the 18-year-old age limit in the estimation of forensic age-is it necessary? Int J Legal Med. 2017;131(2):585-592.		
Population: Country, ethnicity, place and year	CT scans of the chests of patients were performed between February 2014 and October 2016 at the Uludag University, Turkey	
Age and sex, sample	254 patients, 13-28 years, 108 (42.5) females	
Design of the study	Retrospective	
Index test	Kellinghaus 2a-3c, slice thickness 0.6 - 1 mm	
Aim of the study	"our aim was (a) to observe the Kellinghaus substaging system in a large sample, (b) to determine the age limits of the stages relative to sex, and (c) to compare our data with other studies, including surveys conducted within the Turkish population"	
QUADAS-2 assessment		
Patient selection method:	Consecutive	
	Rating	**Comment**
- Consecutive or random sample of patients?	Yes	

- Avoid inappropriate exclusions?	Yes	Patients with endocrine disorders (17 cases), constitutional growth retardation or cerebral palsy (26 cases), clavicular fracture (7 cases), chronic illness (25 cases), developmental abnormalities (9 cases), single clavicle (1 case, excision of clavicle), and those with missing or doubtful data on chronological age (2 cases) were excluded from the study.
DOMAIN 1: Patient selection	Low risk	
DOMAIN 1: Extra questions on age cohorts and age range	High risk	
- Index test interpreted without knowledge of CA?	Yes	"Prior to and during the image assessments, the ages of the individuals were not known to the two radiologists."
DOMAIN 2: Index test interpretation	Low risk	
- CA interpreted without knowledge of SA?	Yes	We assume age was recorded in the medical records when patients went to the hospital prior to this study
DOMAIN 3: Reference standard	Low risk	
- All patients included in analysis?	Yes	
DOMAIN 4: Patient flow and timing bias	Low risk	

Pattamapaspong N, Madla C, Mekjaidee K, Namwongprom S. Age estimation of a Thai population based on maturation of the medial clavicular epiphysis using computed tomography. Forensic Sci Int. 2015;246:123.e1-5.		
Population: Country, ethnicity, place and year	CT scans were taken between January 2007 and 2014 in patients of Thai nationals at Chiang Mai, Thailand.	
Age and sex, sample	409 patients, 11-29 years, 160 (39.1%) females	
Design of the study	Retrospective	
Index test	Schmeling stage 1-5 and Kellinghaus 2a-3c, slice thickness 0.6 - 1 mm	
Aim of the study	"To assess the relationship between development of the medial clavicular epiphysis and age in a Thai population"	
QUADAS-2 assessment		
Patient selection method:	Consecutive	
	Rating	**Comment**
- Consecutive or random sample of patients?	Yes	

- Avoid inappropriate exclusions?	Yes	"Patients with diseases that may affect bone development including previous fractures of the clavicle, chronic illness, and patients who were treated by steroids, chemotherapy, or immunosuppressive drugs were excluded from the study."
DOMAIN 1: Patient selection	Low risk	
DOMAIN 1: Extra questions on age cohorts and age range	High risk	
- Index test interpreted without knowledge of CA?	Low risk	"Both readers were blinded for patient's ages"
DOMAIN 2: Index test interpretation	Low risk	
- CA interpreted without knowledge of SA?	Yes	We assume age was recorded in the medical records when patients went to the hospital prior to this study
DOMAIN 3: Reference standard	Low risk	
- All patients included in analysis?	Yes	
DOMAIN 4: Patient flow and timing bias	Low risk	

Uysal Ramadan S, Gurses MS, Inanir NT, Hacifazlioglu C, Fedakar R, Hizli S. Evaluation of the medial clavicular epiphysis according to the Schmeling and Kellinghaus method in living individuals: A retrospective CT study. Leg Med (Tokyo). 2017;25:16-22.		
Population: Country, ethnicity, place and year	"This retrospective study was conducted in the Radiodiagnostics Clinic of Keçiören Education and Research Hospital, Turkey between September 2014 and June 2016."	
Age and sex, sample	601 patients, 10-35 years, 202 (33.6%) females	
Design of the study	Retrospective	
Index test	Schmeling stage 1-5 and Kellinghaus 2a-3c, slice thickness 0.6 mm	
Aim of the study	"The aim of this study was to evaluate medial clavicular ossification according to the Schmeling and Kellinghaus staging methods, and to compare the data obtained with those of the studies conducted in our country and others."	
QUADAS-2 assessment		
Patient selection method:	Consecutive	
	Rating	**Comment**
- Consecutive or random sample of patients?	Yes	

- Avoid inappropriate exclusions?	Yes	"Patients with endocrine disorders (36 cases), developmental abnormalities (37 cases), genetic disorder (40 cases), clavicular fracture (17 cases), artifacts due to motion or contrast medium (21 cases), and anatomic shape variants (107 cases) were excluded from the study"
DOMAIN 1: Patient selection	Low risk	
DOMAIN 1: Extra questions on age cohorts and age range	High risk	
- Index test interpreted without knowledge of CA?	Yes	"Prior to and during the image assessments, neither of the examiners knew the age of the patients."
DOMAIN 2: Index test interpretation	Low risk	
- CA interpreted without knowledge of SA?	Yes	We assume age was recorded in the medical records when patients went to the hospital prior to this study
DOMAIN 3: Reference standard	Low risk	
- All patients included in analysis?	Yes	
DOMAIN 4: Patient flow and timing bias	Low risk	

Ufuk F, Agladioglu K, Karabulut N. CT evaluation of medial clavicular epiphysis as a method of bone age determination in adolescents and young adults. Diagno Interv Radio. 2016;22(3):241-6.		
Population: Country, ethnicity, place and year	The chest CT and pulmonary CT angiography examinations of patients acquired from September 2012 to June 2013 in Turkey were reviewed for this study	
Age and sex, sample	300 patients, 10-30, 119 (39.7%) females	
Design of the study	Retrospective	
Index test	Modified Schmeling 5 stages, slice thickness 1 - 3 mm	
Aim of the study	"we aimed to assess the medial clavicular epiphysis ossification stage in Turkish population and find a computed tomography (CT) criterion to establish whether an individual is adult or not."	
QUADAS-2 assessment		
Patient selection method:	Consecutive	
	Rating	**Comment**
- Consecutive or random sample of patients?	Yes	

- Avoid inappropriate exclusions?	Yes	"Fifty-four subjects (15.2%) were excluded from the study, due to history of malignancy (n=40, 11.2%), rickets (n=2, 0.5%), growth hormone deficiency (n=1, 0.3%), thyroid hormone deficiency (n=3, 0.8%), and insufficient documentation of the sternoclavicular joints because of artifacts or significant anatomic variations (n=8, 2.3%)"
DOMAIN 1: Patient selection	Low risk	
DOMAIN 1: Extra questions on age cohorts and age range	High risk	
- Index test interpreted without knowledge of CA?	Yes	"The age of the individuals was blinded to the observers"
DOMAIN 2: Index test interpretation	Low risk	
- CA interpreted without knowledge of SA?	Yes	We assume age was recorded in the medical records when patients went to the hospital prior to this study
DOMAIN 3: Reference standard	Low risk	
- All patients included in analysis?	Yes	
DOMAIN 4: Patient flow and timing bias	Low risk	

Vieth V, Schulz R, Brinkmeier P, Dvorak J, Schmeling A. Age estimation in U-20 football players using 3.0 tesla MRI of the clavicle. Forensic Sci Int. 2014;241:118-22.		
Population: Country, ethnicity, place and year	German males football players took the MRI examination at Munster, Germany from February 2011 to June 2011	
Age and sex, sample	152 males football players, 18-22 year	
Design of the study	Prospective	
Index test	MRI Schmeling stage 1-5, Kellinghaus 2a-3c	
Aim of the study	"the present pilot study aims to verify whether an MRI examination of the clavicles appears a promising means of proving completion of the 20th year of life"	
QUADAS-2 assessment		
Patient selection method:	Selective	
	Rating	**Comment**
- Consecutive or random sample of patients?	Unclear	"The study population comprised 30 test persons in each of the 18-, 19- and 21-year-old age categories and 31 test persons in each of the 20- and 22-year-old age categories"

- Avoid inappropriate exclusions?	Yes	79 clavicles were not evaluable due to norm variants (61 cases) or movement artefacts (18 cases).
DOMAIN 1: Patient selection	Unclear risk	
DOMAIN 1: Extra questions on age cohorts and age range	High risk	Subpopulation distributed relatively even, but population covered narrow age spectrum
- Index test interpreted without knowledge of CA?	Yes	"All the MRI images were assessed consensually by two examiners who had no knowledge of the chronological age of the test persons."
DOMAIN 2: Index test interpretation	Low risk	
- CA interpreted without knowledge of SA?	Yes	The CA is known before the MRI examination
DOMAIN 3: Reference standard	Low risk	
- All patients included in analysis?	Yes	
DOMAIN 4: Patient flow and timing bias	Low risk	

Zhang K, Chen XG, Zhao H, Dong XA, Deng ZH. Forensic age estimation using thin-slice multidetector CT of the clavicular epiphyses among adolescent western Chinese. J Forensic Sci. 2015;60(3):675-8.		
Population: Country, ethnicity, place and year	Patients underwent a CT scan of the clavicle at the West China Hospital of Sichuan University, China between July 2008 and November 2011	
Age and sex, sample	752 patients, 15-26 years, 382 (50.8%) females	
Design of the study	Retrospective	
Index test	The original 4 stage classification, slice thickness 1 mm	
Aim of the study	"The aim of this study was to clarify how strong the chronological age relates to clavicular ossification in the West China Han population using CT scans with 1 mm slice thickness."	
QUADAS-2 assessment		
Patient selection method:	Consecutive	
	Rating	**Comment**
- Consecutive or random sample of patients?	Yes	
- Avoid inappropriate exclusions?	Yes	"Cases were excluded due to medication or diseases that could affect skeletal development, clavicle fractures, imaging artefacts, and cases of normal variation (e.g., funnel-shaped clavicular epiphyses)."
DOMAIN 1: Patient selection	Low risk	

DOMAIN 1: Extra questions on age cohorts and age range	High risk	Population distributed relatively even, but population covered narrow age spectrum
- Index test interpreted without knowledge of CA?	Yes	"Prior to and during analysis of the MDCT images, the age of the individuals was not known to the examiner."
DOMAIN 2: Index test interpretation	Low risk	
- CA interpreted without knowledge of SA?	Yes	We assume age was recorded in the medical records when patients went to the hospital prior to this study
DOMAIN 3: Reference standard	Low risk	
- All patients included in analysis?	Yes	
DOMAIN 4: Patient flow and timing bias	Low risk	

Appendix 3. Separate list

In addition to the 10 included studies above, we identified 12 studies with relevant study design but no available data. These studies were listed below.

Reference	Country	Scoring tool	Scoring scale	Sample size	Sex	Age range
Wang YH, Wei H, Ying CL, Wan L, Zhu GY. The staging method of sternal end of clavicle epiphyseal growth by thin layer CT scan and imaging reconstruction. Fa Yi Xue Za Zhi. 2013;29(3):168-71.	China	CT	1-5	460	Both	15-25
Kellinghaus M, Schulz R, Vieth V, Schmidt S, Schmeling A. Forensic age estimation in living subjects based on the ossification status of the medial clavicular epiphysis as revealed by thin-slice multidetector computed tomography. Int J Legal Med. 2010;124(2):149-54.	Germany	CT	1-5	592	Both	10-35
Kreitner KF, Schweden F, Schild HH, Riepert T, Nafe B. Computerized tomography of the epiphyseal union of the medial clavicle: an auxiliary method of age determination during adolescence and the 3d decade of life?. Rofo. 1997;166(6):481-6.	Germany	CT	1-4	279	Both	0-29
Kreitner KF, Schweden FJ, Riepert T, Nafe B, Thelen M. Bone age determination based on the study of the medial extremity of the clavicle. Eur Radiol. 1998;8(7):1116-22.	Germany	CT	1-4	248	Both	0-29
Milenkovic P, Djuric M, Milovanovic P, Djukic K, Zivkovic V, Nikolic S. The role of CT analyses of the sternal end of the clavicle and the first costal cartilage in age estimation. Int J Legal Med. 2014;128(5):825-39.	Serbia	CT	1-5	154	Both	15-35
Schulz R, Mühler M, Mutze S, Schmidt S, Reisinger W, Schmeling A. Studies on the time frame for ossification of the medial epiphysis of the clavicle as revealed by CT scans. Int J Legal Med. 2005;119(3):142-5.	Germany	CT	1-5	556	Both	15-30
Schulze D, Rother U, Fuhrmann A, Richel S, Faulmann G, Heiland M. Correlation of age and ossification of the medial clavicular epiphysis using computed tomography. Forensic Sci Int. 2006;158(2-3):184-9.	Germany	CT	2-4	100	Both	16-25
Vieth V, Kellinghaus M, Schulz R, Pfeiffer H, Schmeling A, Beurteilung des Ossifikationsstadiums der medialen Klavikulaepiphysenfuge. Rechtsmedizin. 2010;20(6):483-8.	Germany	CT, MRI	1-5	Unclear	Both	Unclear
Hillewig E, De Tobel J, Cuche O, Vandemaele P, Piette M, Verstraete K. Magnetic resonance imaging of the medial extremity of the clavicle in forensic bone age determination: a new four-minute approach. Eur Radiol. 2011;21(4):757-67.	Belgium	MRI	1-5	121	Both	11-30
Tangmose S, Jensen KE, Villa C, Lynnerup N. Forensic age estimation from the clavicle using 1.0T MRI--preliminary results. Forensic Sci Int. 2014;234:7-12.	Danmark	MRI	1-4	74	Both	12-33
Houpert T, Rérolle C, Savall F, Telmon N, Saint-Martin P. Is a CT-scan of the medial clavicle epiphysis a good exam to attest to the 18-year threshold in forensic age estimation? Forensic Sci Int. 2016;260:103.e1-3.	France	CT	1-5	319	Both	15-30

Hua W, Guang-you Z, Lei W, Chong-liang Y, Ya-hui W. Correlation between age and the parameters of medial epiphysis and metaphysis of the clavicle using CT volume rendering images. Forensic Sci Int. 2014;244:316.e1-7.	China	CT	Not applicable	795	Both	15-25

Appendix 4. Excluded studies

Author	Reason
Benito M, Sánchez JA, Codinha S. Age-at-death estimation based on radiological and image analysis methods in clavicle in a current Spanish population. Int J Legal Med. 2014;128(3):523-33.	This study used X-ray approach, not CT approach
Brough AL, Bennett J, Morgan B, Black S, Rutty GN. Anthropological measurement of the juvenile clavicle using multi-detector computed tomography--affirming reliability. J Forensic Sci. 2013;58(4):946-51.	Population is not living people
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Appendix 5. Project protocol

Note: *This protocol is published on December 2016, which is a combination for several projects, including age estimation with hand, third molar teeth, clavicle and knee and ankle.*

We will conduct systematic reviews of the precision and accuracy of methods for age estimation of young people (10 to 25 years of age).

Literature search

Research librarian, Gyri Hval Straumann (GHS), will plan the searches in collaboration with the project group. Another research librarian will peer review the search strategy. GHS will execute the electronic searches for literature in the following databases:

- MEDLINE
- Embase
- Cochrane Central Register of Controlled Trials (CENTRAL)
- Google scholar

In addition, we will search for ongoing trials in Clinicaltrials.gov and WHO International Clinical Trials Registry Platform, and check references and citations of relevant articles in Web of Science.

Inclusion criteria

Study design: We will include studies that compare an age indicator of one of the index tests specified below with known chronological age.

Population: Living persons between the age of 10 and 25 years old

Index test: Age estimation tests including:

- X-ray of the hand-wrist
- dental X-ray
- CT or MR of the clavicle, knee or ankle

Reference test: Known chronological age

Outcome: For x-ray of the hand: The difference between the estimated age and chronological age, or the distribution of chronological age

given a specific age indicator (typically a pre-defined development stage).
For x-ray of the teeth or CT or MR of the clavicle, knee or ankle: The distribution of chronological age given a specific age indicator (typically a pre-defined development stage).

Language: No restrictions in the search

Exclusion criteria

We will exclude studies that have fewer than 50 living persons that qualify for our analysis.

Article selection

At least two reviewers will independently screen each of the identified references. We will conduct one combined literature search. Because we expect many studies relevant for inclusion, we plan to separate the potentially relevant references into three groups for full-text screening where we will handle each index test separately, resulting in three systematic reviews. At least two authors will independently screen each of the full-text references considered potentially relevant.

Assessment of methodological quality and data extraction

At least two authors will independently use QUADAS-2 to assess methodological quality of each of the included studies. We will resolve any disagreement by discussion or by consulting a third reviewer. One person will collect data about population (age, ethnicity and sex), where and when the studies were conducted, the reference and index tests used, and the results. Another person will check the extraction.

Statistical methods

In the current project, we would like to estimate the mean chronological age and its variation given a certain pre-defined developments stage. Therefore, we will present the mean chronological age and its 95% confidence interval separately in both genders (male/female) for all relevant development stages or categories of age (when mean difference is the outcome).

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We will use random effects models to pool summary data at trial level. Potential heterogeneity of country and publication date will be explored in Meta-regression. Publication bias will be assessed with Funnel plots and Egger's regression model (1).

Diagnostic test accuracy methods

All results will be checked for statistical heterogeneity using the Cochrane Q statistic (P<0.10) and I^2 methodology (I^2>50%). Statistical significance is set at a P value<0.05. The meta-analysis will be performed using R software (R Core Team, Vienna, Austria; version 3.3.2; using packages “glm”, “lme4” and “metafor”).

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