2017

RAPPORT

EN SYSTEMATISK OVERSIKT

Samsvar mellom kronologisk alder og skjelettalder basert på Greulich og Pyle-atlaset for aldersestimering

folkehelseinstituttet

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Oslo juli 2017.

Innhold

Hovedbudskap

Greulich og Pyle-atlaset benyttes til å anslå alder på barn og unge. Denne systematiske oversikten sammenfatter den forskningsbaserte dokumentasjonen på samsvaret mellom skjelettalder fra Greulich og Pyle-atlaset (heretter kalt GP skjelettalder) og kronologisk alder.

Totalt 17 artikler oppfylte kriteriene våre. 13 studier fremstilte resultater for GP skjelettalder fra kronologisk alder, 2 fremstilte resultater som beskriver kronologisk alder fra GP skjelettalder og 2 var datasett som vi har kunnet fremstille på begge måter. Disse fremstillingene er ikke sammenlignbare, og vi har derfor utført to separate analyser.

Forskjellen mellom GP skjelettalder og kronologisk alder var sjelden over ett år for gjennomsnittet i hver aldersgruppe.

Studiene som har beskrevet fordelingen av kronologisk alder fra GP skjelettalder er de som er mest relevante hvis Greulich og Pyle-atlaset skal anvendes til aldersestimering. Her gjorde vi ingen samlet analyse, ettersom tre av fire studier var så preget av fenomenet «aldersmimikering» at resultatene ikke var pålitelige. Vi vurderte at kun en av studiene var utført på en slik måte at den gir en god nok beskrivelse av metodens evne til å anslå alder.

Tittel:

Samsvar mellom kronologisk alder og skjelettalder basert på Greulich og Pyle-atlaset for aldersestimering: 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?

Søk etter studier ble avsluttet Januar 2017.

Eksterne fagfeller:

- Bjørn Anton Graff, Klinikk for medisinsk diagnostikk, Vestre Viken HF
- Lil-Sofie Ording Müller, Oslo universitetssykehus

Sammendrag

Innledning

Hvert år kommer det unge asylsøkere til Norge som ikke vet hvor gamle de er eller ikke kan dokumentere dette. For å sikre at barn får de rettigheter de har krav på og at voksne ikke blir behandlet som barn, er det nødvendig å fastsette en kronologisk alder. I Norge har det i flere år vært benyttet evaluering av modning av skjelett i hånd og av tannutvikling for å estimere alder på asylsøkere hvor det foreligger tvil. Disse metodene har i stor grad blitt kritisert for ikke å være presise, men per dags dato er det ikke funnet bedre metoder. I 2016 fikk Folkehelseinstituttet et nasjonalt fagansvar for å evaluere og forbedre metodene (fra 1.1. 2017 overført med Avdeling for Rettsmedisinske fag til Oslo universitetssykehus). Den rettsmedisinske faggruppen har i samarbeid med Kunnskapssenteret for helsetjenesten i Folkehelseinstituttet gjennomført en systematisk kartlegging av det vitenskapelige grunnlaget for flere metoder som benyttes til medisinske aldersvurderinger.

Formålet med denne systematiske oversikten er å sammenfatte den forskningsbaserte dokumentasjonen om samsvaret mellom kronologisk alder og skjelettalder basert på modningsstadier fra Greulich og Pyle-atlaset (GP skjelettalder), og eventuelt å belyse variasjoner mellom ulike populasjoner. Siden Greulich og Pyle-atlaset er den mest anvendte metoden for estimering av kronologisk alder basert på håndrøntgen, valgte vi å fokusere analysen på dette systemet. Parallelt har vi også gjennomført en systematisk oversikt på aldersestimering med Demirjians utviklingsstadier av visdomstenner.

Metode

Vi søkte etter studier i Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase og Google Scholar. Søket ble avsluttet mai 2016. Det ble utført ett felles søk for studier som benyttet røntgen av tenner eller hånd, samt CT eller MR av krageben, kne og ankel til aldersvurdering for barn og unge mellom 10 og 25 år. Søket for studier som benyttet Greulich og Pyle-atlaset på håndrøntgen ble oppdatert i januar 2017. To personer leste uavhengig av hverandre tittel og sammendrag for 10640 referanser. Av disse fant vi 658 publikasjoner som kunne være relevante for aldersestimering basert på håndrøntgen. To personer vurderte disse uavhengig av hverandre i fulltekst. Vi inkluderte 17 studier som har estimert alder basert på Greulich og Pyle-atlaset og samtidig har oppgitt data for hvert kronologiske år. Vi har inkludert to ulike måter å fremstille dataene på (i denne rapporten kalt fremstilling A og B). Begge metodene forutsetter en kjent kronologisk alder og en observert skjelettalder:

A) tar utgangspunkt i kronologisk alder og fremstiller gjennomsnittlig forskjell mellom kronologisk alder og GP skjelettalder basert på modningsstadier i Greulich og Pyle atlaset for aldersgrupper separat (ikke slått sammen aldre i mer enn årlige intervaller).

B) tar utgangspunkt i skjelettalder og fremstiller gjennomsnittlig kronologisk alder fra GP skjelettalder i Greulich og Pyle-atlaset.

To personer vurderte uavhengig av hverandre risiko for systematiske skjevheter i de inkluderte studiene ved QUADAS-2 sjekklisten for å vurdere kvaliteten av studier av diagnostisk nøyaktighet.

Resultat

Vi fant 17 studier som hadde sammenlignet kronologisk alder med GP skjelettalder basert på håndrøntgen og GP-atlaset. Studiene inkluderte fra 68 til 2614 personer med kjent kronologisk alder. Alle unntatt én studie inkluderte både gutter og jenter. Det var tre studier fra Tyrkia, fire studier fra India, og én studie hver fra henholdsvis Canada, Frankrike, Italia, Iran, Kina, Nederland, Spania, Taiwan, Pakistan og USA. Vi vurderte at flertallet av studiene hadde enten lav eller uklar risiko for systematiske skjevheter basert på QUADAS sjekklisten. Ett unntak var studiene med fremstilling B, hvor tre av fire studier hadde resultater med høy risiko for en spesiell form for seleksjonsskjevhet kalt aldersmimikering.

Det klare flertall av studiene har oppgitt resultatene som gjennomsnittlig forskjell mellom kronologisk alder og GP skjelettalder for aldersgrupper basert på modningsstadier i Greulich og Pyle-atlaset (fremstilling A). Analysen viser at variasjonen mellom studiene var større enn man kan forvente ved tilfeldighet, men samtidig var det relativt moderate variasjoner mellom studier fra ulike deler av verden. Det var sjelden at differansen mellom GP skjelettalder og kronologisk alder oversteg ett år i gjennomsnitt for en gruppe.

Fire studier, inkludert to vi analyserte basert på forfatternes rådata, fremstilte resultatene som gjennomsnittlig kronologisk alder i modningsstadier fra Greulich og Pyle-atlaset (fremstilling B). Vi fant at resultatene fra tre av disse studiene i høy grad var påvirket av alderssammensetningen av testpersonene. Denne skjevheten er tidligere beskrevet som aldersmimikering (*engelsk: age mimicry*). Aldersmimikering fører til at gjennomsnittsalder for hvert utviklingsstadium preges av alderssammensetningen i den inkluderte studiepopulasjonen. Kun én av de fire studiene med denne fremstillingsmåten hadde en stor inkludert populasjon som var relativt jevnt fordelt på alder: Chaumoitre 2016. Resultatene fra denne, som er en forholdsvis stor studie på en multietnisk populasjon i Marseille (Frankrike), fant at differensen mellom GP skjelettalderen på bildene i atlaset (modningsstadiene) aldri var større enn 0,5 år fra gjennomsnittet i kronologisk alder. Chaumoitre 2016 anga et pålitelig estimat for variasjonen i alder for denne populasjonen dersom man skal bruke atlaset til estimering av kronologisk alder. Basert på denne studien varierte bredden på 95 % prediksjonsintervaller for aldrene 10-19 år for gutter fra 4,0 år til 5,9 år.

Diskusjon

Vi inkluderte studier med to ulike måter å fremstille resultatene på (fremstilling A og B). Flest studier presenterte funnene som gjennomsnittlig forskjell mellom kronologisk

alder og GP skjelettalder for separate aldersgrupper basert på årskull (fremstilling A). Denne analysemetoden gir samlede resultater for GP skjelettalderen til en gruppe individer av ett årskull (for eksempel alle gutter som er 14 år). Fremstillingen reflekterer at Greulich og Pyle-atlaset opprinnelig er utviklet for å beskrive barns normale skjelettmodning. Flere av de inkluderte studiene hadde som mål å utvikle nasjonale referansestandarder. Vi har oppsummert disse studiene, og funnet at samsvaret mellom GP skjelettalder og kronologisk alder i snitt er relativt godt, selv om visse aldersgrupper i enkeltstudier kan ha en gjennomsnittsforskjell på over ett år. Disse studiene viser at Greulich og Pyle-atlaset, som er utviklet basert på røntgenbilder av barn tatt på 1930-tallet, fremdeles beskriver normal skjelettutvikling relativt godt i ulike populasjoner som er undersøkt de siste 10-15 årene. Imidlertid kan ikke standardavvikene som viser hvordan GP skjelettalder fordeler seg fra kjent alder legges til grunn for prediksjonsintervall hvis Greulich og Pyle-atlaset skal brukes til å estimere kronologisk alder (det vil si et «omvendt» scenario).

Analyser av hvordan kronologisk alder fordeler seg fra GP skjelettalder (fremstilling B) er mest egnet for å anslå usikkerheten når Greulich og Pyle-atlaset benyttes til kronologisk aldersestimering. Disse studiene må imidlertid ha en studiepopulasjon som er jevnt fordelt på alder, og sørge for at nedre og øvre aldersgrense ikke settes henholdsvis for høyt eller for lavt. For at resultatene skal bli så riktige som mulig må den inkluderte populasjonen være tilstrekkelig stor, ha tilstrekkelig mange og omtrent like mange individer i hvert alderstrinn samt dekke hele den forventede aldersspredningen for de stadiene man ønsker å undersøke. Hvis ikke kan studien bli preget av fenomenet aldersmimikering, og resultatene blir upålitelige. Vi vurderte at kun én studie unngikk dette og hadde tilstrekkelig godt studiedesign til å gi en mer korrekt skildring av hvordan kronologisk alder fordeler seg fra skjelettalderen: Chaumoitre 2016.

Først når det finnes flere tilsvarende studier er det mulig å vurdere metodens pålitelighet på tvers av studier, regioner og etnisiteter. En alternativ løsning er et prosjekt der man samler inn grunndata der observasjonene av kronologisk alder og modningsstadium er angitt per individ. Tilgangen på slike rådata vil også gi mulighet til å statistisk modellere dataene slik at effekten av aldersmimikering minimeres også i datasett med en ujevn aldersfordeling.

Konklusjon

Vi har oppsummert studiene som fremstiller GP skjelettalder fra kjent kronologisk alder, og funnet at samsvaret mellom GP skjelettalder og kronologisk alder i snitt er relativt godt, selv om visse aldersgrupper i enkeltstudier kan ha en gjennomsnittsforskjell på over ett år. Disse studiene kan ikke legges til grunn når Greulich og Pyle skal brukes til å estimere kronologisk alder.

Studiene som viser hvordan kronologisk alder fordeler seg fra GP skjelettaldrene (modningsstadiene) illustrerer direkte med hvilken usikkerhet Greulich og Pyle-atlaset estimerer kronologisk alder for en populasjon. Vi fant kun én studie med fremstilling B som hadde et pålitelig studiedesign: Chaumoitre 2016. Denne studien viste at for den inkluderte populasjonen vil 95 % prediksjonsintervall være på det minste 4 år bredt og på det meste 5,9 år bredt for gutter mellom 10 og 19 år. Dette gir et inntrykk av hvor stor variasjonen kan være når metoden tas i bruk på en gitt populasjon.

For å utforske usikkerheten for Greulich og Pyle-atlaset til å estimere kronologisk alder for andre populasjoner trengs det flere studier med tilsvarende studiedesign som Chaumoitre 2016. En alternativ løsning dersom grunndata hadde vært tilgjengelig, er å anvende andre statistiske metoder for å unngå aldersmimikering av resultatene.

Key messages (English)

The Greulich and Pyle atlas is used to estimate the age of children and adolescents. This systematic review summarizes the scientific evidence on the agreement between skeletal age from the Greulich and Pyle atlas (hereafter called GP skeletal age) and chronological age.

A total of 17 studies met our criteria. 13 studies presented results for GP skeletal age from chronological age, 2 presented results for chronological age from GP skeletal age and 2 were datasets which we used to present both types of results. These two approaches are not comparable and we have therefore conducted two separate analyzes.

The difference between GP skeletal age and chronological age was on average rarely more than one year for each age group.

The studies that presented the distribution of chronological age from GP skeletal age are the most relevant if the Greulich and Pyle atlas is used for age estimation. Here we did no meta-analysis, since results from three of the four studies were so affected by the phenomenon «age mimicry» that we do not have confidence in the results. We considered that only one study was conducted in such a way that it can adequately describe the method's ability to estimate age.

Title:

Agreement between chronological age and bone age based on the Greulich & Pyle-atlas for age estimation: a systematic review.

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:

- Excludes studies that fall outside of the inclusion criteria
- No health economic evaluation
- No recommendations

Publisher:

Norwegian Institute of Public Health

Updated:

Last search for studies:
January 2017.

Peer review:

- Bjørn Anton Graff, Research leader, Diagnostics, Vestre Viken HF

- Lil-Sofie Ording Müller, Consultant Paediatric Radiologist, Oslo University Hospital

Executive summary (English)

Background

Every year, young unaccompanied asylum seekers arrive in Norway, many without knowing how old they are or unable to document their age. To ensure that children receive their rights and that adults are not treated as children, it is necessary to assign a chronological age for these individuals. Evaluation of skeletal maturation of the hand and tooth development has been used for age assessment of asylum seekers in Norway in cases of doubt. These methods have been criticized for their lack of precision, but currently no better methods have been suggested.

In 2016, the Norwegian Institute of Public Health was assigned a national professional responsibility to evaluate and improve the methods used for medical age estimation (from 1.1. 2017 transferred with the Department of Forensic Sciences to Oslo University Hospital). Department of Forensic Sciences has, in cooperation with the Knowledge Centre for the Health Services, conducted a systematic examination of the scientific evidence on several of the medical age estimation methods.

The objective of this systematic review is to assess the scientific evidence on the agreement between chronological age and bone age based on the maturation stages of the Greulich and Pyle atlas (GP skeletal age), and, if possible, to describe any variations between different populations.

Since the Greulich and Pyle atlas is the most widely used method for age estimating based on x-ray of the hand, we chose to focus on this system. In parallel, we have also conducted a systematic review of age estimation using Demirjians development stages on wisdom teeth.

Method

We searched for studies in the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase and Google Scholar. Our search date was May 2016. The literature search covered studies that use x-ray of the teeth or hand, and CT or MRI of the clavicle, knee and ankle for age estimation of children and adolescents between 10 and 25 years. The search for studies that used the Greulich and Pyle atlas was updated in January 2017. Two people independently read title and summary for 10640 references. Of these, we found 658 potentially relevant publications for age estimation using x-ray of the hand. Two people independently considered these studies in full text. We included 17 studies with results that present age estimation based on the Greulich & Pyle atlas. We included two different approaches to present the data (in this report referred to

as approach A and B). Both approaches require a known chronological age and an observed skeletal age:

A) is based on the chronological age and presents the average difference between chronological age and GP skeletal age based on the maturation stages of the Greulich and Pyle atlas for separate age groups (ages not combined in more than annual increments).

B) is based on the GP skeletal age and presents the average chronological age from GP skeletal age in the Greulich and Pyle atlas.

Two people independently assessed risk of bias in the included studies by the QUADAS-2 checklist to assess the quality of diagnostic accuracy studies.

Results

We found 17 studies that compared chronological age with skeletal age based on hand x-ray and the GP atlas. The studies included from 68 to 2614 persons with known chronological age. All but one study included both boys and girls. Three studies were from Turkey, four studies from India, and one study each from Canada, China, France, Iran, Italy, the Netherlands, Pakistan, Spain, Taiwan, and the United States respectively. We considered that the majority of studies had either low or unclear risk of bias based on the QUADAS-2 assessments. The exception was results from the studies with approach B, where three of four studies had a high risk of a particular form of selection bias called “age mimicry”.

The majority of studies present results as the average difference between chronological age and GP skeletal age within age groups (approach A). The analysis shows that the variation between studies was greater than expected by chance, even though the variations between studies from different parts of the world were moderate. The difference between GP skeletal age and chronological age rarely exceeded one year for the average of a group in single studies.

Four studies, including two that we analyzed based on the authors' original data, present results as average chronological age within maturation stages from the Greulich and Pyle atlas (approach B). We found that results from three of these studies were influenced by the age composition of the included study population. This bias has previously been described as “age mimicry”, which means that the average age observed in each development stage is affected by the included age range and number of participants in each age group. Only one of the four studies with results using approach B had a large study population with a relatively even distribution in age groups: Chaumoitre 2016. This study of a multi-ethnic population in Marseille (France), found that the difference between GP skeletal age from the atlas (maturation stages) was on average never greater than 0.5 years from chronological age. Chaumoitre 2016 gives an appropriate estimate of the variation in age for this population if the atlas is to be used for estimation of chronological age. The width of 95% prediction intervals for boys aged 10 to 19 years ranged from 4.0 years to 5.9 years.

Discussion

We included studies with two different analytical approaches (approach A and B). Most studies presented the average difference between chronological age and GP skeletal age for separate age groups based on age cohorts (approach A). This approach provides overall results for GP skeletal age for a group of individuals within an age cohort (for example, all boys who are 14 years), and reflects that the original use of the Greulich and Pyle atlas was to describe normal skeletal maturation. We have summarized these studies, and found that on average there is a relatively strong association between GP skeletal age and chronological age on a group level, although certain ages in individual studies can have an average difference of more than one year. These studies show that the GP atlas, which is based on radiographs taken of children in the 1930s, still describes normal skeletal development relatively well in different populations studied the last 10-15 years. However, standard deviations from studies presented as approach A cannot be used to estimate predict intervals if the GP atlas is used for estimation of chronological age (which is a "reverse" scenario).

Studies on how chronological age is distributed from GP skeletal age (approach B) are most appropriate to illustrate the uncertainty of the GP atlas when it is used for age estimation. However, these studies must have a study population with an even age distribution, and ensure that the lower and upper age limits are appropriate. For the results to be as correct as possible, the study population must be sufficiently large, have roughly the same number of individuals in each age group and cover the entire expected age range for the stages one aims to examine. Otherwise, the study will be affected by the phenomenon age mimicry and the results will be unreliable. We considered that only one study had a sufficiently good study design to describe appropriately how chronological age is distributed from skeletal age: Chaumoitre 2016.

More studies similar to this example are needed to evaluate the method's ability to predict age in different populations. An alternative solution is to assemble primary data sets on chronological age and development stage for individuals. Such data will make it possible to use statistical models in order to minimize the effect of age mimicry even in datasets with an uneven age distribution.

Conclusion

We have summarized studies presenting GP skeletal age from known chronological age, and found that there is good agreement between the average values of GP skeletal age and chronological age, although certain age groups in individual studies may have an average difference of about one year. These studies cannot be used to estimate prediction intervals if the GP atlas is used for age estimation.

The studies showing how chronological age is distributed from GP skeletal ages (maturation stages) are most appropriate to illustrate the uncertainty of the GP atlas when it is used for age estimation. We found only one study with approach B that had a reliable study design: Chaumoitre 2016. This study showed that for the included population, 95% prediction intervals vary from 4 years to 5.9 years for boys between 10 and 19 years. This illustrates the uncertainty of the method when it is used on a given population to estimate age.

To explore the uncertainty of the Greulich and Pyle atlas for age estimation in other populations, more studies with the design of Chaumoitre 2016 is needed. An alternative solution is to assemble primary data sets of chronological age and development stage for individuals, and apply statistical models to minimize the effect of age mimicry.

Forord

Norske myndigheter overførte i 2016 det nasjonale ansvaret for aldersestimering av enslige unge asylsøkere til Område for rettsmedisinske fag ved Folkehelseinstituttet (nå Avdeling for rettsmedisinske fag ved Oslo universitetssykehus). I samarbeid med Kunnskapssenteret for helsetjenesten i Folkehelseinstituttet har vi kartlagt det vitenskapelige grunnlaget for flere metoder som benyttes til medisinske aldersvurderinger.

I denne systematiske oversikten oppsummerer vi vitenskapelig dokumentasjon om samsvaret mellom kronologisk alder og skjelettalder som definert i Greulich og Pyle-atlaset for aldersestimering av tenåringer. Parallelt har vi utarbeidet en systematisk oversikt om samsvaret mellom kronologisk alder og Demirjians utviklingsstadier for visdomstenner (1). Vi har utført et litteratursøk som også inkluderte aldersvurdering ved bruk av CT eller MR av krageben, kne eller ankel. Vi har valgt å skrive disse to systematiske oversiktene som separate dokument, men bruker den samme teksten på tvers av dokumentene der det er relevant. Dette gjelder spesielt i introduksjonen, i beskrivelse av metodene og i deler av diskusjonen.

Prosjektgruppen har bestått av personer fra Folkehelseinstituttet (FHI) og Oslo Universitetssykehus (OUS):

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Signe Flottorp	Gunn E Vist	Pål Skage Dahlberg
Avdelingsdirektør	*Seksjonsleder*	*prosjektleder*

Innledning

Det finnes mange situasjoner der det kan råde tvil rundt en ung persons reelle kronologiske alder, blant annet i tilknytning til barnearbeid, prostitusjon, idrett, seksuell lavalder, kriminell lavalder og asylsaker. I Norge er det primært usikkerhet om alder i saker der utlendingsmyndighetene er i tvil om asylsøkeren er mindreårig eller ikke. En enslig, mindreårig asylsøker er en asylsøker under 18 år som ikke har følge av foreldre eller andre med foreldreansvar. Ofte knytter det seg usikkerhet til unge asylsøkeres alder. Dette er fordi mange land ikke har rutiner eller systemer for registrering av fødsler og fordi mange unge asylsøkere ikke kjenner til egen alder eller ikke kan dokumentere dette. Alle personer som skal bli en del av det norske samfunnet må få en kronologisk alder, og denne er avgjørende for personens krav på blant annet beskyttelse, helsehjelp, omsorg og utdannelse.

De europeiske landene har ulik praksis for medisinske aldersvurderinger og aldersfastsettelse (2). I Norge er det Utlendingsdirektoratet som fastsetter alder. Dersom det mangler dokumenter som kan bekrefte søkernes alder eller identitet, er det aktuelt å tilby søkerne en medisinsk aldersundersøkelse. Når medisinske aldersvurderinger er gjennomført inngår det som et underlagsmateriale for aldersfastsettelsen.

Fra 1. januar 2016 fikk Folkehelseinstituttet (nå overført med Rettsmedisinske fag til Oslo Universitetssykehus) i oppdrag fra Helse- og omsorgsdepartementet å ha et overordnet medisinskfaglig ansvar for de medisinske aldersvurderingene. Bakgrunnen for dette var at Utlendingsdirektoratet selv ikke har faglig kompetanse til å vurdere kvaliteten i de benyttede metodene eller til å drive forsknings- og utviklingsarbeid. Det var derfor et ønske om at ansvaret skulle legges hos et offentlig medisinskfaglig miljø med bred kompetanse innen sakkyndigvirksomhet og forskning.

Som et ledd i arbeidet for å bygge opp kompetanse innen medisinske aldersvurderinger, ble det innledet et samarbeid mellom det rettsmedisinske miljøet og Kunnskapssenteret for helsetjenesten i Folkehelseinstituttet. Det utføres i den forbindelse systematiske forskningsoppsummeringer for flere av de mest sentrale metodene som ligger til grunn for dagens praksis for medisinske aldersvurderinger i Norge og Europa.

Det skjer en rekke biologiske endringer i takt med at et menneske vokser og utvikles. Vurderingen av spesifikke utviklingsstadier danner grunnlag for medisinske aldersvurderinger. De mest brukte metodene internasjonalt er basert på vurdering av skjelett- (som oftest hånd) og tannutvikling.

Når det er tatt et røntgenbilde av hånd og håndrot, kan man vurdere bildet opp mot et graderingssystem som igjen vil gi et estimat av kronologisk alder. Det fins ingen konsensus om hvilket graderingssystem som er best egnet til dette formålet, men systemet

det finnes flest vitenskapelige publikasjoner på er det såkalte Greulich og Pyle-atlaset (3).

Formålet med denne systematiske oversikten er å sammenfatte den forskningsbaserte dokumentasjonen om samsvaret mellom kronologisk alder og skjelettalder basert på modningsstadier fra Greulich og Pyle-atlaset, og eventuelt å belyse variasjoner mellom populasjoner. Denne systematiske oversikten vil sammen med de andre kunnskaps-oppsummeringene inngå i et grunnlag for en videre drøfting og anbefaling av hvordan medisinske aldersvurderinger bør gjennomføres i Norge.

Beskrivelse av Greulich og Pyle-atlaset

Skjelettalder (*engelsk: bone age*) vurderes ofte hos barn og unge for å kontrollere vekst, vurdere vekstpotensial, estimere slutthøyde og følge skjelettmodning hos et enkelt individ fordi dette påvirkes både av biologisk variasjon og av en rekke endokrine tilstander og pediatriske sykdommer. En slik kontroll gir informasjon om pasientens relative skjelettmodning ved et gitt tidspunkt, og kan sammen med andre kliniske observasjoner gi grunnlag for å vurdere om pasienten har en utvikling som faller utenom normalområdet. Hos normale barn og unge bør skjelettalderen falle omtrent innen to standardavvik fra referansenormene. En kilde som beskriver referansenormene for skjelettmodning er Greulich og Pyle-atlaset (3).

Denne bruken, det vil si vurdering av et individ opp mot normal skjelettalder, var bakgrunnen for at Greulich og Pyle-atlaset ble utviklet. Valideringsstudien som er gjengitt i Greulich og Pyle-atlaset er derfor bygd opp slik at den inkluderte populasjonen er gruppert etter kronologisk alder, og at skjelettalderen (med gjennomsnitt og standardavvik) er beskrevet gruppevis for hver av disse kronologiske aldrene.

«The Radiographic Atlas of Skeletal Development of the Hand and Wrist» (3), også kjent som Greulich og Pyle-atlaset, ble første gang publisert i 1950 av Dr. William Walter Greulich og Dr. Sarah Idell Pyle. Det er fremdeles en av de mest brukte referansenormene for å bedømme skjelettalder. Atlaset består av referansebilder for jenter og gutter separat, og strekker seg fra fødsel og opp til 18 år for jenter og 19 år for gutter. Ved siden av hvert bilde står det en alder (i denne rapporten kalt GP skjelettalder). Fordelingen av GP skjelettalder i atlaset er ikke identisk for gutter og jenter. Figur 1 viser modningsstadier for henholdsvis gutter og jenter fra ti år og oppover.

Gutter	Jenter
10 år	10 år
11 år	11 år
11 år og 6 måneder	
	12 år
12 år og 6 måneder	
13 år	13 år
13 år og 6 måneder	13 år og 6 måneder
14 år	14 år
15 år	15 år
15 år og 6 måneder	
16 år	16 år
17 år	17 år
18 år	18 år
19 år	

Figur 1: En oversikt over modningsstadier (bilder) i Greulich og Pyle-atlaset for henholdsvis gutter og jenter fra 10 år og oppover.

Ved siden av hvert bilde i Greulich og Pyle-atlaset står en beskrivelse av viktige endringer man kan observere for dette stadiet. Metoden er komparativ, slik at den som vurderer skjelettalderen til en person, finner bildet og beskrivelsen som ligner mest på røntgenbildet som er tatt. Stadiene er det man kaller diskrete, som betyr at analysen kun kan falle ned på akkurat de modningsstadiene som er gitt i atlaset. Det står i motsetning til kronologisk alder, som er en kontinuerlig skala.

Atlaset ble bygd opp på basis av ett datamateriale av hvite barn fra høyere sosioøkonomiske kår i Ohio på 1930-tallet. Bildene i atlaset er plukket ut ved at forfatterne skjønnsmessig fant det bildet de syntes best representerte et barn med alderen som står oppgitt ved bildet. Individet kunne ha et reelt aldersavvik på maksimalt +/-2 % fra alderen som er angitt ved bildet. Forfatterne plukket ut 100 bilder av barn med samme alder og kjønn og sorterte bildene etter deres «relative skjelettstatus», fra den minst modne til den mest modne. Så plukket de ut et bilde som de syntes best representerte den «sentrale tendensen». Dette bildet lå ofte, men ikke alltid, omtrent i midten av de 100 sorterte bildene. Slik satte de sammen et atlas av omtrent 30 bilder av henholdsvis jenter og gutter, ettersom jenters håndskjelett modnes raskere enn gutter.

Bruken av Greulich og Pyle-atlaset

Den opprinnelige bruken av atlaset var altså som verktøy for å bedømme hvorvidt et barn hadde en skjelettutvikling innen normalområdet og slik brukes det fremdeles i klinisk praksis. Disse dataene er ikke direkte overførbare til estimering av kronologisk alder, som er en situasjon der man ønsker å vise gjennomsnitt og variasjon for kronologisk alder fordelt fra et modningsstadium (det vil si fra bildene i atlaset som angir skje-

lettalder). Det er en vesensforskjell mellom disse to måtene å strukturere dataene på, selv om de reflekterer det samme fenomenet: korrelasjonen mellom modning av skjelettet og økt kronologisk alder.

Det finnes en valideringsstudie i selve Greulich og Pyle-atlaset der det er angitt gjennomsnitt (mean) og standardavvik (SD) for ulike aldersgrupper av henholdsvis jenter og gutter. Resultatene av denne studien er oppgitt i atlasets tabell V og VI, og formålet med disse tabellene er å kunne estimere hvorvidt et barn med kjent alder har en skjelettutvikling innen normalområdet. De inkluderte barna i tabellen er derfor sortert etter kronologisk alder før de statistiske dataene er oppgitt. Disse resultatene er derfor ikke overførbare til en situasjon der man ønsker å gjøre «det motsatte»: å estimere kronologisk alder basert på skjelettutviklingen. Statistikken for disse to situasjonene er ulik og man må legge ulike referansetabeller til grunn for beskrivelsen av disse.

I atlaset er det heller ikke oppgitt standardavvik for gutter 18 og 19 år og for jenter 16, 17 og 18 år, som er de avsluttende bildene for henholdsvis gutter og jenter i atlaset. Særlig det helt avsluttende bildet (18 år for jenter og 19 år for gutter) er problematisk ettersom dette angir en ferdig utviklet hånd og dermed et endestadium. Hvis man skal bruke GP-atlaset til aldersestimering er det to hovedutfordringer knyttet til endestadiet og den statistiske beskrivelsen av dette:

1. Man vet ikke hvor lenge individene som er i endestadiet faktisk har vært der (altså kan en nittenåring med en helt ferdig utviklet hånd ha vært i dette stadiet siden vedkommende var for eksempel 16 år).
2. Når man skal beskrive fordelingen av kronologisk alder for endestadiet vil denne påvirkes av den øvre alderen for de inkluderte individer i studien som ligger til grunn (det vil påvirke gjennomsnitt og standardavvik for endestadiet om man inkluderer individer opp til for eksempel 20 år i stedet for til for eksempel 22 år).

Valideringsstudier av Greulich og Pyle-atlaset

Det finnes en stor mengde studier fra ulike deler av verden som har hatt som målsetning å validere Greulich og Pyle-atlaset. En del av disse studiene har ønsket å beskrive hvordan GP skjelettalder fordeler seg for ulike aldersgrupper i deres populasjon. Dette perspektivet samsvarer med Greulich og Pyle-atlasets opprinnelige intensjon og anvendelse. En annen del av studiene har ønsket å vise hvordan kronologisk alder fordeler seg fra GP skjelettalder. Disse studiene beskriver direkte hva et bilde i atlaset «betyr» i kronologisk alder, og dette perspektivet er mer relevant for atlasets bruk til estimering av kronologisk alder. Disse to typene av studier fremstiller resultatene på ulikt vis, her angitt som fremstilling A og B:

(A) Forskjell mellom kronologisk alder og estimert GP skjelettalder (Greulich og Pyle modningsstadier) for hele aldersgrupper (f. eks. gutter mellom 13,0 og 13,9 år).

(B) Hvordan den kronologiske alderen fordeler seg ut fra bildene i atlaset (modningsstadiene eller GP skjelettalder)

Fremstilling A

Kronologisk alder	Antall		Skjelettalder
Alle gutter alder 11 år: 11.05 ± 0.24	20	⇨	10.80 ± 0.69
Alle gutter alder 12 år: 12.02 ± 0.23	30	⇨	11.63 ± 0.84
Alle gutter alder 13 år: 13.07 ± 0.25	42	⇨	12.75 ± 1.35
Alle gutter alder 14 år: 14.05 ± 0.24	30	⇨	14.18 ± 1.23

Fremstilling B

GP age category		n	mean	s
	⇨	58	11.09	1.11
	⇨	49	11.98	0.90
	⇨	29	12.21	0.90
	⇨	46	13.86	0.97

Figur 2: Fremstilling A (venstre figur) beskriver gjennomsnitt og standardavvik for GP skjelettalder for hver gruppe av kronologisk alder. Disse verdiene kan videre brukes til å beskrive differansen mellom kronologisk alder og GP skjelettalder. Dette krever at også korrelasjonskoeffisienten mellom GP skjelettalder og kronologisk alder er oppgitt. Fremstilling B (høyre figur) beskriver gjennomsnitt og standardavvik for kronologisk alder for hver GP skjelettalder (angitt som et bilde i atlaset).

Det finnes også flere andre måter å fremstille samsvaret mellom kronologisk alder og GP skjelettalder. Disse er imidlertid ofte vanskelige å sammenligne og sammenstille, og har derfor ikke blitt inkludert med kriteriene som vi har satt for denne systematiske oppsummeringen.

Metode

Vi har systematisk oppsummert studier som har vurdert samsvaret mellom kronologisk alder og GP skjelettalder for aldrene 14 år og oppover basert på røntgenbilder av hånd sammenlignet med Greulich og Pyle-atlaset (3), samt kartlagt studier av andre aldersestimeringssystemer basert på håndrøntgen. Siden vi arbeidet parallelt med flere systematiske oversikter om aldersestimering, har vi utført ett stort litteratursøk etter metoder basert på røntgen av tenner eller hånd, samt aldersvurdering ved bruk av CT eller MR av krageben, kne eller ankel som sammenholdes med data på kronologisk alder. Arbeidet baserte seg på Kunnskapssenterets metodebok «Slik oppsummerer vi forskning» (4), med følgende spesifikasjoner:

Inklusjonskriterier

Studiedesign:	Studier som sammenlignet modningsstadier basert på røntgenbilder av hånd med kjent kronologisk alder
Populasjon:	Personer med bekreftet alder mellom 10 og 25 år
Index test:	Modningsstadier basert på røntgen av hånd, slik som Greulich og Pyle-atlaset.
Referansetest:	Kjent kronologisk alder
Utfall:	Gjennomsnittlig forskjell mellom kronologisk alder og GP skjelettalder: CA - SA. Gjennomsnitt av kronologisk alder for hver GP skjelettalder.

Eksklusjonskriterier:

- Studier som ikke er presentert i fulltekst (konferanseabstrakt og postere)
- Studier som har inkludert døde mennesker (f.eks. levninger)
- Studier som har inkludert færre enn 50 personer mellom 10 og 25 års alder

Litteratursøking

Bibliotekar Gyri Hval Straumann gjennomførte litteratursøket og Marit Johansen fagfellevurderte dette. Det ble utført ett felles søk for studier som utførte aldersestimering basert på røntgen av tenner eller hånd, samt CT eller MR av krageben, kne eller ankel til aldersestimering i det angitte aldersspennet. Appendix 1 inneholder søkestrategien.

Vi søkte etter primærstudier uten tids- og språkbegrensing i følgende databaser:

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

I tillegg søkte vi i registre over pågående studier som beskrevet i Appendix 1.

Artikkelutvelging

Alle identifiserte titler og sammendrag ble lest og vurdert av to prosjektmedarbeidere uavhengige av hverandre. Vi benyttet web-programmet Rayyan til å håndtere referansene i utvelgelsen (5) og fordelte arbeidet mellom oss (PSD, KYD, AM, GHS, GEV). Vi markerte hvilke av de potensielt relevante artiklene som omhandlet aldersestimering basert på tenner, hånd eller CT og MR av kragebein, kne eller ankel. De utvalgte referansene for aldersestimering basert på håndrøntgen ble deretter vurdert i fulltekst av to personer uavhengige av hverandre (PSD, KYD, AM, GEV, MSM) ut fra inklusjonskriteriene. Prosjektgruppen har lest og vurdert studier på engelsk, skandinaviske språk, kinesisk, japansk og polsk. Vi har fått hjelp av kolleger på Folkehelseinstituttet til å vurdere studier på fransk, tysk, spansk, portugisisk og italiensk. Vi har fått hjelp av andre bekjente til å vurdere studier på russisk og hebraisk.

I tillegg vurderte vi om de relevante artiklene presenterte data på en slik måte at de kunne inngå i analysene våre. Resultatene måtte enten være presentert som gjennomsnitt og standardavvik for kronologisk alder og GP skjelettalder, som differansen mellom disse to, for hvert år av kronologisk alder, eller som gjennomsnitt og standardavvik av kronologisk alder for hver av modningsstadiene fra Greulich og Pyle-atlaset (GP skjelettalder). I den første fremstillingen måtte også korrelasjonskoeffisienten mellom GP skjelettalder og kronologisk alder være oppgitt. Studier basert på andre aldersestimeringsmetoder på håndrøntgen enn Greulich og Pyle ble kartlagt.

Kvalitetsvurdering og dataekstraksjon

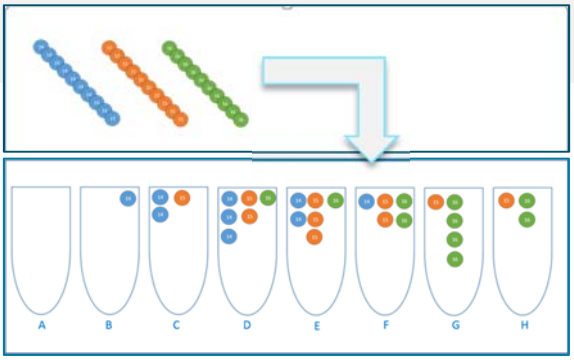
Vi vurderte den metodologiske kvaliteten av de inkluderte studiene ved hjelp av QUADAS-2 (6). AM vurderte alle de inkluderte studiene og MSM, GEV og PSD ca 1/3 hver, før vurderingene ble sammenlignet og eventuell uenighet løst ved diskusjon. QUADAS-2 er en sjekkliste for å vurdere anvendbarhet og risiko for systematiske skjevheter i valideringsstudier av diagnostiske tester. Vi anser at QUADAS-2 er den sjekklisten for kvalitetsvurdering som passer best for denne systematiske oversikten. Vi tilpasset vurderingen av risikoen for systematiske skjevheter som beskrevet under.

QUADAS-2 sjekklisten har fire domener (6): Utvelgelse av deltakere; Indekstest; Referansetest; og Flyt og tidsaspekt. I metoden er det angitt støttespørsmål som benyttes i vurderingen. Det første domenet vurderer om det er risiko for at deltakere er valgt slik at resultatene ikke blir representative for populasjonen de kom fra (seleksjonsskjev-

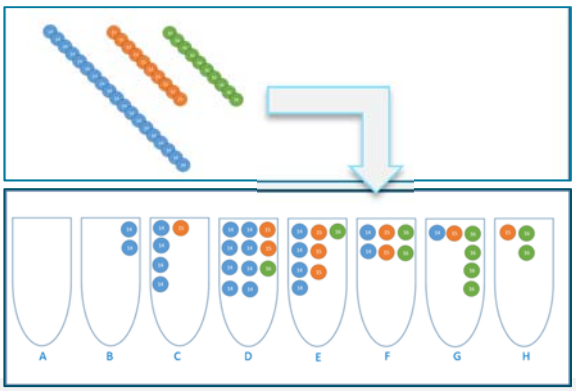
het). Det andre domenet vurderer om det kan være risiko for systematisk skjevheter ved gjennomføring eller tolkning av indekstesten - i dette tilfellet spesielt om de som vurderte røntgenbildet hadde kjennskap til barnets kronologiske alder. Siden kjent alder var et inklusjonskriterium vurderte vi at alle studiene hadde lav risiko for systematisk skjevheter for domenet «Referansetest». I domenet «Flyt og tidsaspekt» vurderes det om gjennomføring av studien og analysene er utført på en slik måte at systematiske skjevheter ikke introduseres underveis.

Ujevn fordeling av alder og aldersspennet til studiepopulasjonen kan gi opphav til fenomenet aldersmimikering (7) (illustrert i figur 3).

Aldersmimikering oppstår når individene som er inkludert i en studie ikke har jevn aldersfordeling, enten ved at visse aldersgrupper er overrepresentert eller at nedre og/eller øvre inkluderte alder er slik at det kan påvirke resultatene. Problemet kan oppstå når man forsøker å skildre en variabel (her kronologisk alder) ved å fordele individene på diskrete stadier (her modningsstadium) og deretter beskriver variabelen per stadie.



La oss si man gjør en studie som inkluderer 30 individer, fordelt likt på tre aldersgrupper: 14 år (blå), 15 år (oransje) og 16 år (grønn). Disse kan fordele seg i åtte mulige utviklingsstadier angitt med bokstavene A til H. I den tenkte studien fordeler aldersgruppene seg i de åtte stadiene som til venstre.



Så bestemmer man seg for å doble antallet fjortenåringer i studien, men beholder antallet femten- og sekstenåringer. Utgangspunktet er illustrert på bildet til venstre. Illustrasjonen viser et eksempel på hvordan disse individene kan fordele seg på stadiene.

Hvis vi betrakter stadium D i de to eksemplene er det åpenbart at disse to oppsettene vil gi svært ulik gjennomsnittsalder i dette stadiet (fjortenåringene blir mer dominerende på det nederste bildet). I tillegg vil gjennomsnittsverdien og standardavvik påvirkes av at det ikke finnes individer som er 13 år eller yngre, samt 17 år og eldre. For å unngå effekten av aldersmimikering i denne typen studier må man undersøke tilstrekkelig mange individer som er jevnt fordelt i kronologisk alder og at aldersspennet minst dekker de modningsstadiene man er interessert i.

Figur 3: Illustrasjon av fenomenet aldersmimikering (7)(engelsk: age mimicry).

Aldersmimikering er en form for seleksjonsskjevhet, forstått som forskyvning av resultatene som følge av fremgangsmåten for innsamling av prøver. I QUADAS-2 sjekklisten

faller fenomenet aldersmimikering inn under kategorien spektrumbias – som er et underpunkt under domenet «Utvelgelse av deltakere» (6). Vi vurderte derfor studiene opp mot to ekstra spørsmål: 1) Om det var likt antall deltakere i årskull, og 2) om aldersspennet var relevant for de analyserte modningsstadiene. Siden aldersmimikering kan ha stor innvirkning på de aktuelle statistiske analysene har vi vurdert dette forholdet separat for å tydeliggjøre den relevante informasjonen.

VR, AM og GEV hentet ut informasjon om populasjonen (alder, etnisitet/region og kjønn), land og årstall for når studien var utført, informasjon om studiedesign og hvilke aldersestimeringsmetoder som var benyttet, og informasjonen ble sjekket av en annen person. KYD hentet ut relevante data fra studiene og PSD dobbeltsjekket uttrekket. Vi hentet ut informasjon om:

- Hvor studien var gjennomført, og eventuelt informasjon om etnisitet
- Datainnsamlingsperiode
- Deltakernes kjønn, alder og antall
- Studiedesign
- Metode for å velge ut deltakerne
- Informasjon om aldersestimeringsmetoden
- Formålet med studien

Vi hentet ut følgende data (avhengig av hvordan resultatene var oppgitt):

- Gjennomsnitt og standardavvik (SD) av kronologisk alder (CA)
- Gjennomsnitt og SD av GP skjelettalder (SA)
- Gjennomsnittet av differansen mellom CA og SA for gitte kronologiske alderskategorier (hele eller halve år)
- Korrelasjonskoeffisienten (Pearson's) mellom CA og SA.

Analyser

For studier som kun oppga kvartilene av kronologisk alder, og ikke standardavvikene (SD), beregnet vi SD ved bruk av normalantagelse.

For den første analysen er vi interessert i å beskrive hvordan differansen mellom kronologisk alder og GP skjelettalder, CA-SA, fordeler seg (basert på fremstilling A). Noen av studiene beregnet SD av denne differansen direkte (basert på differansene på individnivå), mens andre studier oppga SD av kronologisk alder og GP skjelettalder, og korrelasjonen mellom disse to variablene. For de sistnevnte studiene estimerte vi SD for differansen mellom kronologisk alder og GP skjelettalder (for gitte kronologiske alderskategorier) med følgende formel:

$$SD_{diff} = \sqrt{SD_{CA}^2 + SD_{SA}^2 - (2 * Corr * SD_{CA} * SD_{SA})}$$

der SD_{CA} er SD av kronologisk alder, SD_{SA} er SD av GP skjelettalder og $Corr$ er korrelasjonskoeffisienten mellom CA og SA.

De studiene som oppga gruppert gjennomsnitt og SD av kronologisk alder og GP skjelettalder, men ikke korrelasjonskoeffisienten, ble satt til separat liste.

Databehandling av originale datasett

For mange studier manglet det informasjon slik at vi ikke kunne inkludere dem i metaanalysen. For alle disse studiene etterspurte vi den nødvendige informasjonen for å kunne inkludere dem. Vi mottok det originale datasettet fra to av disse studiene. Fra disse ekstraherte vi nødvendig informasjon slik som beskrevet ovenfor, og inkluderte dem i metaanalysen.

Utfallsmål i analysene

Det er to primære utfall i dette prosjektet:

- Gjennomsnittlig forskjell mellom kronologisk alder og GP skjelettalder: CA - SA.
- Gjennomsnitt av kronologisk alder for hver gitte GP skjelettalder.

Estimatene av disse to målene presenteres med 95% konfidensintervall (95 % KI).

Ved å beregne gjennomsnittlig forskjell mellom kronologisk alder og GP skjelettalder får vi målt hvor presist Greulich og Pyle-atlaset angir kronologisk alder på populasjonsnivå/gruppenivå. Gjennomsnitt og varians av kronologisk alder for hver gitte GP skjelettalder vil være knyttet til å kunne anslå hvilken kronologisk alder som bør oppgis (prediksjon) for en person som har observert en gitt skjelettalder (praksis).

Statistisk utførelse

Vi utførte metaanalysen ved bruk av statistikkprogrammet R (versjon 3.3.2) med R-pakken "metafor". Denne utfører inferens om heterogeniteten mellom studiene ved å anta en «random effects» modell.

Vurdering av heterogenitet

For å vurdere statistisk heterogenitet mellom studiene, benyttet vi p-verdien fra heterogenitetstesten (basert på «Cochran's Q» testobservator), og andel av den totale variasjonen som kan forklares av heterogenitet ved I^2. Dersom p-verdien fra testen er lav (f.eks. <0,1), indikerer dette at den observerte forskjellen mellom studiene er større enn forskjellen man forventer ved tilfeldig variasjon mellom resultatene i studiene. I^2 statistikken anvendes for å kvantifisere nivået av statistisk heterogenitet. En viktig konsekvens av vurderingen om heterogenitet er at der det er stor heterogenitet mellom studiene, så må det samlede resultatet fra en metaanalyse tolkes med forsiktighet.

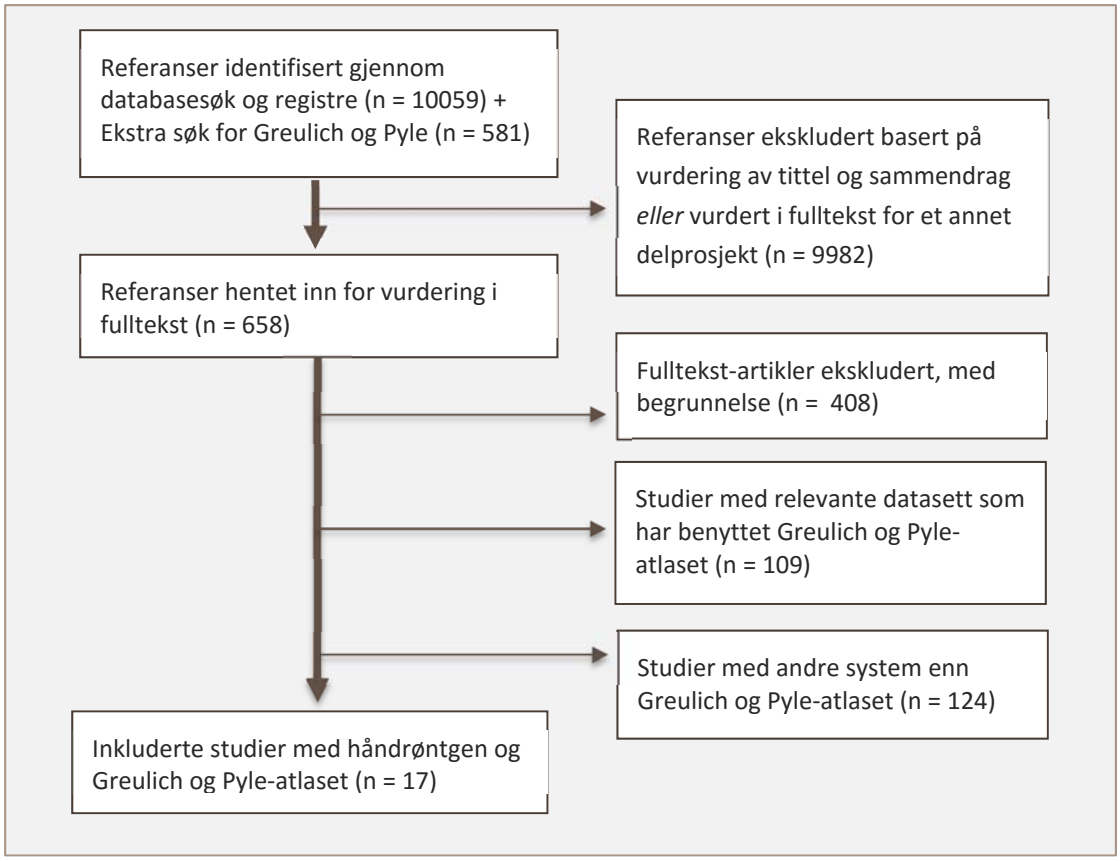
Etikk

Vi har valgt å ikke ha en drøfting av etikk i denne rapporten. De etiske aspektene ved aldersestimering basert på Greulich og Pyle-atlasets modningsstadier er spesielt knyttet til hvordan metoden anvendes. Dette drøftes i flere andre publikasjoner (8-10).

Resultater

Resultater av litteratursøket

Søket i elektroniske databaser og registre fram til mai 2016 ga 10059 antatt unike referanser. I tillegg utførte vi et oppdateringssøk kun etter studier som benyttet Greulich og Pyle-atlaset i januar 2017. Dette ga ytterligere 581 treff. Vi vurderte at 9982 referanser enten ikke var relevante eller de ble vurdert i fulltekst for ett av de andre delprosjektene. Vi hentet inn 658 publikasjoner i fulltekst som vi antok kunne være relevante for aldersestimering basert på håndrøntgen. Vi inkluderte 17 studier. Håndtering av de resterende 641 referansene beskrives under.



Figur 4: Flytskjema for søkeresultater og håndtering av referanser

I tillegg kontaktet vi forfattere som hadde relativt store, relevante datasett, men hvor resultatene ikke var presentert slik i publikasjonen at de kunne benyttes i de planlagte analysene. Vi spurte om forfatterne var villige til å gi ytterligere opplysninger eller pre-

sentere resultatene slik at de kunne inngå i analysene, alternativt om de var villige til å dele det originale datasettet slik at vi kunne reanalysere disse.

Beskrivelse av de inkluderte studiene

Vi inkluderte 17 studier som analyserte samsvaret mellom kronologisk alder og skjelettalder basert på modningsstadier fra Greulich og Pyle-atlaset. Tabell 1 gir en enkel beskrivelse av de inkluderte studiene. Ytterligere beskrivelser finnes i Appendix 2.

Tabell 1: Beskrivelse av de inkluderte studiene

Forfatter id (referanse)	Land	Etnisitet* eller region	Antall**	Gutter/ jenter	Aldersspenn
Bala 2010 (11)	India	Nord-vest	160	80/80	8-14 år
Buken 2007 (12)	Tyrkia	Nord-vest, Kaukasiere	492	251/292	11-20 år
Cantekin 2012 (13)	Tyrkia	Øst	767	342/425	7-17 år
Chaumoitre 2016 (14)	Frankrike	Etnisk variert	2614	1423/1191	1-20 år
Chiang 2005 (15)	Taiwan	-	370	230/140	0-18 år
Griffith 2007 (16)	Kina	Hong Kong	535	276/259	0-18 år
Jimenez-Castellanos 1996 (17)	Spania	Sør	239	139/100	0-14 år
Johnston 1963 (18)	USA	«White»	120	58/62	7-17 år
Koc 2001 (19)	Tyrkia	Sør-Øst	255	255/0	7-17 år
Mohammed 2015 (20)	India	Andhra Pradesh	660	330/330	9-20 år
Nahid 2010 (21)	Iran	Kurdistan	228	102/126	2-22 år
Patel 2015 (22)	India	Gujarat	180	90/90	6-16 år
Patil 2012 (23)	India	Maharashtra	375	194/181	0-19 år
Suri 2013 (24)	Canada	«White»	68	35/33	9-18 år
Tise 2011 (25)	Italia	Kaukasiere	484	349/125	11-19 år
Van Rijn 2001 (26)	Nederland	Kaukasiere	572	278/294	5-20 år
Zafar 2010 (27)	Pakistan	Etnisk variert	889	535/354	0-18 år

** Basert på eventuell betegnelse benyttet av artikkelforfatterne.*
*** Totalt antall deltakere og aldersspenn inkludert i studien. I analysene av differansen mellom kronologisk alder og estimert skjelettalder er kun årskullene fra 14 år og oppover inkludert.*
For ytterligere detaljer om gjennomføring av studiene, se Appendix 2.

De fleste artiklene var publisert etter 2000, med unntak av to studier publisert i 1963 og 1996. Det var tre studier fra Tyrkia, fire studier fra India, og én studie hver fra henholdsvis Canada, Frankrike, Italia, Iran, Kina, Nederland, Spania, Taiwan, Pakistan og USA. Alle studiene inkluderte begge kjønn, bortsett fra én studie som bare undersøkte gutter (19). I tabell 1 er totalt antall deltakere og aldersspenn i studien presentert. Stu-

diene varierte i størrelse fra kun 68 deltakere (24) til totalt 2614 deltakerne (14). Det smaleste aldersspennet i studien var fra 8-14 år med totalt 7 årskull (11), og det bredeste var 2-22 år med 21 årskull (21). I våre analyser av differansen mellom kronologisk alder og GP skjelettalder (fremstilling A) er kun årskullene fra 14 år og oppover inkludert. For analyser av gjennomsnittlig kronologisk alder fra GP skjelettalder (fremstilling B) er hele studiepopulasjonen benyttet. Vi mottok og reanalyserte datasett fra to studier av van Rijn og medarbeidere (26) og Zafar og medarbeidere (27).

Andre studier vurdert fra fulltekst

Studier basert på Greulich og Pyle-atlaset med mulig relevante datasett

Vi identifiserte ytterligere 109 studier som hadde samlet inn data både av håndskjelettmodning basert på Greulich og Pyle-atlaset og kronologisk alder. Disse studiene ble lagt til side fordi resultatene var presentert på en slik måte at de ikke kunne inkluderes i våre analyser. Noen av disse studiene var analysert med tanke på en annen problemstilling enn vår. Vi har samlet informasjon om disse studiene fordi de representerer mulige relevante datasett for videre analyser. Vi mener at videre arbeid i størst mulig grad bør basere seg på datasett som allerede finnes snarere enn å utføre flere nye studier. Appendix 3 inneholder en oversikt over disse studiene.

Studier som benytter andre indeks-tester enn Greulich og Pyle

Ytterligere 124 studier hadde validert aldersestimeringsmetoder med utgangspunkt i røntgenbilder av hånd som benyttet andre indeks-tester enn Greulich og Pyle-atlaset. Appendix 4 gir en oversikt over disse studiene.

Ekskluderte studier

Av de 658 referansene som ble innhentet i fulltekst, ekskluderte vi 408 etter vurdering mot inklusjons- og eksklusjonskriteriene. Se Appendix 5 for liste over ekskluderte studier med begrunnelse for eksklusjon. Blant disse var det også 19 artikler som ikke ble hentet inn fordi de var vanskelig å skaffe til veie eller svært dyre i innkjøp.

Kvalitetsvurdering av inkluderte studier basert på QUADAS-2

Basert på spørsmålene i QUADAS-2 sjekklisten (6) vurderte vi at sju studier hadde lav risiko og ti studier hadde uklar risiko for at deltakere ikke var representative for populasjonen de kom fra. Fjorten studier hadde spesifisert at de som vurderte røntgenbildene var blindet for deltakernes kronologiske alder, mens de øvrige ikke omtalte blinding (uklar risiko for systematisk skjevhet). Siden kjent kronologisk alder var et inklusjonskriterium vurderte vi at alle studiene hadde lav risiko for systematisk skjevhet for referansetesten. Vi vurderte at én av studiene hadde ekskludert deltakere underveis i analysene på en slik måte at det introduserte høy risiko for systematiske skjevheter (15). For ytterligere fire studier vurderte vi at det var uklart om flyt og tidsaspekt i studien kan ha introdusert systematiske skjevheter i resultatene.

Tabell 2: Kvalitetsvurdering av de inkluderte studiene basert på QUADAS-2 sjekklistens fire domener, samt ekstra vurdering av risiko for aldersmimikering.

	Domener for kvalitetsvurdering basert på QUADAS-2				
	Seleksjonsskjevhet		Tolkning av indekstesten	Referanse-test	Flyt og tidsaspekt
Forfatter, år	Utvelgelse av deltakere	Alders-mimikering [1]			
Bala 2010	?	-	?	+	+
Buken 2007	+ [2]	-	+	+	+
Cantekin 2012	?	-	+	+	+
Chaumoitre 2016	+	+	+	+	+
Chiang 2005	?	-	+	+	−
Griffith 2007	?	-	+	+	?
Jimenez-Castellanos 1996	?	-	+	+	?
Johnston 1963	?	-	?	+	?
Koc 2001	?	-	+	+	+
Mohammed 2015	+	-	+	+	+
Nahid 2010	?	-	+	+	?
Patel 2015	+	-	?	+	+
Patil 2012	?	-	+	+	+
Suri 2013	?	-	+	+	+
Tise 2011	+	−	+	+	+
Van Rijn 2001	+	○ [3]	+	+	+
Zafar 2010	+	○ [3]	+	+	+

+ Lav risiko, ? uklar risiko og − høy risiko for systematiske skjevheter i studien.

[1] Vurderingene gjelder for studier med analyser i fremstillingsmåte B.

[2] Høy risiko for systematisk skjevhet i aldergruppene 18 og 19 år.

[3] Forfatterne har gitt oss tilgang til originale data som er re-analysert for denne systematiske oversikten med fremstillingsmåte B. Symbolet ○ viser at antall individer og fordeling mellom aldersgrupper gir høy risiko for aldersmimikering i disse analysene.

For ytterligere detaljer om gjennomføring av studiene, se beskrivelser i Appendix 2.

I analyser av gjennomsnittlig kronologisk alder i modningsstadier fra Greulich og Pyle-atlaset er det risiko for systematiske skjevheter i form av aldersmimikering (7). Fire studier inngikk i disse analysene. Vi vurderte at kun én av studiene hadde en inkludert populasjon med et relativt likt antall deltakere fra hvert årskull og at aldersspennet var relevant for de analyserte modningsstadiene. Vi vurderte at risikoen for systematiske skjevheter i form av aldersmimikering i denne ene studien var lav. I de tre andre studiene var det stor variasjon i antall deltakere per årskull. En av disse hadde også et rela-

tivt smalt aldersspenn med deltakere fra 11 til 19 år (8 årskull). Vi vurderte at risikoen for systematiske skjevheter i form av aldersmimikering i disse tre studiene var høy.

Differansen mellom kronologisk alder og GP skjelettalder

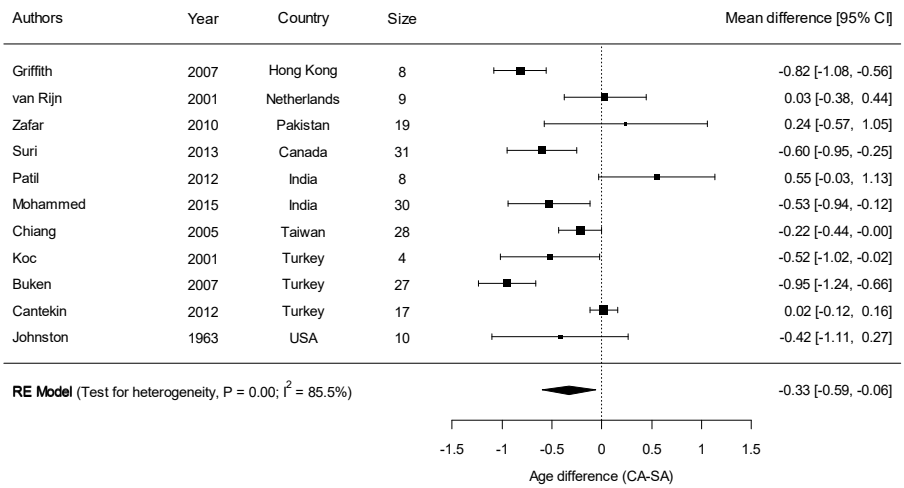
Femten studier presenterte resultater som differansen mellom kronologisk alder og GP skjelettalder for hver aldersgruppe separat (fremstillingsmåte A). For tre av disse studiene (16;26;27) var hvert år definert med leveårets start som midtpunkt (f.eks. barn i et alderskull fra 13,5 år til 14,49 år) mens de resterende studiene definerte halvåret som midtpunkt (f.eks. barn i et alderskull 13,0 år til 13,99 år). Siden resultatene omfatter separate analyser av to kjønn og mange årskull har vi valgt å legge alle analyser i Appendix 6 og kun presentere eksempler og oppsummeringer i teksten.

Vi vurderte først om det var hensiktsmessig å sammenfatte resultatene fra disse studiene i metaanalyser. Alle studiene hadde tilsvarende design og gjennomføring, og var godt utført for denne problemstillingen. Studiedeltagerne er gruppert for kronologisk alder før resultatene fremstilles, og aldersfordeling av deltakere i studiene som helhet vil derfor ikke påvirke resultatene. Vi vurderte at studiepopulasjonene kunne betraktes som én populasjon – det vil si barn og unge i en gitt aldersgruppe. Vi vurderte at det ikke var tilstrekkelig informasjon til å gruppere studiene i kategorier etter region eller etnisitet av deltakerne.

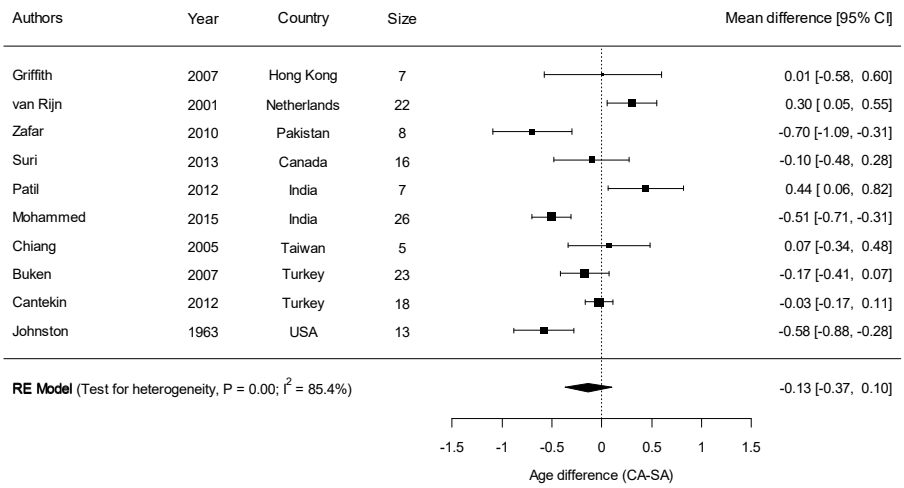
Appendix 6 inneholder alle metaanalysene av differansen mellom kronologisk alder og estimert skjelettalder for alle aldersgrupper fra 14 år til 19 år for gutter (Figurene A1-A6) og fra 14 år til 18 år for jenter (Figurene A7-A11). Figurene 5 og 6 viser disse analysene for gutter og jenter med kronologisk alder 17 år. Årskullet 17 år er valgt som eksempel fordi det ligger mellom to viktige grenseverdier i mange juridiske sammenhenger. Figur 5 viser resultatene fra 11 studier for gutter og figur 6 resultatene fra 11 studier for jenter. For hver studie angis antall observasjoner, den gjennomsnittlige differansen mellom kronologisk alder og GP skjelettalder for alle deltakerne, samt usikkerheten i estimatene som 95% KI[1] for gjennomsnittet i hver studiepopulasjon. Dette presenteres både som et punktestimat med en vannrett linje for 95% KI og som tall til høyre i figurene. Flere studier bidro med relativt få observasjoner, fra kun 4 deltakere fra én studie til maksimalt 31 deltakere i dette alderskullet.

[1] Klammene på hver side av firkantene angir 95% konfidensintervall for populasjonsgjennomsnittet som studien baserer seg på. Gjennomsnittsverdien vil variere hvis man hadde gjort studien flere ganger for samme populasjon. Konfidensintervallet angir usikkerheten på estimatet av populasjonsgjennomsnittet. Det vil si at dersom samme studie hadde vært utført med samme antall på samme populasjon, ville populasjonsgjennomsnittet havnet innen disse klammene med 95% sannsynlighet (eller 95 av 100 ganger). Jo smalere konfidensintervall jo mer presist vil estimatet for populasjonsgjennomsnittet være. Konfidensintervallet blir generelt bredere dersom estimatet er basert på færre observasjoner.

Figur 5
Gutter,
17 år



Figur 6
Jenter,
17 år



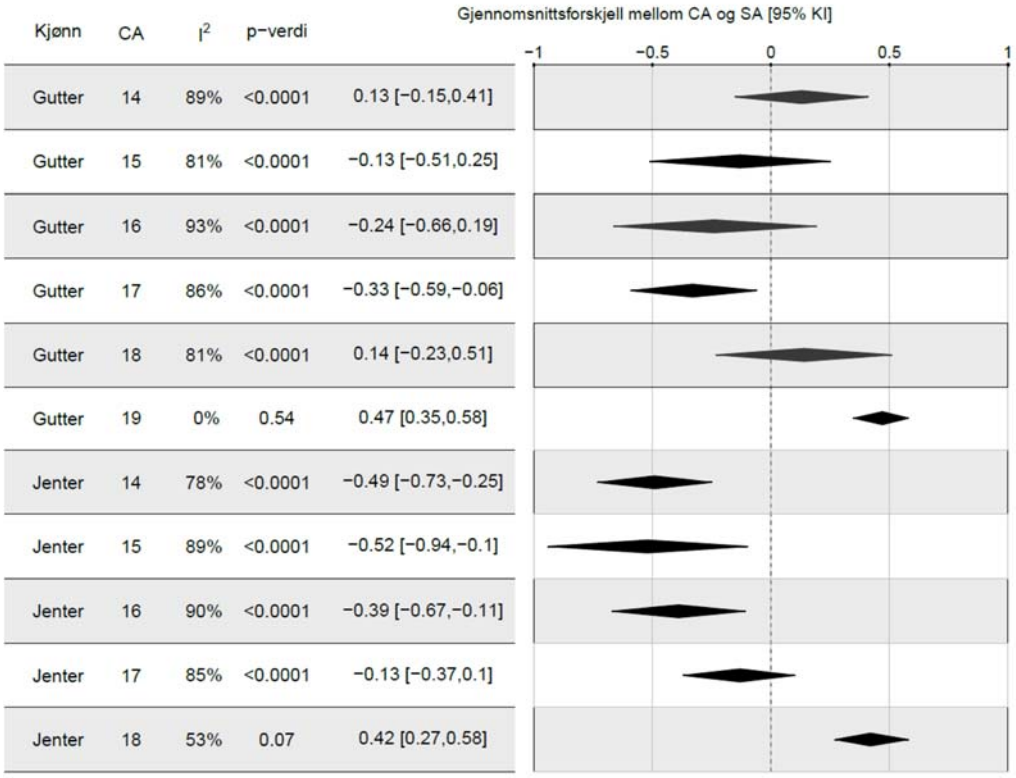
Figurene 5 og 6: Differansen (i år) mellom kronologisk alder og GP skjelettalder (modningsstadier fra Greulich og Pyle-atlaset) i de inkluderte studiene for henholdsvis gutter og jenter med kronologisk alder 17 år.
CA: kronologisk alder; SA: GP skjelettalder; 95% CI: 95 % konfidensintervall for gjennomsnittet

For alderskullet 17 år varierer gjennomsnittsdifferansen mellom kronologisk alder og GP skjelettalder i de ulike studiene fra en underestimering på 0,95 år til en overestimering på 0,55 år for gutter og en underestimering på 0,70 år til en overestimering på 0,44 år for jenter. Metaanalysen (angitt med «diamanten» og verdiene under hver av figurene) viser en samlet gjennomsnittsforskjell over alle studiene mellom kronologisk alder og GP skjelettalder på -0,33 år (95% KI: -0,59 til -0.06) for gutter og -0,13 år (95% KI: -0,37 til 0,10) for jenter. For begge kjønn er det samlede gjennomsnittlige avviket mellom kronologisk alder og GP skjelettalder derfor mindre enn fire måneder. Sammen med relativt snevre konfidensintervall bekrefter disse analysene at det er et godt samsvar mellom kronologisk alder og GP skjelettalder på gruppenivå.

Resultatene fra heterogenitetstestene i figur 5 og 6 viser imidlertid at det er større variasjon/forskjell mellom disse studiene enn det man vil forvente bare på grunn av tilfeldigheter. Andelen av variansen i metaanalysene som kan tilskrives heterogenitet angis ved I^2-verdien og er på 86 % for guttene og 85 % for jentene. I diskusjonen drøfter vi hvilke faktorer som kan ha bidratt til denne heterogeniteten. Vi valgte å ikke gå

videre med analyser for å forsøke å forklare hvilke faktorer som kan ha bidratt til heterogeniteten (se Diskusjons-kapittelet for begrunnelser).

Hvis man ser på gjennomsnittsdifferansene mellom kronologisk alder og GP skjelettalder i individuelle studier slik de er presentert for alle årskull av gutter fra 14 år til 19 år (Figurene A1-A6) og fra 14 år til 18 år for jenter (Figurene A7-A11) kan man trekke ut følgende funn: vi ser at denne gjennomsnittlige differansen mellom de to variablene i hver studie sjelden overstiger ett år for gutter (kun i 4 av totalt 58 verdier). For gutter i alderen fra 17 år til 19 år er disse differansene aldri over ett år. For jenter er variasjonen noe større (6 av 52 har gjennomsnittsdifferanse på mer enn ett år), men også for de eldste jentene (17 og 18 år) er gjennomsnittsdifferansene fra individuelle studier aldri over ett år. Dette til tross for at det er relativt få observasjoner for hver aldersgruppe i flere av studiene. Figur 7 presenterer det samlede estimatet fra hver av metaanalysene for gutter og jenter i alle årskull (hentet fra Figurene A1-A11).



Figur 7: Samlet gjennomsnittsdifferanse (95 % KI) mellom kronologisk alder og GP skjelettalder fra metaanalysene for alle analyserte årskull og begge kjønn. Figuren angir også p-verdi fra heterogenitetstesten og andelen av den totale variasjonen som kan forklares av studieheterogenitet gjennom I^2-verdien. Hver diamant illustrerer estimert gjennomsnitt med 95% konfidensintervallene.

Figuren viser at gjennomsnittsforskjellen mellom estimert alder og skjelettalder ligger tett på verdien 0. Gutter 19 år og jenter 18 år er den høyest mulige skjelettalderen (endestadiet), noe som gjør at kronologisk alder nødvendigvis blir høyere enn skjelettalder for begge disse gruppene. For gutter 19 år blir heterogeniteten (uttrykt ved I^{2-} verdiene) svært lav som en følge av at analysen kun består av to studier som har svært like resultater. For de øvrige aldrene var det gjennomgående større variasjon mellom hver

studie i metaanalysene enn det man kan forvente bare på grunn av tilfeldigheter, angitt som p-verdier og I^{2-} verdiene som varierer fra 53 % til 93% for alle aldersgruppene. Mulige årsaker til heterogeniteten og vår vurdering om å ikke utføre videre analyser av denne er lik for alle aldersgruppene (se diskusjonskapittelet).

Fra figur 7 kan man se en viss tendensen til at samlet sett (på tvers av alle studiene) har yngre og eldre gutter (14 og 18 år) noe høyere gjennomsnittlig kronologisk alder enn GP skjelettalder. For de andre aldersgruppene ser vi ingen systematisk forskjell mellom GP skjelettalder og den kronologiske alderen. For jentene observerer vi at GP skjelettalder i gjennomsnitt ligger foran kronologisk alder frem til og med 17 år. Disse trendene er basert på en sammenstilling av flere studier, men kan likevel skyldes tilfeldig variasjon.

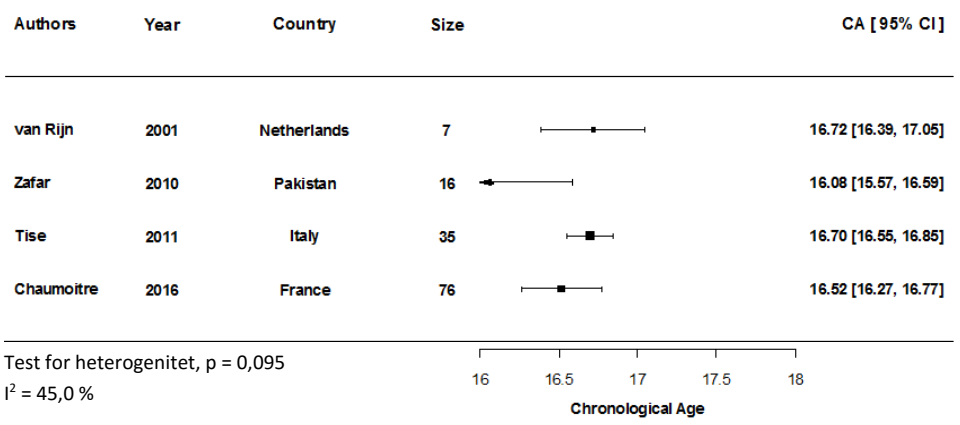
Gjennomsnittlig kronologisk alder i utviklingsstadier fra Greulich og Pyle-atlaset

Fire studier (14;25-27), inkludert to studier der vi har reanalysert dataene selv (26;27), presenterte resultater for gjennomsnittlig kronologisk alder i et utviklingsstadium fra Greulich og Pyle-atlaset (fremstilling B). Vi vurderte først om det var hensiktsmessig å sammenfatte resultatene fra disse studiene i metaanalyser. Gjennom QUADAS-2 vurderingene hadde vi vurdert at tre av disse studiene har høy risiko for at resultatene påvirkes av aldersmimikering. Vi vurderer at effekten av aldersmimikering for tre av disse studiene potensielt er så stor at det er høy risiko for at estimatene av gjennomsnittlig kronologisk alder i hvert utviklingsstadium er systematisk forskjøvet. Derfor vurderer vi at det ikke er hensiktsmessig å slå resultatene sammen i metaanalyser, men presenterer funnen grafisk i plottene.

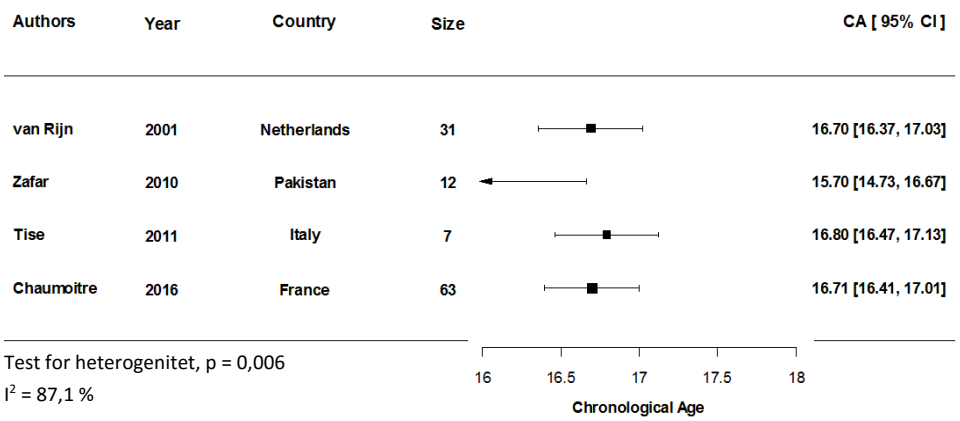
Figurene 8 og 9 viser gjennomsnittlig kronologisk alder i utviklingsstadiet 17 år i Greulich og Pyle-atlaset for henholdsvis gutter og jenter. Appendix 6 inneholder tilsvarende framstilling for alle utviklingsstadiene som er oppgitt fra 10 år til 19 år for gutter (Figurene A12-A23) og 10 til 18 år for jenter (Figurene A7-A11). Siden det er ulikt aldersspenn i studiene er det ulikt antall studier for hvert årskull.

Figur 8 viser resultatene fra 4 studier for gutter og figur 9 resultatene fra de samme 4 studiene for jenter. For hver studie angis antall observasjoner, gjennomsnittlig kronologisk alder blant deltakere som fikk vurdert skjelettutviklingen til stadiet 17 år, samt usikkerheten i estimatene som 95% KI for gjennomsnittet, grafisk og med tall. For eksempel viser figur 9 at laveste gjennomsnittsalder for jenter i utviklingsstadium 17 år er 15,7 år i studien fra Pakistan og høyeste gjennomsnittsalder er 16,8 år i studien fra Italia. Det er større heterogenitet mellom studiene enn det en ville forvente bare på grunn av tilfeldigheter. Det er grunn til å tro at en vesentlig andel av den observerte heterogeniteten for denne fremstillingen av resultater er knyttet til fenomenet aldersmimikering.

Figur 8 Gutter GP-bilde 17 år



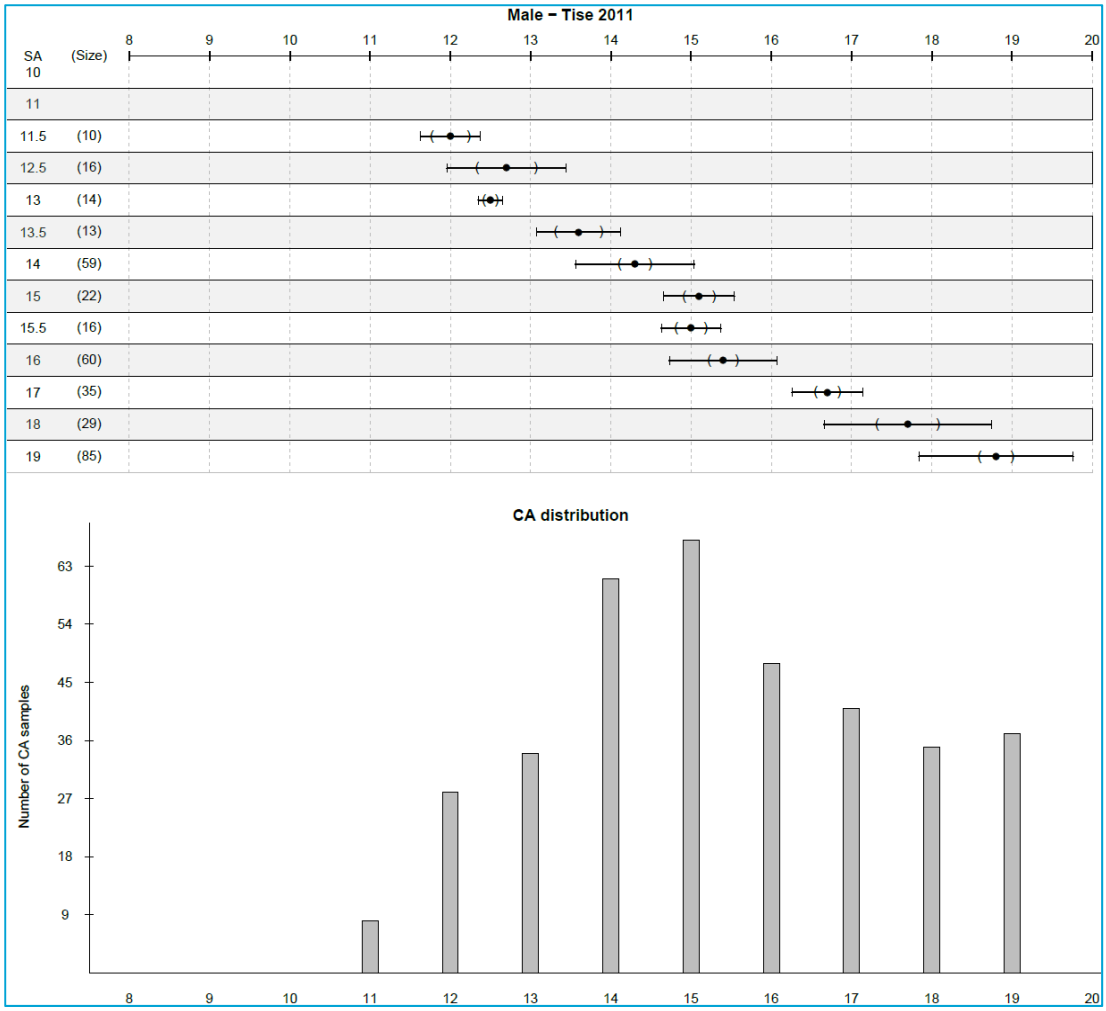
Figur 9 Jenter GP-bilde 17år



Figurer 8 og 9: Gjennomsnittlig kronologisk alder for individer i utviklingsstadiet 17 år fra Greulich og Pyle-atlaset for henholdsvis gutter og for jenter.
CA: kronologisk alder; 95% CI: 95 % konfidensintervall for populasjonsgjennomsnittet

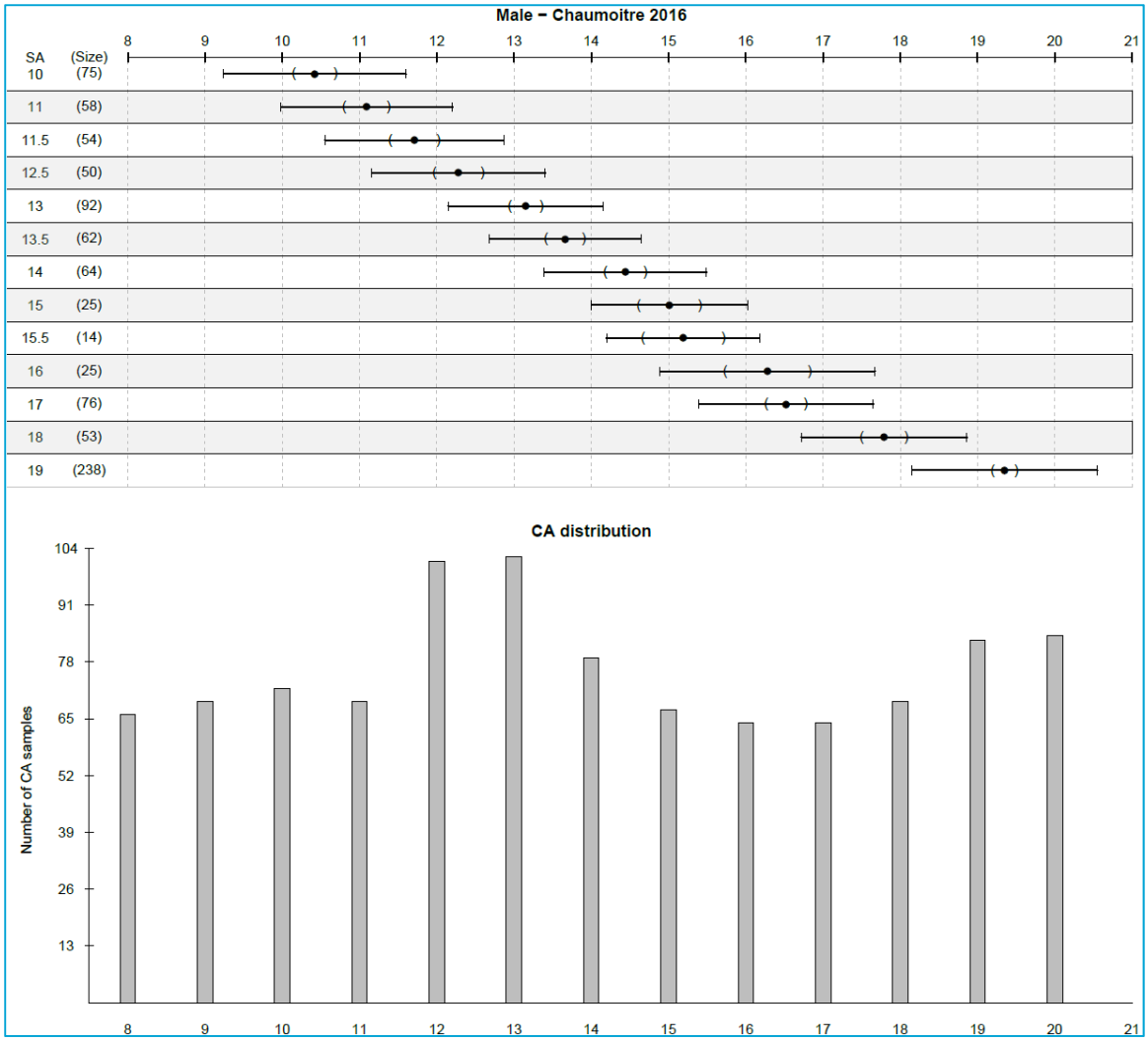
Tre av de fire studiene som er presentert her, Tise 2001 (25), van Rijn 2001 (26) og Zafar 2010 (27), har studiepopulasjoner med relativ ujevn fordeling av antall deltakere i de ulike aldergruppene. Det er forventet at dette kan påvirke resultatene i stor grad, noe som også kan observeres.

To eksempler vises her, mens Appendix 6 viser tilsvarende plott for alle studiene for gutter og jenter separat. Eksempel på en studie med ujevn aldersfordeling i studiepopulasjonen er Tise 2011 (25). Funnene fra studien for alle guttene i studien vises grafisk i figur 10.



Figur 10. Grafisk fremstilling av resultater fra Tise 2011 (25) for gutter med GP skjelettalder fra 10 til 18 år. Den øverste delen av figuren viser hver GP skjelettalder for gutter fra 10 til 18 år, med antall, gjennomsnitt (punktet i midten) med ett standardavvik ut til hver side (avslutning på linjene) og 95% konfidensintervall for populasjonsgjennomsnitt (parentes). Den nedre delen av figuren viser den inkluderte populasjonens fordeling på kronologisk alder.

Den eneste inkluderte studien med fremstilling B som har en relativ jevn aldersfordeling er Chaumoitre 2016 (14). I tillegg er antall observasjoner i hver aldersgruppe relativt høy. Funnene fra studien for gutter vises grafisk i figur 11. Vi betrakter dette som et eksempel på en godt designet studie som vil være i stand til å beskrive hvordan den inkluderte populasjonens kronologiske alder fordeler seg fra modningsstadiene (GP skjelettalder) på en mer korrekt måte. Ideelt sett skulle flere studier vært designet på denne måten.



Figur 11. Grafisk fremstilling av resultater fra Chaumoitre 2016 (14) for gutter med GP skjelettalder fra 10 til 19 år. Den øverste delen av figuren viser hver GP skjelettalder for gutter fra 10 til 19 år, med antall, gjennomsnitt (punktet i midten) med ett standardavvik ut til hver side og 95% konfidensintervall for populasjonsgjennomsnitt (parentes). Den nedre delen av figuren viser den inkluderte populasjonens fordeling på kronologisk alder.

Tilsvarende plot for alle de fire studiene og begge kjønn ligger i Appendix 6. Det kan visuelt observeres at det er store forskjeller mellom studiene fremstilt i figur 10 og 11. Aldersmimikering er ikke den eneste forklaringen på forskjellene mellom studiene, men det er en åpenbar kilde til noe av den observerte heterogeniteten, og effekten er mulig å forklare teoretisk i tillegg til at den kan fremvises empirisk.

Diskusjon

Hovedfunn

I denne rapporten har vi systematisk oppsummert primærforskning om samsvaret mellom kronologisk alder og skjelettalder som definert i Greulich og Pyle-atlaset. Vi inkluderte 17 studier som oppfylte kriteriene og som oppga tilstrekkelig data til at vi kunne inkludere dem.

GP skjelettalder øker når kronologisk alder øker. I oppsummeringen fant vi at gjennomsnittsdifferansen mellom disse to variablene sjelden er større enn et år for hver kronologisk aldersgruppe i hver enkelt studie. For eksempel var denne differansen aldri større enn 0,5 år i noen aldersgruppe i en stor studie av Chaumoitre 2016 (14).

Hvis man ønsker å bruke atlaset til estimering av kronologisk alder er det essensielt å beregne et prediksjonsintervall som sier noe om sikkerhetsmarginen for hvor gammelt et individ kan være (i kronologisk alder) gitt den observerte GP skjelettalderen (fremstillingsmåte B). Chaumoitre 2016 var den eneste av studiene som vi vurderte til å være godt nok utført til å kunne beregne et slikt prediksjonsintervall direkte. Her fant vi at bredden på 95% prediksjonsintervallene varierer fra 4,0 år til 5,9 år for gutter i alderen 10-19 år (se figur 12).

Resultatene fra Chamouitre 2016 er en beskrivelse av den inkluderte populasjonen, som beskrives som multi-etnisk fra Marseille (Frankrike). Det er ikke uproblematisk å anvende resultatene fra Chaumoitre 2016 på enhver populasjon før den aktuelle populasjonen er testet og kartlagt på samme måte.

Kvaliteten på forskningsresultatene

Det har vært rettet mye kritikk mot bruken av Greulich og Pyle-atlaset til estimering av kronologisk alder. Blant annet har ett av ankepunktene vært at atlaset er basert på kaukasiske barn fra høyere sosioøkonomiske kår i Ohio (USA) på 1930-tallet. Selv om flere nye systemer har vært lansert til estimering av alder basert på røntgen av hånd (28-31) forblir Greulich og Pyle-atlaset det mest anvendte. Resultatene i denne oppsummeringen tyder på at de oppgitte skjelettaldrene fra metoden, i gjennomsnitt, samsvarer relativt godt med kronologisk alder også i populasjoner som er undersøkt de siste 15 årene. Estimering av kronologisk alder på individnivå ut fra et gitt skjelettmodningsstadium er imidlertid usikkert ved anvendelse i praksis.

Studier med fremstilling B er mer egnet til å skildre atlasets prediksjonsevne for enkeltindivider enn fremstilling A. Av disse fant vi at kun én studie (14) hadde tilstrekkelig godt studiedesign til å unngå fenomenet aldersmimikering.

GP skjelettalder fordelt på grupperte kronologiske aldersintervaller (fremstilling A)

I denne fremstillingen er individene gruppert etter kronologisk alder, og resultatene presenterer GP skjelettalder for hver gruppe. Svært mange studier innen dette kunnskapsfeltet er organisert på denne måten. Disse studiene har ønsket å beskrive hvordan skjelettalderen fordeler seg for ulike aldersintervaller av deres populasjon. Dette perspektivet samsvarer med Greulich og Pyle-atlasets opprinnelige intensjon og anvendelse. Denne fremstillingen er mest egnet til å fremstille skjelettutviklingen for en gruppe av en populasjon, la oss si gutter med kronologisk alder 14 år, representert som gjennomsnitt og standardavvik av GP skjelettalder. Fremstilling A påvirkes ikke av aldersmimikering ettersom man ikke fordeler individene i studien på stadier (fenomenet er beskrevet i detalj i figur 3).

Vi kan se fra analysene at kronologisk alder og GP skjelettalder følger hverandre. Det betyr, som forventet, at når kronologisk alder øker, så øker også GP skjelettalder for alle aldersgrupper og begge kjønn i vår analyse. Analysen viser at det i gjennomsnitt (på gruppenivå) er relativt liten forskjell mellom kronologisk alder og GP skjelettalder. Det gir en indikasjon på metodens validitet. Vi observerer imidlertid større variasjon mellom studiene i metaanalysen enn det man ville forventet med statistisk tilfeldighet alene. Forskjeller mellom populasjoner og regioner kan spille inn, men mange andre faktorer kan også ha bidratt til heterogeniteten. Det finnes flere kilder til målefeil i analysene som er utført, blant annet den subjektive tolkningen av bildene opp mot atlaset og røntgenbilder som ikke viser detaljene ved håndskjelettet godt nok (bildene er ofte tatt ved mistenkte skader). Vi valgte å ikke gå videre med analyser for å forsøke å forklare hvilke faktorer som kan ha bidratt til heterogeniteten. På grunn av den store variasjonen mellom studiene, må resultatene basert på sammenslåingen av studiene («diamantene» nederst i hver analyse) tolkes med varsomhet.

Fremstilling A angir ikke direkte hvordan kronologisk alder fordeler seg for gitt GP skjelettalder. Det finnes statistiske metoder som baserer seg på å bygge en modell som beskriver skjelettutviklingen for gitt kronologisk alder (32-34). Disse metodene krever selvsagt at dataene er angitt på individnivå. Et problem med studiene fra litteraturen er at de kun oppgir dataene gruppevis i form av gjennomsnitt og standardavvik, noe som gjør det ekstra krevende å bygge en fornuftig statistisk modell.

Kronologisk alder fordelt fra GP skjelettalder (fremstilling B)

Fremstilling B beskriver hvordan kronologisk alder fordeler seg direkte fra modningsstadiene (bildene i atlaset), angitt som GP skjelettalder. Det er denne fremstillingen som er mest relevant for å beskrive hvor god en metode er til estimere den kronologiske alderen til et individ med ukjent alder. Ulempen med denne fremstillingen er at den kan være sårbar for fenomenet aldersmimikering. Fenomenet aldersmimikering drøf-

tes mer inngående i vår parallelle systematiske oversikt om samsvaret mellom kronologisk alder og Demirjians utviklingsstadier for visdomstenner (1).

Vi fant totalt fire studier som ble inkludert i metaanalysen. Tre av studiene (25-27) hadde et studieutvalg som ikke var jevnt fordelt på kronologisk alder (se vedlegg 6). Et slikt ujevnt utvalg vil kunne påvirke resultatene (gjennomsnitt og standardavvik av kronologisk alder) i stor grad. Vi har derfor ikke slått sammen resultatene til et samlet estimat, ettersom vi anser aldersmimikering som et så betydelig problem at det ikke er forsvarlig å gjøre en metaanalyse.

Den eneste studien som har et studieutvalg som er relativt jevnt fordelt på kronologisk alder er Chaumoitre 2016 (14). Dette er et eksempel på en godt designet studie som kan beskrive hvordan den inkluderte populasjonens kronologiske alder fordeler seg på de gitte modningsstadiene (GP skjelettalder) på en mer pålitelig måte. Chaumoitre har brukt resultatene til å beregne 95% prediksjonsintervall, som er gjengitt i figur 12.

SA	Antall	Gj.snitt	St.av.	95% PI-grenser	
				Nedre	Øvre
10	75	10.42	1.18	8.05	12.78
11	58	11.09	1.11	8.86	13.33
11.5	54	11.71	1.16	9.37	14.06
12.5	50	12.28	1.12	10.02	14.55
13	92	13.15	1.00	11.16	15.14
13.5	62	13.66	0.98	11.68	15.64
14	64	14.44	1.05	12.33	16.55
15*	25	15.01	1.01	12.89	17.12
15.5*	14	15.19	0.99	12.98	17.40
16	25	16.28	1.39	13.36	19.21
17	76	16.52	1.13	14.25	18.78
18	53	17.79	1.07	15.62	19.95
19	238	19.35	1.20	16.99	21.72

Figur 12. Tabellen er en gjengivelse av tabell 6 fra Chaumoitre 2016 (14) som viser fordelingen av kronologisk alder fra GP skjelettalder for gutter. Tabellen viser antall individer for hver skjelettalder (Antall), gjennomsnittlig kronologisk alder (Gj. Snitt), Standardavvik (St.av.) og 95% prediksjonsintervall er til høyre i tabellen gjengitt med nedre og øvre grenseverdier. Markeringen "" betyr at prediksjonsintervallene må brukes med forsiktighet siden de individbaserte dataene ikke passer med normalantagelsen.*

Det siste stadiet, som kalles 19 år, er et endestadium som angir en ferdig utviklet hånd. Dette stadiet skiller seg fra alle andre ved at det ikke tar slutt. I en tverrsnittsstudie, der man observerer ett individ én gang, er det derfor umulig å vite hvor lenge individet har vært i et endestadium. Dataene for dette stadiet blir også påvirket av den øvre alderen til den inkluderte populasjonen (øvre «cut-off»). Chaumoitre 2016 har oppgitt at det ikke er noen individer over 21 år i den inkluderte populasjonen (14). Hvis denne alderen hadde vært satt til for eksempel 23 år, ville dette ha påvirket gjennomsnittsverdi og

fordeling av kronologisk alder for endestadiet. I en studie som Chaumoitre 2016 vil endestadiet således skille seg fra de andre stadiene og må tolkes med forsiktighet.

Fra Chaumoitre 2016 ser vi at bredden på 95 % prediksjonsintervaller for aldersintervaller 10-19 år er fra 4,0 til 5,9 år. Dette innebærer at 95 % av de aldersestimerte individene (fra samme populasjon som studien) statistisk sett er estimert til å ligge innenfor de angitte prediksjonsintervallene dersom man hadde brukt denne metoden systematisk på denne populasjonen.

Ideelt sett hadde vi ønsket å finne flere studier med like store og jevnere fordelte aldersgrupper som Chaumoitre 2016 for å kunne belyse Greulich og Pyle-atlasets presisjon og varians til estimering av kronologisk alder for populasjoner i ulike deler av verden. De inkluderte studiene hadde i utgangspunktet lignende design, der det ble utført en blindet vurdering av hvilket skjelettstadium røntgenbildene lignet mest på. Fremstillingen av resultatene er det som begrenser hvorvidt vi kan benytte dataene eller ikke. Det betyr at dersom vi hadde fått tilgang til de individbaserte dataene fra disse studiene, kunne vi bruke statistiske metoder for å fremstille resultatene på en mer egnet måte, og bidra til å belyse bruken av Greulich og Pyle-atlaset for estimering av kronologisk alder.

Regionale forskjeller

Et sentralt spørsmål innen feltet medisinsk aldersestimering er hvor store forskjellene i skjelettmodning er mellom ulike populasjoner fra ulike deler av verden, enten de er forårsaket av genetisk heterogenitet eller ytre årsaker som levekår og levevaner. Fra et medisinsk perspektiv er det spesielt relevant at ulike populasjoner og etniske grupper kan ha genetisk likhet gjennom slektskap, liknende sosioøkonomisk status og levekår, og liknende levevaner (35). Disse faktorene kan hver for seg påvirke vekstmønster, men det er svært krevende å måle den relative betydningen av hver enkelt faktor. I denne systematiske oversikten har vi ikke definert kriterier for inndeling av studier etter geografiske regioner eller etnisiteter. Heterogeniteten vi ser mellom de ulike studiene kan ha en rekke årsaker. Det finnes mange kilder til målefeil i analysene som er utført, blant annet den subjektive tolkningen av bildene opp mot atlaset og røntgenbilder som ikke viser detaljene ved håndskjelettet godt nok (bildene er ofte tatt ved mistenkte skader). De aller fleste av gruppene i analysene våre er små, noe som øker variasjon og kan være en feilkilde. Analysene våre viser imidlertid at en gjennomsnittsforskjell på mer enn ett år mellom GP skjelettalder og kronologisk alder for en gruppe er sjelden i aldersintervallet vi har sett på, til tross for de kjente kildene til skjevheter.

Styrker og svakheter

Styrken ved denne systematiske oversikten er den systematiske og transparente tilnærmingen vi har benyttet for å svare på spørsmålet. Vi har gjennomført systematiske litteratursøk i mange elektroniske databaser. Vi har benyttet klare inklusjonskriterier og eksklusjonskriterier. To personer har uavhengig av hverandre vurdert hver referanse etter disse kriteriene, samt uavhengig av hverandre vurdert kvaliteten på de inklu-

derte studiene. Uavhengige vurderinger er med på å redusere feil og redusere sjansen for feilkilder. Det skal være mulig å etterprøve alle ledd i arbeidet som vi har utført og vurderingene som vi har lagt til grunn for våre konklusjoner.

Selv om vi har utført et grundig litteratursøk med høy grad av sensitivitet, er det alltid mulig at det finnes studier som vi ikke har identifisert. En svakhet ved systematiske oversikter er at de kan bli utdatert når det publiseres flere nye studier, noe som skjer kontinuerlig. Datagrunnlaget i denne systematiske oversikten er antatt å være oppdatert fram til januar 2017.

Overensstemmelse med andre oversikter

En tidligere metodevurdering fra Kunnskapssenteret (nå Kunnskapssenteret i Folkehelseinstituttet), Graff og medarbeidere 2006 (8), omhandlet flere metoder for aldersvurdering av personer mellom 16 og 20 år, deriblant Greulich og Pyle-atlaset. Deres søk ble utført i 2006 og de inkluderte 11 studier som omhandler bruk av Greulich og Pyle-atlaset. Graff og medarbeidere presenterte analysene for begge kjønn, alle aldersgruppene og etniske grupper samlet, mens vi presenterer gutter og jenter separat og for hver kronologiske aldersgruppe. Vi hadde også noe ulike krav til dataformatet på inkluderte studier. Disse forskjellene fører til av det kun er to studier som er overlappende blant de inkluderte i vår rapport og rapporten til Graff og medarbeidere 2006. De andre ni studiene i Graff og medarbeidere er på vår liste over relevante datasett (Appendix 4), og 11 av våre inkluderte studier ble publisert etter deres søkedato.

En systematisk oversikt av Serinelli og medarbeidere (36) har også undersøkt metoder for å vurdere alder etter røntgen av hender. Oversikten til Serinelli og medarbeidere baserte seg på et søk fra desember 2009 og omhandlet både Greulich og Pyle, Tanner-Whitehouse og Fels metodene. For hver aldersvurderingsmetode ble aldersgruppene presentert samlet, mens gutter og jenter ble behandlet separat, og de ble også delt inn i etniske grupper for hvert kjønn. To av de fem studiene som er i metaanalysen til Serinelli og medarbeidere er også med i vår oversikt. Elleve av studiene som vi har inkludert er publisert etter søkedatoen i denne oversikten.

Både Graff 2006 (8) og Serinelli 2011 (36) oppsummerte studier med fremstilling A, altså studier som beskriver fordeling av skjelettalder for individer gruppert etter kronologisk alder. Vi har tidligere redegjort for hvorfor denne fremstillingen ikke direkte beskriver usikkerheten ved bruk av Greulich og Pyle-atlaset til estimering av kronologisk alder.

En forskjell mellom vår oversikt og de to tidligere oversiktene er at de begge har delt opp etter etnisitet, mens vi ikke har gjort det. Vi har konkludert med at variasjonen mellom studiene muligens helt kan skyldes tilfeldigheter og metodiske skjevheter. Vi har på grunnlag av dette begrensede datagrunnlaget ment at det ikke er forsvarlig å gå videre til å undersøke andre forklaringsvariabler (subgruppeanalyser), slik som etnisitet eller regionale forskjeller. Vi vurderte også at informasjonen fra studiene ikke var tilstrekkelig til å gruppere studiene i kategorier. For eksempel hadde studien til Chaumoitre (14) en multi-etnisk populasjon som trolig inneholdt immigranter fra tidligere franske kolonier og Nord-Afrika. Videre vurderte vi at deltakerne i studiene fra

Tyrkia (12;13;19;37;38) kunne representere ulike etnisiteter, siden ulike regioner i Tyrkia har ulike populasjonssammensetninger.

Kunnskapshull

Dersom Greulich og Pyle-atlaset skal anvendes til estimering av kronologisk alder i tilfeller der denne er ukjent, er det studier som Chaumoitre 2016 (14) (med fremstilling B) som direkte viser metodens usikkerhet. Denne studien viser hvordan kronologisk alder fordeler seg fra modningsstadiene/skjelettaldrene (bildene i atlaset) direkte. Studien inkluderte mange individer som var relativt jevnt fordelt på kronologisk alder, noe som er en forutsetning for å få representative resultater for å beskrive hvordan kronologisk alder på individnivå fordeler seg på ulike modningsstadier. Flere studier av denne typen kan gi et mer komplett bilde av metodens pålitelighet på tvers av ulike populasjoner og regioner.

En annen mulig løsning er å samle inn grunndata fra mange studier og sammenstille disse. Alle studiene er i utgangspunktet basert på de samme dataoppsettene; registrert kronologisk alder og observert GP skjelettalder for hvert individ. Med en stor og variert mengde av slike datasett kunne man sammenstille og presentere data på en optimal måte for å løse problemet knyttet til fenomenet aldersmimikering.

Konklusjon

I denne systematiske oversikten har vi oppsummert vitenskapelig litteratur om samsvaret mellom skjelettalder gitt i Greulich og Pyle-atlaset og kronologisk alder.

Flertallet av studiene undersøkte hvordan GP skjelettalder fordeler seg for gitte aldersgrupper (kalt fremstilling A i denne rapporten). Dette er den tradisjonelle bruken av atlaset og grunnen til at det ble etablert. Vi har oppsummert disse studiene, og funnet at samsvaret mellom GP skjelettalder og kronologisk alder i snitt er relativt godt, selv om visse aldersgrupper i enkeltstudier kan ha en gjennomsnittsforskjell på over ett år. Disse studiene kan ikke legges til grunn når Greulich og Pyle skal brukes til å estimere kronologisk alder (som blir et «omvendt» scenario).

Studiene som undersøkte hvordan kronologisk alder fordeler seg fra skjelettaldrene (kalt fremstilling B i denne rapporten) illustrerer direkte med hvilken usikkerhet Greulich og Pyle-atlaset estimerer kronologisk alder for en populasjon. Vi fant kun én studie med fremstilling B med en studiedesign og gjennomføring som gir en god beskrivelse av metodens evne til å predikere alder: Chaumoitre 2016. Denne studien viser at for den inkluderte populasjonen vil bredden på 95 % prediksjonsintervall være på det minste 4 år og på det meste 5,9 år for gutter i aldersintervallet 10-19 år. Dette gir et inntrykk av hvor stor variasjonen kan være når metoden tas i bruk på en gitt populasjon.

For å utforske usikkerheten for Greulich og Pyle-atlaset til å estimere kronologisk alder for andre populasjoner, trengs det relevante resultater som er representert på fremstilling B med et tilstrekkelig godt studiedesign. Dersom grunndata hadde vært tilgjengelig, kunne vi anvendt andre statistiske metoder der vi først beskriver hvordan GP skjelettalderen utvikler seg når kronologisk alder øker, og deretter undersøker hvilke kronologiske aldre som mest sannsynlig beskriver en gitt GP skjelettalder.

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method and the tanner and whitehouse method. Hong Kong Medical Journal 2007;13(3 Supplement 3):28-32.
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Vedlegg (Appendixes)

Appendix 1: Literature search

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: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
Search date: 2017-01-03

1 Age Determination by Skeleton/ (4617)
2 (age adj3 (determinat* or estimat* or assess*)).ti. (3296)
3 ((forensic or radiological) adj age).ti,ab. (201)
4 ((age or maturation or mature or ossification) adj5 (determinat* or estimat* or assess* or examinat*)).ti,ab. (50880)

5 (hand$1 or wrist$ or carpal or metacarpal or metacarpus).ti,ab. (423891)
6 (roentgen or x-ray* or xray* or radiolog* or radiograp*).ti,ab. (738776)
7 4 and 5 and 6 (534)
8 1 or 2 or 3 or 7 (7429)
9 exp Animals/ (23024664)
10 Humans/ (18186804)
11 9 not (9 and 10) (4837860)
12 8 not 11 (7013)
13 (greulich adj2 pyle).ti,ab. (286)
14 12 or 13 (7059)

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: Embase 1974 to 2016 December 30
Search date: 2017-01-03
1 age determination/ (5542)
2 (age adj3 (determinat* or estimat* or assess*)).ti. (3437)
3 ((forensic or radiological) adj age).ti,ab. (225)
4 ((age or maturation or mature or ossification) adj5 (determinat* or estimat* or assess* or examinat*)).ti,ab. (62094)
5 (hand$1 or wrist$ or carpal or metacarpal or metacarpus).ti,ab. (502099)
6 (roentgen or x-ray* or xray* or radiolog* or radiograp*).ti,ab. (776099)
7 4 and 5 and 6 (641)
8 1 or 2 or 3 or 7 (7816)
9 exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/ (24312061)

10 human/ or normal human/ or human cell/ (18443969)
11 9 not (9 and 10) (5914908)
12 8 not 11 (7052)
13 (greulich adj2 pyle).ti,ab. (374)
14 12 or 13 (7225)

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: Central
Search date: 2017-01-03

#1	MeSH descriptor: [Age Determination by Skeleton] explode all trees	99
#2	(age near/3 (determinat* or estimat* or assess*)):ti	34
#3	((forensic or radiological) next age)	1
#4	((age or maturation or mature) near/5 (determinat* or estimat* or assess* or examinat*))	3740
#5	(hand or hands or wrist or wrists or dental or teeth or tooth or (third next molar*) or carpal or metacarpal or metacarpus)	54096
#6	(roentgen* or x-ray* or xray* or radiolog* or radiograp*)	39127
#7	#4 and #5 and #6	167
#8	#1 or #2 or #3 or #7	288
#9	(greulich near/2 pyle)	7
#10	#8 or #9 in Trials	138

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: PubMed
Dato for søk: 2017-01-03

Search (((publisher [sb]) OR pubstatusaheadofprint)) AND (((age determinat*[Title/Abstract]) OR age estimat*[Title/Abstract]) OR age assess*[Title/Abstract])	76

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"	Leste første 100 treff.

Database: Google Scholar
Dato for søk: 2017-01-03

"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"	Leste første 100 treff.

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" OR "assessment of age"	16
greulich OR pyle OR demirjian OR haavikko OR kullman OR nortje OR liversidge OR kvaal	14

Database: Clinicaltrials.gov
Dato for søk: 2017-01-03

"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"	16
greulich OR pyle	8

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

Database: WHO - International Clinical Trials Registry Platform (ICTRP)
Dato for søk: 2017-01-03

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	22
greulich OR pyle	2

Appendix 2: Description of included studies with quality assessment

Abbreviations used: CA: Chronological age; SA: Skeletal age based on the index test.

Bala M, Pathak A, Jain RL. Assessment of skeletal age using MP3 and hand-wrist radiographs and its correlation with dental and chronological ages in children. Journal of the Indian Society of Pedodontics and Preventive Dentistry. 2010;28(2):95-9.		
Population: Country, ethnicity, place and year	India (North-West), from outpatient department of Pedodontics and Preventive Dentistry, Government Dental College and Hospital, Patiala, and various schools. Only children of normal weight (between 3rd and 97th percentile curves for a particular age). All radiographs taken at the same day (year not specified).	
Sample, sex and age	160 participants, 80 boys and 80 girls, aged 8-14 years.	
Study design	Cross-sectional.	
Index test	Radiographed for middle phalanx of third finger (MP_3) and hand-wrist of the right hand. Greulich & Pyle atlas.	
Other comments	Dental age was assessed from IOPA radiographs of right permanent maxillary canine based on Nolla's calcification stages	
Aim of the study	"…to assess skeletal age using MP 3 and hand-wrist radiographs and to find the correlation amongst the skeletal, dental and chronological ages"	
QUADAS- 2 assessment	**Rating**	**Comment**
Patient selection method:	"…children were selected from…" No further description of sampling method. No discussion of uniform distribution into age cohorts found in article.	
- Consecutive or random sample of patients?	Unclear	
- Avoid inappropriate exclusions?	Yes	Weight criteria considered appropriate.
DOMAIN 1: Patient selection	**Unclear risk of bias**	
DOMAIN 1: Extra questions on age cohorts and age range	Not relevant for included analyses.	
- Index test interpreted without knowledge of CA?	Unclear	Not mentioned
DOMAIN 2: Index test interpretation	**Unclear risk of bias**	
- CA interpreted without knowledge of SA?	Yes	Assumed ok
DOMAIN 3: Reference standard	**Low risk of bias**	
- All patients included in analysis?	Yes	All numbers included in results-tables
DOMAIN 4: Patient flow and timing bias	**Low risk of bias**	

Buken B, Safak AA, Yazici B, Buken E, Mayda AS. Is the assessment of bone age by the Greulich-Pyle method reliable at forensic age estimation for Turkish children? Forensic Science International. 2007;173(2):146-53.	
Population: Country, ethnicity, place and year	Turkey (North West). Schoolchildren in Central Düzce, and students at Abant Izzet Baysal University. Physically and mentally healthy, no history of chronic or severe illness, right handed with no history of trauma to the left hand and wrist. Caucasian with low-middle socioeconomic status. Data collection period not clear.
Sample, sex and age	492 participants, 251 boys aged 11-17 years, 241 girls aged

	11-19 years.	
Study design	Cross-sectional.	
Index test	Radiograph of right hand and wrist, Greulich & Pyle atlas.	
Aim of the study	"…we investigated whether or not the Greulich–Pyle (G–P) method is sufficient at forensic age estimation for Turkish Children."	
QUADAS-2 assessment	**Rating**	**Comment**
Patient selection method:	Random selection of schools in the area, random selection of children from these schools. Subjects 18 years and older were volunteers. No discussion of uniform distribution into age cohorts found.	
- Consecutive or random sample of patients?	Unclear	
- Avoid inappropriate exclusions?	11-17 years: Yes 18-19 years: No	18-19 years: 20 female and 50 males were excluded because epiphyseal union were completed.
DOMAIN 1: Patient selection	**High risk of bias for 18 and 19 years** **Low risk of bias for 11 to 17 years**	
DOMAIN 1: Extra questions on age cohorts and age range	Not relevant for included analyses.	
- Index test interpreted without knowledge of CA?	Yes	The persons who interpreted the radiograph only knew the participants' gender.
DOMAIN 2: Index test interpretation	**Low risk of bias**	
- CA interpreted without knowledge of SA?	Yes	Assumed ok
DOMAIN 3: Reference standard	**Low risk of bias**	
- All patients included in analysis?	Yes	
DOMAIN 4: Patient flow and timing bias	**Low risk of bias**	

Cantekin K, Celikoglu M, Miloglu O, Dane A, Erdem A. Bone age assessment: the applicability of the Greulich-Pyle method in eastern Turkish children. Journal of Forensic Sciences. 2012;57(3):679-82.		
Population: Country, ethnicity, place and year	Turkey (East). Children attending the Department of Orthodontics at the University of Ataturk. Physically and mentally healthy with no history of chronic or severe disease, no history of trauma on left hand-wrist. Data collection period not clear.	
Sample, sex and age	767 participants, 342 boys and 425 girls, aged 7-17 years	
Study design	Cross-sectional.	
Index test	Conventional roentgenograms of left hand and wrist, Greulich & Pyle atlas.	
Aim of the study	"… to investigate whether or not the Greulich–Pyle (GP) method is adequate for Turkish children."	
QUADAS-2 assessment	**Rating**	**Comment**
Patient selection method:	Random selection of radiographs at the Department. No discussion of uniform distribution into age cohorts found in article.	
- Consecutive or random sample of patients?	Yes	Random selection of radiographs at the Department
- Avoid inappropriate exclusions?	Unclear	
DOMAIN 1: Patient selection	**Unclear risk of bias**	
DOMAIN 1: Extra questions on age cohorts and age range	Not relevant for included analyses.	

- Index test interpreted without knowledge of CA?	Yes	Dental and skeletal maturation assessments performed without any knowledge of the children's CAs.
DOMAIN 2: Index test interpretation	**Low risk of bias**	
- CA interpreted without knowledge of SA?	Yes	Assumed ok
DOMAIN 3: Reference standard	**Low risk of bias**	
- All patients included in analysis?	Unclear	Assumed
DOMAIN 4: Patient flow and timing bias	**Low risk of bias**	

Chaumoitre K, Saliba-Serre B, Adalian P, Signoli M, Leonetti G, Panuel M. Forensic use of the Greulich and Pyle atlas: prediction intervals and relevance Eur Radiol. 2017 Mar;27(3):1032-1043. doi: 10.1007/s00330-016-4466-4. Epub ahead of print 2016 Jun 29.		
Population: Country, ethnicity, place and year	France (South) with multi-ethnic sample. The authors write that France forbid ethic registration, but that Marseilles is a cosmopolitan melting pot with many immigrants. Patients consulting for minor injuries at University hospital of Marseilles from 2006 to 2011. Included if medical records contained no disease that could affect bone maturation.	
Sample, sex and age	2614 participants, 1423 boys aged 0-21 years and 1191 girls aged 0-20 years.	
Study design	Cross-sectional, from archives.	
Index test	Radiograph of right or left hand and wrist, Greulich & Pyle atlas. Both hands used indifferently.	
Aim of the study	"… to assess its [the Greulich & Pyle atlas] accuracy and to calculate the prediction intervals at 95% for forensic use."	
QUADAS-2 assessment	**Rating**	**Comment**
Patient selection method:	Individuals were consecutively recruited from the x-rays database in order to have sufficient number of patients by year of chronological age and equally distributed between boys and girls for prediction interval calculation. The article states that "they restrained the sample to boys aged less than 21 and girls less than 20 years, taking into account higher GP categories (19 for boys and 18 for girls) and not distorting the calculation of prediction interval."	
- Consecutive or random sample of patients?	Yes	Consecutive
- Avoid inappropriate exclusions?	Yes	
DOMAIN 1: Patient selection	**Low risk of bias**	
DOMAIN 1: Extra questions on age cohorts and age range	Uniform distribution of participants in age cohorts considered by authors. Number of participants in each age cohort varies from 58 to 102 observations among boys (highest numbers in age cohorts 12 and 13 years) and from 57 to 76 observations among girls (highest numbers in age cohort 14 years). Age range 0-21 years (boys)/0-20 years (girls). Our judgement is that the age cohorts are quite uniform and larger than in most studies, although not equal. Age range appropriate for the analyses. **Low risk of bias**	
- Index test interpreted without knowledge of CA?	Yes	The readers only knew the sex of the child and were blinded to the chronological age
DOMAIN 2: Index test interpretation	**Low risk of bias**	
- CA interpreted without	Yes	Assumed ok.

knowledge of SA?		
DOMAIN 3: Reference standard	**Low risk of bias**	
- All patients included in the analysis?	Yes	
DOMAIN 4: Patient flow and timing bias?	**Low risk bias**	

Chiang KH, Chou ASB, Yen PS, Ling CM, Lin CC, Lee CC, et al. The reliability of using Greulich-Pyle method to determine children's bone age in Taiwan. Tzu Chi Medical Journal. 2005;17(6):417-20+53.		
Population: Country, ethnicity, place and year	Taiwan (Hualien), children who came to an emergency outpatient department because of suspected trauma. Included radiographs that did not show bone or soft tissue abnormality and with no record of congenital disorder or developmental disturbances. Data collection period not clear.	
Sample, sex and age	370 participants, 230 boys and 140 girls, aged 0-18 years.	
Study design	Cross-sectional.	
Index test	Radiograph of the left hand and wrist, Greulich & Pyle atlas.	
Aim of the study	"… we investigated whether or not the Greulich-Pyle method is sufficient for the determination of the skeletal age of children in Taiwan."	
QUADAS-2 assessment	**Rating**	**Comment**
Patient selection method:	Consecutive children at an emergency outpatient department. No discussion of uniform distribution into age cohorts found in article.	
- Consecutive or random sample of patients?	Yes	Consecutive
- Avoid inappropriate exclusions?	Unclear	
DOMAIN 1: Patient selection	**Unclear risk of bias**	
DOMAIN 1: Extra questions on age cohorts and age range	Not relevant for included analyses.	
- Index test interpreted without knowledge of CA?	Yes	Analysed by two radiologists who were unaware of the age of the children
DOMAIN 2: Index test interpretation	**Low risk of bias**	
- CA interpreted without knowledge of SA?	Yes	Assumed ok
DOMAIN 3: Reference standard	**Low risk of bias**	
- All patients included in the analysis?	No	Radiographs were excluded if the inter-observer variation was more than 12 months. 108 cases excluded because of poor film quality (58), inter-observer difference (40), and 10 of other causes.
DOMAIN 4: Patient flow and timing bias?	**High risk of bias**	

Griffith JF, Cheng JCY, Wong E. Are western skeletal age standards applicable to the Hong Kong Chinese population? A comparison of the Greulich and Pyle method and the Tanner and Whitehouse method. Hong Kong Med J 2007;13(Suppl 3):S28-32.	
Population: Country, ethnicity, place and year	China (Hong Kong). Children attending the accident and emergency departments of Prince of Wales, North District, and Tuen Mun hospitals with suspected fractures from October 2000 to December 2002.
Sample, sex and age	535 participants, 276 females, 259 males, aged 10-18 years
Study design	Cross-sectional.

Index test	Radiographs of the hand and wrist, both the left and right sides were used. Greulich & Pyle atlas.	
Other comments	Radiographs also scored based on the Tanner and Whitehouse RUS and carpal scores.	
Aim of the study	"to (1) assess whether skeletal age standards currently used are applicable to modern day Hong Kong children/adolescents, and (2) to compare the GP and TW3 methods of skeletal age assessment with reference to modern day Hong Kong children/adolescents."	
QUADAS-2 assessment	**Rating**	**Comment**
Patient selection method:	All consecutive patients. No discussion of uniform distribution into age cohorts found in article.	
- Consecutive or random sample of patients?	Yes	Consecutive
- Avoid inappropriate exclusions?	Unclear	
DOMAIN 1: Patient selection	**Unclear risk of bias**	
DOMAIN 1: Extra questions on age cohorts and age range	Not relevant for included analyses.	
- Index test interpreted without knowledge of CA?	Yes	"undertaken […] without prior knowledge of the patient's age"
DOMAIN 2: Index test interpretation	**Low risk of bias**	
- CA interpreted without knowledge of SA?	Yes	Assumed ok.
DOMAIN 3: Reference standard	**Low risk of bias**	
- All patients included in analysis?	Unclear	
DOMAIN 4: Patient flow and timing bias	**Unclear risk of bias**	

Jiménez-Castellanos J, Carmona A, Catalina-Herrera CJ, Viñuales M. Skeletal maturation of wrist and hand ossification centers in normal Spanish boys and girls: a study using the Greulich-Pyle method. Acta Anatomica. 1996;155(3):206-11.		
Population: Country, ethnicity, place and year	Spain (South). Radiographs from the records of Seville University Hospital. Radiographs chosen to be made between ± 15 days from the child's birthday. Data collection period not clear.	
Sample, sex and age	239 participants, boys and girls, aged 1-14 years	
Study design	Cross-sectional, from archives.	
Index test	Radiograph of the hand and wrist, side not mentioned, Greulich & Pyle atlas.	
Aim of the study	"We aimed to establish both a chronological sequence of postnatal skeletal maturation in Spanish children and, at the same time intersexual differences."	
QUADAS-2 assessment	**Rating**	**Comment**
Patient selection method:	Selection method not specified. No discussion of uniform distribution into age cohorts found in article.	
- Consecutive or random sample of patients?	Unclear	Not specified.
- Avoid inappropriate exclusions?	Unclear	Not mentioned
DOMAIN 1: Patient selection	**Unclear risk of bias**	
DOMAIN 1: Extra questions on age cohorts and age range	Not relevant for included analyses.	
- Index test interpreted without knowledge of CA?	Unclear	In order to minimise subjectivity, the radiograph series was studied twice by the same researcher with an interval between

		observations, and also by two different workers, we judge that they was likely blinded to CA.
DOMAIN 2: Index test interpretation	**Low risk of bias**	
- CA interpreted without knowledge of SA?	Yes	Assumed ok
DOMAIN 3: Reference standard	**Low risk of bias**	
- All patients included in the analysis?	Unclear	
DOMAIN 4: Patient flow and timing bias?	**Unclear of bias**	

Johnston FE. Skeletal age and its prediction in Philadephia children. Human Biology. 1963;35:192-202.		
Population: Country, ethnicity, place and year	USA (Philadelphia). From the files of the Philadelphia Center for Research in Child Growth, the Growth Center school series. Described as "White" schoolchildren. Selected based on "clinical normality" (unspecified). Examined serially throughout their school years. Data collection period not clear.	
Sample, sex and age	120 participants, 58 boys and 62 girls, age range for examinations 7-17 years.	
Study design	Mixed longitudinal sample	
Index test	Radiograph of the hand and wrist, side not mentioned, Greulich & Pyle atlas, standards from 1959.	
Aim of the study	"Information is presented here on the rate of skeletal maturation of Philadelphia white children as evaluated from standards based upon the Brush series. It, therefore, compares rates of development in normal Philadelphia children with their Cleveland age-peers."	
QUADAS-2 assessment	**Rating**	**Comment**
Patient selection method:	Selection method not specified. No discussion of uniform distribution into age cohorts found in article.	
- Consecutive or random sample of patients?	Unclear	Selection method not specified.
- Avoid inappropriate exclusions?	Unclear	"Due to the inevitable dropouts, and to some later additions, the data are mixed longitudinal, and sample size varies for each age".
DOMAIN 1: Patient selection	**Unclear risk of bias**	
DOMAIN 1: Extra questions on age cohorts and age range	Not relevant for included analyses.	
- Index test interpreted without knowledge of CA?	Unclear	Not described.
DOMAIN 2: Index test interpretation	**Unclear risk of bias**	
- CA interpreted without knowledge of SA?	Yes	Assumed ok
DOMAIN 3: Reference standard	**Low risk of bias**	
- All patients included in the analysis?	Unclear	Not described.
DOMAIN 4: Patient flow and timing bias?	**Unclear risk of bias**	

Koc A, Karaoglanoglu M, Erdogan M, Kosecik M, Cesur Y. Assessment of bone ages: is the Greu-

lich-Pyle method sufficient for Turkish boys? Pediatrics International. 2001;43(6):662-5.		
Population: Country, ethnicity, place and year	Turkey (South-East). Boys with weight and height outside 3rd and 97th growth percentile or with chronic deses were excluded. Data collection period not clear.	
Sample, sex and age	255 participants, all boys, aged 7-17 years.	
Study design	Cross-sectional.	
Index test	Conventional roentgenograms of left hand and wrist, Greulich & Pyle atlas. Rated by two radiologists and one paediatrician separately, the average value used as bone age.	
Aim of the study	"…we investigated whether or not the GP method is sufficient for Turkish children for the determination of the skeletal age."	
QUADAS-2 assessment	**Rating**	**Comment**
Patient selection method:	Selection method not described. No discussion of uniform distribution into age cohorts found in article.	
- Consecutive or random sample of patients?	Unclear	Selection method not described.
- Avoid inappropriate exclusions?	Unclear	Selection method not described.
DOMAIN 1: Patient selection	**Unclear risk of bias**	
DOMAIN 1: Extra questions on age cohorts and age range	Not relevant for included analyses.	
- Index test interpreted without knowledge of CA?	Yes	Rated without any knowledge of chronological age.
DOMAIN 2: Index test interpretation	**Low risk of bias**	
- CA interpreted without knowledge of SA?	Yes	Assumed ok.
DOMAIN 3: Reference standard	**Low risk of bias**	
- All patients included in analysis?	Yes	Assumed ok.
DOMAIN 4: Patient flow and timing bias	**Low risk of bias**	

Mohammed RB, Rao DS, Goud AS, Sailaja S, Thetay AA, Gopalakrishnan M. Is Greulich and Pyle standards of skeletal maturation applicable for age estimation in South Indian Andhra children? Journal of pharmacy and bioallied sciences. 2015;7(3):218-25.		
Population: Country, ethnicity, place and year	India (Andhra Pradesh). Randomly selected patients from the outpatient Department of Oral Medicine, GITAM Dental College, Andhra Pradesh. Parents belonged to middle socioeconomic status groups. Included children that were local residents, with left hand with neither bone (including fracture) or soft tissue abnormalities, and no congenital and growth/ nutritional disturbances or history of chronic illness. Data collection period not clear.	
Sample, sex and age	660 participants, 330 boys and 330 girls, aged 9-20 years	
Study design	Cross-sectional.	
Index test	Digital radiographs of left hand and wrist, Greulich & Pyle atlas.	
Aim of the study	"… to evaluate the applicability of the G-P standards to contemporary South Indian children of 9-20 years age and also the assess the possible relation between estimated SA and CA."	
QUADAS-2 assessment	**Rating**	**Comment**
Patient selection method:	Randomly selected from patients. No discussion of uniform distribution into age cohorts found in article, but each sex and age cohort has almost the same number of participants.	
	Rating	**Comment**

- Consecutive or random sample of patients?	Yes	Random.
- Avoid inappropriate exclusions?	Yes	
DOMAIN 1: Patient selection	**Low risk of bias**	
DOMAIN 1: Extra questions on age cohorts and age range	Not relevant for included analyses.	
- Index test interpreted without knowledge of CA?	Yes	Undertaken without prior knowledge of the CA.
DOMAIN 2: Index test interpretation	**Low risk of bias**	
- CA interpreted without knowledge of SA?	Yes	Assumed ok.
DOMAIN 3: Reference standard	**Low risk of bias**	
- All patients included in the analysis?	Yes	
DOMAIN 4: Patient flow and timing bias?	**Low risk of bias**	

Nahid G, Abdorrahim A, Gharib SM, Anvar E. Assessment of bone age in Kurdish children in Iran. Pakistan Journal of Medical Sciences. 2010;26(1):36-9.		
Population: Country, ethnicity, place and year	Iran (Kurdistan state). Healthy children and adolescents recruited from schools. Only children of normal height and weight (between 3rd and 97th percentile curves for a particular age) without chronic illness, on medications, vitamin preparations, calcium supplements, or ill for longer than two weeks during previous six months, or hospitalized any time since birth. Data collection in 2007.	
Sample, sex and age	228 participants, 102 boys and 126 girls, aged 7-14 years.	
Study design	Cross-sectional.	
Index test	Radiograph of the left hand and wrist, Greulich & Pyle atlas.	
Aim of the study	"To investigate whether or not the Greulich- Pyle method is sufficient for Kurdish children for determination of the skeletal age."	
QUADAS-2 assessment	**Rating**	**Comment**
Patient selection method:	Recruited from schools. No discussion of uniform distribution into age cohorts found in article.	
- Consecutive or random sample of patients?	Unclear	
- Avoid inappropriate exclusions?	Unclear risk	Many exclusion criteria.
DOMAIN 1: Patient selection	**Unclear risk of bias**	
DOMAIN 1: Extra questions on age cohorts and age range	Not relevant for included analyses.	
- Index test interpreted without knowledge of CA?	Low risk	Description of blinding.
DOMAIN 2: Index test interpretation	**Low risk of bias**	
- CA interpreted without knowledge of SA?	Yes	Assumed ok
DOMAIN 3: Reference standard	**Low risk of bias**	
- All patients included in the analysis?	No	If the inter-observer variation was more than 12 months, the radiographs were excluded (22 case).
DOMAIN 4: Patient flow and timing bias?	**Unclear risk of bias**	

Patel PS, Chaudhary AR, Dudhia BB, Bhatia PV, Soni NC, Jani YV. Accuracy of two dental and one skeletal age estimation methods in 6-16 year old Gujarati children. Journal of forensic dental sciences : JFDS. 2015;7(1):18-27.		
Population: Country, ethnicity, place and year	India (Gurajat). Patients of the outpatient department of Oral Medicine and Radiology in Gandhinagar district. Subjects with all teeth of mandibular left quadrant at least partially erupted and right hand and wrist intact were included. Exclusion criteria were uncertain date of birth, missing, impacted, embedded or transposed left quadrant, trauma/injury to face or hand-wrist region, growth disorder/systemic illness. Data collection period not clear.	
Sample, sex and age	180 participants, 90 boys and 90 girls, aged 6-16 years.	
Study design	Cross-sectional.	
Index test	Radiograph of the right hand and wrist, Greulich & Pyle atlas.	
Comment	Subjects also scored according Demirjian's and Willem's method of dental age estimation.	
Aim of the study	"To test the applicability of Demirjian's and Willem's dental age assessment methods as well as Greulich and Pyle skeletal age assessment method in children residing in the Gandhinagar district."	
QUADAS-2 assessment	**Rating**	**Comment**
Patient selection method:	Random selection from patients. No discussion of uniform distribution into age cohorts found in article, but each sex and age cohort has almost the same number of participants.	
- Consecutive or random sample of patients?	Yes	Random
- Avoid inappropriate exclusions?	Yes	
DOMAIN 1: Patient selection	**Low risk of bias**	
DOMAIN 1: Extra questions on age cohorts and age range	Not relevant for included analyses.	
- Index test interpreted without knowledge of CA?	Unclear	No description of blinding
DOMAIN 2: Index test interpretation	**Unclear risk of bias**	
- CA interpreted without knowledge of SA?	Yes	Assumed ok
DOMAIN 3: Reference standard	**Low risk of bias**	
- All patients included in the analysis?	Yes	All x-rayed children were included in analysis- assumed
DOMAIN 4: Patient flow and timing bias?	**Low risk of bias**	

Patil ST, Parchand MP, Meshram MM, Kamdi NY. Applicability of Greulich and Pyle skeletal age standards to Indian children. Forensic Science International. 2012;216(1):200.e1-4.	
Population: Country, ethnicity, place and year	India (Maharashtra). Children attending at the radiology department, Government medical college, Nagpur for x-ray of inferior extremity for injury. Healthy children of middle socioeconomic status, with no chronic diseases, endochrinopathies, metabolic disorders or any other disease affecting skeletal maturation. Data collection 2007- 2009.
Sample, sex and age	375 participants, 194 boys and 181 girls, aged 0-19 years.
Study design	Cross-sectional.
Index test	Radiograph of the left hand and wrist if possible, otherwise the right, Greulich & Pyle atlas.
Aim of the study	"In this study we have to find out whether Indian children have advanced skeletal age or lag behind skeletally or same

	as American children (GP atlas). So that applicability of Greulich and Pyle atlas to Indian children can be determined."	
QUADAS-2 assessment	**Rating**	**Comment**
Patient selection method:	Selection method not specified. No discussion of uniform distribution into age cohorts found in article.	
- Consecutive or random sample of patients?	Unclear	
- Avoid inappropriate exclusions?	Yes	
DOMAIN 1: Patient selection	**Unclear risk of bias**	
DOMAIN 1: Extra questions on age cohorts and age range	Not relevant for included analyses.	
- Index test interpreted without knowledge of CA?	Yes	Description of binding.
DOMAIN 2: Index test interpretation	**Low risk of bias**	
- CA interpreted without knowledge of SA?	Yes	Assumed ok
DOMAIN 3: Reference standard	**Low risk of bias**	
- All patients included in the analysis?	Yes	All x-rayed children included in analysis.
DOMAIN 4: Patient flow and timing bias?	**Low risk of bias**	

Suri S, Prasad C, Tompson B, Lou W. Longitudinal comparison of skeletal age determined by the Greulich and Pyle method and chronologic age in normally growing children, and clinical interpretations for orthodontics. American Journal of Orthodontics & Dentofacial Orthopedics. 2013;143(1):50-60..		
Population: Country, ethnicity, place and year	Canada (Toronto). Described as White Canadian children. Selected from Burlington Growth Centre archives the Faculty of Dentistry. Selected if serial annual hand-wrist radiographs available with 2 consecutive radiographs more than 2 years apart, in age range 9-18 years. Normal facial growth, no/minimal orthodontic treatment and no syndrome or specific disease or growth abnormalities. Data collection period not clear.	
Sample, sex and age	68 participants, 35 boys and 33 girls, aged 9-18 y	
Study design	Longitudinal study design, but analysed as cross-sectional study in this systematic review.	
Index test	Radiograph of the hand and wrist, side not mentioned, Greulich & Pyle atlas.	
Aim of the study	"…to comprehensively analyze the concordance between skeletal and chronologic ages determined by using the Greulich and Pyle method at different ages in the preadolescent and adolescent periods, and to determine any age- and sex-related differences in the concordance."	
QUADAS-2 assessment	**Rating**	**Comment**
Patient selection method:	Selection method unclear. No discussion of uniform distribution into age cohorts found in article.	
- Consecutive or random sample of patients?	Unclear	
- Avoid inappropriate exclusions?	Yes	Assumed ok.
DOMAIN 1: Patient selection	**Unclear risk of bias**	
DOMAIN 1: Extra questions on age cohorts and age range	Not relevant for included analyses.	
- Index test interpreted without knowledge of CA?	Yes	Description of blinding

DOMAIN 2: Index test interpretation	**Low risk of bias**	
- CA interpreted without knowledge of SA?	Yes	Assumed ok
DOMAIN 3: Reference standard	**Low risk of bias**	
- All patients included in analysis?	Yes	
DOMAIN 4: Patient flow and timing bias?	**Low risk of bias**	

Tisè M, Mazzarini L, Fabrizzi G, Ferrante L, Giorgetti R, Tagliabracci A. Applicability of Greulich and Pyle method for age assessment in forensic practice on an Italian sample. International Journal of Legal Medicine. 2011;125(3):411-6.		
Population: Country, ethnicity, place and year	Italy (Central Italia). Described as Italian-Caucasian children. Trauma patients hospitalized in the Azienda Ospedaliero Universitaria Ospedali Riuniti of Ancona. X-rays with evidence of bone fracture or soft tissue abnormalities were discarded. No information about patients' growth disorders or other illnesses were available. Data collection 2006-2007.	
Sample, sex and age	484 participants, 359 boys and 125 girls, aged 11-19 years	
Study design	Cross-sectional, retrospective from archives.	
Index test	Radiograph of the hand and wrist, side not mentioned, Greulich & Pyle atlas.	
Aim of the study	Since the Greulich and Pyle method is one of the most frequently used in age estimation, the aim of this study was to assess the reproducibility and accuracy of the method on a large Italian sample of teenagers, to ascertain the applicability of the Atlas at the critical age thresholds of 14 and 18 years.	
QUADAS-2 assessment	**Rating**	**Comment**
Patient selection method:	Selection method unclear. No discussion of uniform distribution into age cohorts found in article.	
- Consecutive or random sample of patients?	Yes	
- Avoid inappropriate exclusions?	Yes	Assumed ok
DOMAIN 1: Patient selection	Low risk	
DOMAIN 1: Extra questions on age cohorts and age range	Number of participants in each age cohort varies from 8 to 67 observations among boys (highest numbers in age cohort 15 years) and from 8 to 19 observations among girls (highest numbers in age cohort 12 years). Age range 11-19 years. Our judgement is that the size of the age cohorts vary considerably and some age cohorts have very few observations. Age mimicry is likely to influence analyses. Age range may limit analyses of the Greulich & Pyle development stages for lower and upper teenage age cohorts. **High risk of bias**	
- Index test interpreted without knowledge of CA?	Yes	Description of blinding.
DOMAIN 2: Index test interpretation	**Low risk of bias**	
- CA interpreted without knowledge of SA?	Yes	Assumed ok.
DOMAIN 3: Reference standard	**Low risk of bias**	
- All patients included in the analysis?	Yes	Assumed ok.
DOMAIN 4: Patient flow and timing bias?	**Low risk of bias**	

van Rijn RR, Lequin MH, Robben SG, Hop WC, van Kuijk C. Is the Greulich and Pyle atlas still valid for Dutch Caucasian children today? Pediatric Radiology. 2001;31(10):748-52.		
Population: Country, ethnicity, place and year	Nederland (Amsterdam). Described as Dutch Caucasian. Data collection in 1997.	
Sample, sex and age	572 participants, 278 boys and 294 girls, aged 5-20 years.	
Study design	Cross-sectional.	
Index test	Radiograph of the left hand and wrist, Greulich & Pyle atlas.	
Aim of the study	"To compare skeletal age and calendar age in a healthy Dutch Caucasian population in order to test the applicability of this specific population".	
QUADAS-2 assessment	**Rating**	**Comment**
Patient selection method:	Selection method unclear. No discussion of uniform distribution into age cohorts found in article.	
- Consecutive or random sample of patients?	Yes	
- Avoid inappropriate exclusions?	Yes	Assumed ok
DOMAIN 1: Patient selection	Low risk	
DOMAIN 1: Extra questions on age cohorts and age range	*The relevant analyses (average skeletal age in development stages from the Greulich & Pyle atlas) were not part of the results presented in the article. Re-analysed for this systematic review based on access to original data granted by authors.* Number of participants in each age cohort varies. Our judgement is that the size of the age cohorts vary considerably and some age cohorts have very few observations. Age mimicry is likely to influence analyses. **High risk of bias**	
- Index test interpreted without knowledge of CA?	Yes	Description of blinding.
DOMAIN 2: Index test interpretation	**Low risk of bias**	
- CA interpreted without knowledge of SA?	Yes	Assumed ok.
DOMAIN 3: Reference standard	**Low risk of bias**	
- All patients included in analysis?	Yes	Assumed ok.
DOMAIN 4: Patient flow and timing bias	**Low risk of bias**	

Zafar AM, Nadeem N, Husen Y, Ahmad MN. An appraisal of Greulich-Pyle Atlas for skeletal age assessment in Pakistan. JPMA - Journal of the Pakistan Medical Association. 2010;60(7):552-5.	
Population: Country, ethnicity, place and year	Pakistan. Ethnically diverse. Children examined for indication of trauma. Consecutive patients admitted to one hospital in Karachi, Pakistan for indication of trauma. Less or equal to 216 months of age at time of exposure. Subjects ever investigated for metabolic, growth or nutritional disorders, or with a height or weight chart < 5th and > 95th centile were excluded. Chronological age from hospital records. 17 poor quality scans and 268 duplicate identities were excluded. Final Data collected 2005-2008.
Sample, sex and age	889 participants, Children of both genders, aged up to 216 months
Study design	Cross-sectional.
Index test	Hand-wrist radiographs, left hand if possible, otherwise right hand. Assessed according to the Greulich-Pyle atlas. GP using

	hand-wrist of the right hand	
Aim of the study	"To assess accurate skeletal age (SA) in clinical and medico-legal decisions using the Greulich-Pyle (GP) atlas and to see its applicability across diverse populations in Karachi."	
QUADAS-2 assessment	**Rating**	**Comment**
Patient selection method:	"Consecutive patients admitted"	
- Consecutive or random sample of patients?	Yes	
- Avoid inappropriate exclusions?	Yes	
DOMAIN 1: Patient selection	**Low risk of bias**	
DOMAIN 1: Extra questions on age cohorts and age range	*The relevant analyses (average skeletal age in development stages from the Greulich & Pyle atlas) were not part of the results presented in the article. Re-analysed for this systematic review based on access to original data granted by authors.* Number of participants in each age cohort varies. Our judgement is that the size of the age cohorts vary considerably and some age cohorts have very few observations. Age mimicry is likely to influence analyses. Age range may limit analyses of the Greulich & Pyle development stages upper teenage age cohorts. **High risk of bias**	
- Index test interpreted without knowledge of CA?	Yes	Blinded assessor.
DOMAIN 2: Index test interpretation	**Low risk of bias**	
- CA interpreted without knowledge of SA?	Yes	Assumed ok
DOMAIN 3: Reference standard	**Low risk of bias**	
- All patients included in the analysis?	Yes	
DOMAIN 4: Patient flow and timing bias?	**Low risk of bias**	

Appendix 3: Relevant datasets using the Greulich and Pyle atlas

In addition to the 19 included studies, we identified 107 studies with data on skeletal maturation based on the Greulich & Pyle atlas and chronological age. The population criteria appear fulfilled, i.e. data for > 50 healthy children in age range 10-26 years. These studies were not included because the article did not provide the relevant figures or format on the data presented. Some of these studies were analysed to another problem than ours. We have gathered information about these studies because they may represent potential relevant datasets for further analyses. Some of these studies have used more than one scoring method on the same subjects as described.

Reference	Scoring method	Country	Participants	Sex	Age range
Alhadlaq AM, Al-Shayea EI. New method for evaluation of cervical vertebral maturation based on angular measurements. Saudi Medical Journal. 2013;34(4):388-94.	G&P and Fishman's	Saudi Arabia	197	Boys	10-15 years
Andersen E. Comparison of Tanner-Whitehouse and Greulich-Pyle methods in a large scale Danish Survey. American Journal of Physical Anthropology. 1971;35(3):373-6.	G&P, TW1 and TW2	Denmark	1009	Both	7 - 18 years
Anderson DL, Thompson GW, Popovich F. Interrelationships of dental maturity, skeletal maturity, height and weight from age 4 to 14 years. Growth. 1975;39(4):453-62.	G&P	Denmark	232	Both	4 -14 years
Arat M, Koklu A, Ozdiler E, Rubenduz M, Erdogan B. Craniofacial growth and skeletal maturation: a mixed longitudinal study. European Journal of Orthodontics. 2001;23(4):355-61.	G&P	Turkey	78	Both	10-17 years
Arat ZM, Rubenduz M. Changes in dentoalveolar and facial heights during early and late growth periods: a longitudinal study. Angle Orthodontist. 2005;75(1):69-74.	G&P	Turkey	62	Both	10-17 years
Awais M, Nadeem N, Husen Y, Rehman A, Beg M, Khattak YJ. Comparison between Greulich-Pyle and Girdany-Golden methods for estimating skeletal age of children in Pakistan. Journal of the College of Physicians and Surgeons--Pakistan : JCPSP. 2014;24(12):889-93.	G&P, Girdany-Golden	Pakistan	283	Both	0 -18 years
Beit P, Peltomaki T, Schatzle M, Signorelli L, Patcas R. Evaluating the agreement of skeletal age assessment based on hand-wrist and cervical vertebrae radiography. American Journal of Orthodontics and Dentofacial Orthopedics. 2013;144(6):838-47.	G&P	Switzerland	730	Both	6 -18 years
Berst MJ, Dolan L, Bogdanowicz MM, Stevens MA, Chow S, Brandser EA. Effect of knowledge of chronologic age on the variability of pediatric bone age determined using the Greulich and Pyle standards. American Journal of Roentgenology. 2001;176(2):507-10.	G&P	USA	107	Both	2-20 years

Bezerra IS, Topolski F, Franca SN, Brucker MR, Fernandes A. Assessment of skeletal and dental ages of children and adolescents with type 1 diabetes mellitus. Pesquisa Odontologica Brasileira = Brazilian Oral Research. 2015;29.	G&P and Nolla	Brazil	82	Both	5 -15 years
Blanksby BA, Brogan WF, McKnight HP, Sprague PL. A skeletal age survey of primary school children in Western Australia. Australian Paediatric Journal. 1975;11(3):169-71.	G&P	Australia	594	Both	6 -12 years
Bouchard C, Leblanc C, Malina RM, Hollmann W. Skeletal age and submaximal working capacity in boys. Annals of Human Biology. 1978;5(1):75-8.	G&P	Germany	237	Boys	8 -18 years
Bouchard C, Malina RM, Hollmann W, Leblanc C. Relationships between skeletal maturity and submaximal working capacity in boys 8 to 18 years. Medicine & Science in Sports. 1976;8(3):186-90.	G&P	Germany	237	Boys	8 -18 years
Brown T, Grave KC. Skeletal maturation in Australian Aborigines. Australian Paediatric Journal. 1976;12(1):24-30.	G&P	Australia	123	Both	5- 20 years
Buyukgebiz A, Eroglu Y, Karaman O, Kinik E. Height and weight measurements of male Turkish adolescents according to biological maturation. Acta Paediatrica Japonica. 1994;36(1):80-3.	G&P	Turkish, in USA	879	Boys	11-19 years
Calfee RP, Sutter M, Steffen JA, Goldfarb CA. Skeletal and chronological ages in American adolescents: current findings in skeletal maturation. Journal of Childrens Orthopaedics. 2010;4(5):467-70.	G&P	USA	138	Both	12-18 years
Canals M, Valenzuela C, Avendano A, Samith S. [Bone maturity in children older than 6 years of age. Wrist and hand. I. Quantitative analysis]. Revista Chilena de Pediatria. 1988;59(2):102-5.	G&P, TW2	Chile	1323	Both	6 -20 years
Carling C, Le Gall F, Malina RM. Body size, skeletal maturity, and functional characteristics of elite academy soccer players on entry between 1992 and 2003. Journal of Sports Sciences. 2012;30(15):1683-93.	G&P	France	158	Boys	13 years
Chaudhry, K., A. Agarwal, and U. Rehani, Interrelationship among Dental, Skeletal and Chronological Ages in Urban and Rural Female Children. Jaypees International Journal of Clinical Pediatric Dentistry, 2010. 3(2): p. 79-86.	G&P	India	80	Both	8-14 years
Chaumoitre K, Lamtali S, Baali A, Saliba-Serre B, Lahmam A, Aboussad A, et al. Influence of socioeconomic status and body mass index on bone age. Hormone Research in Paediatrics. 2010;74(2):129-35.	G&P	Morocco	623	Both	6 -19 years
Chen ML, Chiang CH, Chen JS. Skeletal maturation and dietary intakes of Chinese children and young adults. Chinese Medical Journal (Taipei). 1977;24(2):132-41.	G&P	Chinese	4983	Both	2 -20 years

Cole AJ, Webb L, Cole TJ. Bone age estimation: a comparison of methods. British Journal of Radiology. 1988;61(728):683-6.	G&P, TW2	British	97	Both	mean 11 years
Coutinho S, Buschang PH, Miranda F. Relationships between mandibular canine calcification stages and skeletal maturity. American Journal of Orthodontics & Dentofacial Orthopedics. 1993;104(3):262-8.	G&P, TW & Demirjian	American	415	Both	7 -16 years
Cumming GR, Garand T, Borysyk L. Correlation of performance in track and field events with bone age. Journal of Pediatrics. 1972;80(6):970-3.	G&P	Canadian	259	Both	11 -18 years
De Donno A, Santoro V, Lubelli S, Marrone M, Lozito P, Introna F. Age assessment using the Greulich and Pyle method on a heterogeneous sample of 300 Italian healthy and pathologic subjects. Forensic Science International. 2013;229(1):157.e1-6.	G&P	Italian	300	Both	10 -20 years
Ebri Torne B, Ebri Verde I. Comparative Study bone ages Greulich-Pyle Tanner-W2 and Ebri and between predicted adult height. Pediatria Integral. 2012;16(9):741.e1-.e7.	G&P, TW2, Ebri	Spain	160	Both	0 -20 years
Edgren J, Fellman J, Lewin T. Skeletal maturation of the hand and wrist, a longitudinal study covering two years among children of Finnish Lapps. Acta Morphologica Neerlando-Scandinavica. 1974;12(1):1-7.	G&P	Finland	91	Both	3 -23 years
Fleshman K. Bone age determination in a paediatric population as an indicator of nutritional status. Tropical Doctor. 2000;30(1):16-8.	G&P	Nepalese	219		Unclear
Fry EI. Tanner-Whitehouse and Greulich-Pyle skeletal age velocity comparisons. American Journal of Physical Anthropology. 1971;35(3):377-80.	G&P, TW	Hong Kong	233	Both	10 -16 years
Garamendi PM, Landa MI, Ballesteros J, Solano MA. Reliability of the methods applied to assess age minority in living subjects around 18 years old. A survey on a Moroccan origin population. Forensic Science International. 2005;154(1):3-12.	G&P & Demirjian	Morocco	114	Both	13 -25 years
Goldfarb CA, Strauss NL, Wall LB, Calfee RP. Defining ulnar variance in the adolescent wrist: Measurement technique and interobserver reliability. Journal of Hand Surgery. 2011;36(2):272-7.	G&P	USA	138	Both	12-18 years
Goldstein HS. Skeletal maturity and cognitive development of 12- to 17-year-old males. Developmental Medicine & Child Neurology. 1987;29(3):348-50.	G&P	USA	3516	Boys	12 -17 years
Gross GW, Boone JM, Bishop DM. Pediatric skeletal age: determination with neural networks. Radiology. 1995;195(3):689-95.	G&P	USA	521	Both	0 -18 years
Gungor OE, Celikoglu M, Kale B, Gungor AY, Sari Z. The reliability of the Greulich and Pyle atlas when applied to a Southern Turkish population. European journal of dentistry. 2015;9(2):251-4.	G&P	Turkey	535	Both	10-18

Haavikko K, Kilpinen E. Skeletal development of Finnish children in the light of hand-wrist roentgen-ograms. Proceedings of the Finnish Dental Society. 1973;69(5):182-90.	G&P	Finland	1061	Both	2,5 -19 years
Hackman L, Black S. The reliability of the Greulich and Pyle atlas when applied to a modern Scottish population. Journal of Forensic Sciences. 2013;58(1):114-9.	G&P	UK	406	Both	0 -21 years
Haiter-Neto F, Kurita LM, Menezes AV, Casanova MS. Skeletal age assessment: A comparison of 3 methods. American Journal of Orthodontics and Dentofacial Orthopedics. 2006;130(4):435.e15-.e20.	G&P, TW3, Ekløf & Ringertz	Brazil	360	Both	7 -15 years
Hala, L.A., et al., Comparison of accuracy between dental and skeletal age in the estimation of chrono-logical age of Down syndrome individuals. Forensic Science International, 2016. 266: p. 578.e1-578.e10.	G&P	Brazil	216	Both	3-17 years
Hawley NL, Rousham EK, Norris SA, Pettifor JM, Cameron N. Secular trends in skeletal maturity in South Africa: 1962-2001. Annals of Human Biology. 2009;36(5):584-94.	G&P	South Africa	200	Both	9 -11 years
Heppe DH, Taal HR, Ernst GD, Van Den Akker EL, Lequin MM, Hokken-Koelega AC, et al. Bone age assessment by dual-energy X-ray absorptiometry in children: an alternative for X-ray? British Journal of Radiology. 2012;85(1010):114-20.	G&P and dual energy x-ray	Nether-land	95	Both	0-16 years
Kapalin V, Picko V. [the Skeletal Age of School Chil-dren and Its Dependences]. Ceskoslovenska Hy-giena. 1964;9:342-56.	G&P	Czech	2500	Both	7 -15 years
Khan KM, Miller BS, Hoggard E, Somani A, Sara-foglou K. Application of ultrasound for bone age estimation in clinical practice. Journal of Pediatrics. 2009;154(2):243-7.	G&P, TW3	USA	100	Both	Mean age 10 years
Kim HJ, Yoon JR, Modi C, Modi H, Song HR, Song SY. Interrelationship of the Risser sign, knee epiphysis, and bone age in determining skeletal maturity: a case-control study. Journal of Pediatric Orthopae-dics, Part B. 2011;20(3):173-7.	G&P, TW3	South Korea	293	Both	9 -18 years
Kim JR, Lee YS, Yu J. Assessment of bone age in pre-pubertal healthy Korean children: comparison among the Korean standard bone age chart, Greu-lich-Pyle method, and Tanner-Whitehouse method. Korean Journal of Radiology. 2015;16(1):201-5.	G&P, TW3 and KS (Kore-an standard)	South Korea	212	Both	7 -12 years
Kimura K. Age estimation from second metacarpals in children. Okajimas Folia Anatomica Japonica. 1992;69(4):177-82.	G&P	Japan	1241	Both	0 -19 years
Kimura K. Skeletal maturation in Japanese as as-sessed by the Oxford and Tanner-Whitehouse methods. Kaibogaku zasshi. 1972;0(5):358-72.	G&P	Japanese	598	Both	0-18 years
Kopczynska J. [Further studies on the skeletal age evaluated according to examination of bones of the hand and wrist in children in Warsaw. I]. Pediatria Polska. 1961;36:845-53.	G&P	Polish	5396	Both	7 -16 years

Kopczynska J. [Studies on developmental age of school children according to established skeletal age]. Pediatria Polska. 1959;34:859-70.	G&P	Polish	278	Both	6 -15 years
Krailassiri S, Anuwongnukroh N, Dechkunakorn S. Relationships between dental calcification stages and skeletal maturity indicators in Thai individuals. Angle Orthodontist. 2002;72(2):155-66.	G&P AND Demi-rjian	Thailand	361	Both	7 -19 years
Kullman L. Accuracy of two dental and one skeletal age estimation method in Swedish adolescents. Forensic Science International. 1995;75(2):225-36.	G&P	Sweden	72	Both	12 -19 years
Lee MM, Chan ST, Low WD, Chang KS. The relationship between dental and skeletal maturation in Chinese children. Archives of Oral Biology. 1965;10(6):883-91.	G&P	South China	5560	Both	6 -14 years
Lee MM. Maturation disparity between hand-wrist bones in Hong Kong Chinese children. American Journal of Physical Anthropology. 1971;34(3):385-95.	G&P	Hong Kong	571	Both	0 -17 years
Lenko HL. Prediction of adult height with various methods in Finnish children. Acta Paediatrica Scandinavica. 1979;68(1):85-92.	G&P, Tanner, Bay-ley&P, Walker, RWT	Finland	60	Both	7 -19 years
Lewis AB. Comparisons between dental and skeletal ages. Angle Orthodontist. 1991;61(2):87-92.	G&P	Unclear	694	Both	10 years old
Lewis CP, Lavy CBD, Harrison WJ. Delay in skeletal maturity in Malawian children. Journal of Bone and Joint Surgery - Series B. 2002;84(5):732-4.	G&P	Malawi	130	Both	2-28 years
Lin FQ, Zhang J, Zhu Z, Wu YM. Comparative study of Gilsanz-Ratib digital atlas and Greulich-Pyle atlas for bone age estimation in a Chinese sample. Annals of Human Biology. 2015;42(6):523-7.	G&P, Gilsanz-Ratib digital atlas	China	618	Both	0 -13 years
Lin NH, Ranjitkar S, Macdonald R, Hughes T, Taylor JA, Townsend GC. New growth references for assessment of stature and skeletal maturation in Australians. Australian Orthodontic Journal. 2006;22(1):1-10.	G&P	South Australia	2497	Both	9 -18 years
Linhares RV, Matta Mde O, Lima JR, Dantas PM, Costa MB, Fernandes Filho J. [Effects of sexual maturation on body composition, dermatoglyphics, somatotype and basic physical qualities of adolescents]. Arquivos Brasileiros de Endocrinologia e Metabologia. 2009;53(1):47-54.	G&P	Brazil	136	Boys	10 -14 years
Loder RT, Estle DT, Morrison K, Eggleston D, Fish DN, Greenfield ML, et al. Applicability of the Greulich and Pyle skeletal age standards to black and white children of today. American Journal of Diseases of Children. 1993;147(12):1329-33.	G&P	USA	841	Both	0 -18 years

Low WD. Relation between socio-economic status and skeletal maturation of Chinese children. Zeitschrift fur Morphologie und Anthropologie. 1972;64(1):1-11.	G&P	China	33990	Both	6 -20 years
Maggio, A., et al., Assessment of the accuracy of the Greulich and Pyle hand-wrist atlas for age estimation in a contemporary Australian population. Australian Journal of Forensic Sciences, 2016: p. 1-11.	G&P	Australia	360	Both	0-25 years
Makkad RS, Balani A, Chaturvedi SS, Tanwani T, Agrawal A, Hamdani S. Reliability of panoramic radiography in chronological age estimation. Journal of forensic dental sciences : JFDS. 2013;5(2):129-33.	G&P, Demirjian	India	270	Both	17 -25 years
Malik P, Rana V, Rehani U. To Evaluate the Relationship between Mandibular Canine Calcification Stages and Skeletal Age. Jaypees International Journal of Clinical Pediatric Dentistry. 2012;5(1):14-9.	G&P, Demirjian	India	147	girls	10 -13 years
Mansourvar M, Ismail MA, Raj RG, Kareem SA, Aik S, Gunalan R, et al. The applicability of Greulich and Pyle atlas to assess skeletal age for four ethnic groups. Journal of Forensic and Legal Medicine. 2014;22:26-9.	G&P	USA	184	Boys	1 -18 years
Maresh MM. Single versus serial assessment of skeletal age: either, both or neither? American Journal of Physical Anthropology. 1971;35(3):387-92.	G&P	USA	104	Both	10 -15 years
Mathiasen MS. Determination of bone age and recording of minor skeletal hand anomalies in normal children. Danish Medical Bulletin. 1973;20(3):80-5.	G&P	Denmark	1100	Both	1 -16 years
Mazess RB, Cameron JR. Skeletal growth in school children: maturation and bone mass. American Journal of Physical Anthropology. 1971;35(3):399-407.	G&P	USA	322	Both	6 -12 years
McCormack, S.E., et al., Relative Skeletal Maturation and Population Ancestry in Nonobese Children and Adolescents. Journal of Bone & Mineral Research, 2017. 32(1): p. 115-124.	G&P	USA	1592	Both	5-24 years
Michaut E, Niang I, Dan V. Bone maturation during puberty. Apropos of 227 adolescents from Dakar. [French]. Annales de radiologie. 1972;15(9):767-79.	G&P, TW	Senegal	227	Both	11 -15 years
Mora S, Boechat MI, Pietka E, Huang HK, Gilsanz V. Skeletal age determinations in children of European and African descent: applicability of the Greulich and Pyle standards. Pediatric Research. 2001;50(5):624-8.	G&P	USA	534	Both	0 -19 years
Moradi M, Sirous M, Morovatti P. The reliability of skeletal age determination in an Iranian sample using Greulich and Pyle method. Forensic Science International. 2012;223(1):372.e1-4.	G&P	Iran	425	Both	6 -18 years

Murthy KK, Srinivas CN, Lakshmi V, Kumar CV, Krishnaveni M. Assessment of skeletal and dental maturity levels for a given chronological age among Indian children. Journal of Contemporary Dental Practice [Electronic Resource]. 2012;13(3):310-5.	G&P, Nolla	India	260	Both	3 -15 years
Nahid G, Abdorrahim A, Gharib SM, Anvar E. Assessment of bone age in Kurdish children in IRAN. Pakistan Journal of Medical Sciences. 2010;26(1):36-9.	G&P	Kurdish	228	Both	7 -14 years
Napoli MM, Saraiva PA. Bone age. [Portuguese]. Revista do Hospital das Clinicas. 1985;40(5):210-5.	G&P	Brazil	217	Both	0 -20 years
Oh Y, Lee R, Kim HS. Evaluation of skeletal maturity score for Korean children and the standard for comparison of bone age and chronological age in normal children. Journal of Pediatric Endocrinology and Metabolism. 2012;25(3):279-84.	G&P and TW3	South Korea	378	Both	8-15 years
Onat T. Prediction of adult height of girls based on the percentage of adult height at onset of secondary sexual characteristics, at chronological age, and skeletal age. Human Biology. 1975;47(1):117-30.	G&P	Turkish	119	Girls	8.5-13.4 years
Ontell FK, Ivanovic M, Ablin DS, Barlow TW. Bone age in children of diverse ethnicity. American Journal of Roentgenology. 1996;167(6):1395-8.	G&P	USA	765	Both	3-18 years
Öztürk F, Karataş OH, Mutaf HI, Babacan H. Bone age assessment: comparison of children from two different regions with the Greulich–Pyle method In Turkey. Austr J of Forensic Sciences 2016:48(6):694-703.	G&P	Turkey	514	Both	9-17
Pawson IG. Radiographic determination of excessive bone loss in Alaskan Eskimos. Human Biology. 1974;46(3):369-80.	G&P	USA	154	Both	0->50 years
Paxton ML, Lamont AC, Stillwell AP. The reliability of the Greulich-Pyle method in bone age determination among Australian children. Journal of Medical Imaging and Radiation Oncology. 2013;57(1):21-4.	G&P	Australia	350	Both	0-18 years
Pinchi V, De Luca F, Focardi M, Pradella F, Vitale G, Ricciardi F, et al. Combining dental and skeletal evidence in age classification: Pilot study in a sample of Italian sub-adults. Legal Medicine. 2016;20:75-9.	G&P, TW3	Italy	274	Both	6-17 years
Pinchi V, De Luca F, Ricciardi F, Focardi M, Piredda V, Mazzeo E, et al. Skeletal age estimation for forensic purposes: A comparison of GP, TW2 and TW3 methods on an Italian sample. Forensic Science International. 2014;238:83-90.	G&P, TW3, TW2	Italy	307	Both	6-20 years
Rai V, Saha S, Yadav G, Tripathi AM, Grover K. Dental and skeletal maturity- A biological indicator of chronologic age. Journal of Clinical and Diagnostic Research. 2014;8(9):ZC60-ZC4.	G&P, TW2	India	150	Both	5-15 years
Rikhasor RM, Qureshi AM, Rathi SL, Channa NA. Skeletal maturity in Pakistani children. Journal of Anatomy. 1999;195:305-8.	G&P	India	750	Both	1-18 years

Roche AF, Roberts J, Hamill PV. Skeletal maturity of children 6-11 years, United States. Vital & Health Statistics - Series 11: Data From the National Health Survey. 1974;0(140):1-62.	G&P	USA	Ca 7000	Both	6-11 years
Roche AF, Roberts J, Hamill PV. Skeletal maturity of children 6-11 years: racial, geographic area, and socioeconomic differentials, United States. Vital & Health Statistics - Series 11: Data From the National Health Survey. 1975;0(149):1-81.	G&P	USA	Ca 7000	Both	6-11 years
Roche AF, Roberts J, Hamill PV. Skeletal maturity of youths 12--17 years racial, geographic area, and socioeconomic differentials. United States, 1966-1970. Vital & Health Statistics - Series 11: Data From the National Health Survey. 1978;0(167):1-98.	G&P	USA		Both	12-17 years
Roche AF, Roberts J, Hamill PV. Skeletal maturity of youths 12-17 years, United States. Vital & Health Statistics - Series 11: Data From the National Health Survey. 1976;0(160):1-90.	G&P	USA	Ca 7000	Both	12-17 years
Roche AF, Roberts J, Hamill PVV. Skeletal maturity of children 6-11 years. Vital and Health Statistics Ser. 1974;11(140).	G&P	USA	Ca 7000	Both	6-11 years
Russell DL, Keil MF, Bonat SH, Uwaifo GI, Nicholson JC, McDuffie JR, et al. The relation between skeletal maturation and adiposity in African American and Caucasian children. Journal of Pediatrics. 2001;139(6):844-8.	G&P	USA	252	Both	5-12 years
Santoro V, Roca R, De Donno A, Fiandaca C, Pinto G, Tafuri S, et al. Applicability of Greulich and Pyle and Demirijan aging methods to a sample of Italian population. Forensic Science International. 2012;221(1):153.e1-5.	G&P	Italian	532	Both	7-15 years
Santos C, Ferreira M, Alves FC, Cunha E. Comparative study of Greulich and Pyle Atlas and Maturos 4.0 program for age estimation in a Portuguese sample. Forensic Science International. 2011;212(1):276.e1-7.	G&P	Portugal	230	Both	12-20 years
Schedewie H, Braselman A, Willich E, Lachman R. The determination of bone age in the elbow as compared to the hand. A study in 390 children. Revista Interamericana de Radiologia. 1979;4(1):11-7.	G&P	Germany	408	Both	3-18 years
Schmidt S, Koch B, Schulz R, Reisinger W, Schmeling A. Comparative analysis of the applicability of the skeletal age determination methods of Greulich-Pyle and Thiemann-Nitz for forensic age estimation in living subjects. International Journal of Legal Medicine. 2007;121(4):293-6.	G&P, Thiemann & Nitz	Germany	349	Both	1-18 years
Schmidt S, Koch B, Schulz R, Reisinger W, Schmeling A. Studies in use of the Greulich-Pyle skeletal age method to assess criminal liability. Legal Medicine. 2008;10(4):190-5.	G&P	Germany	649	Both	1-18 years

Scoles PV, Salvagno R, Villalba K, Riew D. Relationship of iliac crest maturation to skeletal and chronologic age. Journal of Pediatric Orthopedics. 1988;8(6):639-44.	G&P	USA	388	Both	10-19 years
Shaikh AH, Rikhasor RM, Qureshi AM. Determination of skeletal age in children aged 8-18 years. Jpma. 1998;0(4):104-6.	G&P	Pakistan	402	Both	8-18 years
Shilpa PH, Sunil RS, Sapna K, Kumar NC. Estimation and comparison of dental, skeletal and chronologic age in Bangalore south school going children. Journal of the Indian Society of Pedodontics & Preventive Dentistry. 2013;31(2):63-8 6p.	G&P	India	250	Both	6-15 years
So LL, Yen PK. Secular trend in skeletal maturation in southern Chinese girls in Hong Kong. Zeitschrift fur Morphologie und Anthropologie. 1990;78(2):145-53.	G&P	Hong Kong	117	Girls	11-12 years
So LL. Correlation of sexual maturation with skeletal age of southern Chinese girls. Australian Orthodontic Journal. 1997;14(4):215-7.	G&P	Hong Kong	117	Girls	11-12 years
So LL. Correlation of skeletal maturation with stature and body weight of southern Chinese girls in Hong Kong. Zeitschrift fur Morphologie und Anthropologie. 1991;78(3):307-12.	G&P	Hong Kong	117	Girls	11-12 years
So LL. Skeletal maturation of the hand and wrist and its correlation with dental development. Australian Orthodontic Journal. 1997;15(1):1-9.	G&P	China	117	Girls	12 years
Soudack M, Ben-Shlush A, Jacobson J, Raviv-Zilka L, Eshed I, Hamiel O. Bone age in the 21st century: is Greulich and Pyle's atlas accurate for Israeli children? Pediatric Radiology. 2012;42(3):343-8.	G&P	Israel	679	Both	0-18 years
Takatama H. Roentgenological studies on the skeletal development of the hand and wrist in Japanese and Ainu children. [Japanese]. Sapporo Medical Journal. 1979;48(3):260-84.	G&P	Japan	724	Both	6-15 years
Van Rijn RR, Lequin MH, Robben SGF, Hop WCJ, Van Kuijk C. The Greulich&Pyle atlas for determining the skeletal age can still be used in a contemporary Dutch white population. [Dutch]. Nederlands Tijdschrift voor Geneeskunde. 2003;147(15):701-4.	G&P	Netherland	572	Both	5-20 years
Vignolo M, Milani S, DiBattista E, Naselli A, Mostert M, Aicardi G. Modified Greulich-Pyle, Tanner-Whitehouse, and Roche-Wainer-Thissen (knee) methods for skeletal age assessment in a group of Italian children and adolescents. European Journal of Pediatrics. 1990;149(5):314-7.	G&P, TW2	Italy	221	Both	4-17 years
Zabet D, Rerolle C, Pucheux J, Telmon N, Saint-Martin P. Can the Greulich and Pyle method be used on French contemporary individuals? International Journal of Legal Medicine. 2015;129(1):171-7.	G&P	France	190	Both	10-19 years
Zammit MP, Kalra V, Nelson S, Broadbent BH, Hans MG. Growth patterns of Labrador Inuit youth: II. Skeletal age. Arctic Medical Research. 1994;53(4):176-83.	G&P	USA	100	Both	5-18 years

Zhang A, Sayre JW, Vachon L, Liu BJ, Huang HK. Racial differences in growth patterns of children assessed on the basis of bone age. Radiology. 2009;250(1):228-35.	G&P	China	1390	Both	0-18 years
Zhang J, Lin F, Ding X. Maturation Disparity between Hand-Wrist Bones in a Chinese Sample of Normal Children: An Analysis Based on Automatic BoneXpert and Manual Greulich and Pyle Atlas Assessment. Korean Journal of Radiology. 2016;17(3):435-42.	G&P	China	397	Both	2-14 years

Appendix 4: Relevant datasets using other index tests than Greulich and Pyle atlas to classify bone age on hand x-rays

In addition to the studies based on the Greulich and Pyle atlas, we identified 124 studies that had collected data on hand skeletal maturation based on other classification systems and chronological age. The population criteria appear fulfilled, i.e. data for > 50 healthy children in age range 10-26 years. Some of these studies were analysed to another objective than ours. We have gathered information about these studies because they may represent potential relevant datasets for further analyses.

Reference	Scoring method	Country	Participants	Sex	Age range
Agathos D, Markostamos K, Toutountjakis N. Statural, bone and dental growth in Greek girls of the Athenian region. [French]. L' Orthodontie francaise. 1987;58:507-16.	Tanner	Greece	151	Girls	6-17 years
Agossou-Voyeme AK, Fachehoun CR, Boco V, Hounnou GM, Biaou O. [Osseus age of the black children of Benin. A population study of 600 children aged from 9 to 18 years and living in Cotonou]. Morphologie. 2005;89(285):64-70.	TW2	Benin	600	Both	9-18 years
Aguiar LB, Caldas Mde P, Haiter Neto F, Ambrosano GM. A methodology to measure cervical vertebral bone maturation in a sample from low-income children. Brazilian Dental Journal. 2013;24(1):30-4.	TW3	Brazil	Ca 80	Both	7-15 years
Akridge M, Hilgers KK, Silveira AM, Scarfe W, Scheetz JP, Kinane DF. Childhood obesity and skeletal maturation assessed with Fishman's hand-wrist analysis. American Journal of Orthodontics and Dentofacial Orthopedics. 2007;132(2):185-90.	Fishman	USA	109	Both	9-16 years
Alkhal HA, Wong RW, Rabie AB. Correlation between chronological age, cervical vertebral maturation and Fishman's skeletal maturity indicators in southern Chinese. Angle Orthodontist. 2008;78(4):591-6.	Fishman	Chinese	400 (200x2)	Both	girls 10-15, boys 12 - 17
Al-Qtaitat, A., et al., Bone age determination of epiphyseal union around wrist joint and its correlation with chronological age: A radiological study in a Jordanian population. Biosciences Biotechnology Research Asia, 2016. 13(1): p. 67-73.	McKern & Stewart	Jordan	101	Both	12-22 years
Andersen E. Skeletal maturation of Danish school children in relation to height, sexual development, and social conditions. Acta Paediatrica Scandinavica. 1968;0:Suppl 185:11+.	Various methods	Denmark	ca 700		
Ashizawa K, Asami T, Anzo M, Matsuo N, Matsuoka H, Murata M, et al. Standard RUS skeletal maturation of Tokyo children. Annals of Human Biology. 1996;23(6):457-69.	TW2	Japan	1457	Both	3-18 years
Ashizawa K, Kumakura C, Zhou X, Jin F, Cao J. RUS skeletal maturity of children in Beijing. Annals of Human Biology. 2005;32(3):316-25.	TW3	China	1273	Both	6-8 years
Baughan B, Demirjian A, Levesque GY. Skeletal maturity standards for French-Canadian children of school-age with a discussion of the reliability and validity of such measures. Human Biology. 1979;51(3):353-70.	TW2	Canada	4084	Both	6-17 years

Benso L, Vannelli S, Pastorin L, Benso A, Milani S. Variation of bone age progression in healthy children. Acta Paediatrica Supplement. 1997;423:109-12.	TW2	Italy	407	Boys	7-12 years
Beunen G, Lefevre J, Ostyn M, Renson R, Simons J, Van Gerven D. Skeletal maturity in Belgian youths assessed by the Tanner-Whitehouse method (TW2). Annals of Human Biology. 1990;17(5):355-76.	TW2	Belgium	21174 boys, 9698 girls	Both	boys 12-20 years, girls 6-19 years
Beunen G, Malina RM, Ostyn M, Renson R, Simons J, Van Gerven D. Fatness and skeletal maturity of Belgian boys 12 through 17 years of age. American Journal of Physical Anthropology. 1982;59(4):387-92.	TW1+2	Belgium	14259	Boys	12-17 years
Beunen G, Ostyn M, Renson R, Simons J, Swalus P, Van Gerven D. Skeletal maturation and physical fitness of 12 to 15 year old boys. Acta Paediatrica Belgica. 1974;28:221-32.	TW and Healy	Belgium	7000	Boys	12 to 15
Beunen G, Ostyn M, Simons J, Renson R, Van Gerven D. Chronological and biological age as related to physical fitness in boys 12 to 19 years. Annals of Human Biology. 1981;8(4):321-31.	TW2	Belgium	21052	Boys	12 to 19
Beunen GP, Malina RM, Lefevre JA, Claessens AL, Renson R, Vanreusel B. Adiposity and biological maturity in girls 6-16 years of age. International Journal of Obesity. 1994;18(8):542-6.	TW	Belgium	6029	Girls	6 to 16
Bhat VJ, Kamath GP. Age estimation from root development of mandibular third molars in comparison with skeletal age of wrist joint. American Journal of Forensic Medicine and Pathology. 2007;28(3):238-41.	Kangne et al criteria AND Kullmann	India	735	Both	15 to 25
Briers PJ, Hoorweg J, Stanfield JP. The long-term effects of protein energy malnutrition in early childhood on bone age, bone cortical thickness and height. Acta Paediatrica Scandinavica. 1975;64(6):853-8.	TW	Uganda	72	Both	11 to 17 years
Buken B, Buken E, Safak AA, Yazici B, Erkol Z, Mayda AS. Is the "Gok Atlas" sufficiently reliable for forensic age determination of Turkish children? Turkish Journal of Medical Sciences. 2008;38(4):319-27.	Gok atlas	Turkey	772	Both	11 to 22
Buken B, Erzengin OU, Buken E, Safak AA, Yazici B, Erkol Z. Comparison of the three age estimation methods: which is more reliable for Turkish children? Forensic Science International. 2009;183(1):103.e1-7.	Various methods	Turkey	333	Both	11 to 16
Buken B, Safak AA, Buken E, Yazici B, Erkol Z, Erzengin OU. Is the tanner-whitehouse (TW3) method sufficiently reliable for forensic age determination of Turkish children?. [Turkish]. Turkish Journal of Medical Sciences. 2010;40(5):797-805.	TW3	Turkey	324	Both	girls 11 to 16, boys 11 to 16
Caldas Mde P, Ambrosano GM, Haiter-Neto F. Use of cervical vertebral dimensions for assessment of children growth. Journal of Applied Oral Science. 2007;15(2):144-7.	TW3	Brazil	238	Both	7 to 16
Caltabiano M, Leonardi R, Zaborra G. [Evaluation of cervical vertebrae for determination of skeletal age]. Rivista Italiana di Odontoiatria Infantile. 1990;1(3):15-20.	Demirjian, unknown hand-method and cervical vertebrae	Italy	72	Both	10 to 15

Camacho-Basallo, P., et al., Five radiographic methods for assessing skeletal maturity in a Spanish population: is there a correlation? Acta Odontologica Scandinavica, 2016: p. 1-7.	Björk, Grave &Brown	Spain	200	Both	13 years
Cameriere R, De Luca S, Biagi R, Cingolani M, Farronato G, Ferrante L. Accuracy of three age estimation methods in children by measurements of developing teeth and carpals and epiphyses of the ulna and radius. Journal of Forensic Sciences. 2012;57(5):1263-70.	Cameriere Ferrante	Italy	288	Both	5 to 15
Cameriere R, Ferrante L, Ermenc B, Mirtella D, Strus K. Age estimation using carpals: study of a Slovenian sample to test Cameriere's method. Forensic Science International. 2008;174(2):178-81.	Cameriere & TW3	Slovenia	158	Both	6 to 16
Cameriere R, Ferrante L, Mirtella D, Cingolani M. Carpals and epiphyses of radius and ulna as age indicators. International Journal of Legal Medicine. 2006;120(3):143-6.	TW3	Italy	150	Both	5 to 17
Cameriere R, Ferrante L. Age estimation in children by measurement of carpals and epiphyses of radius and ulna and open apices in teeth: a pilot study. Forensic Science International. 2008;174(1):60-3.	Own method	Italy	150	Both	5 to 15
Chang HP, Liao CH, Yang YH, Chang HF, Chen KC. Correlation of cervical vertebra maturation with hand-wrist maturation in children. Kaohsiung Journal of Medical Sciences. 2001;17(1):29-35.	Fishman	Taiwan	503	Both	8 to 18
Chen LL, Xu TM, Jiang JH, Zhang XZ, Lin JX. Quantitative cervical vertebral maturation assessment in adolescents with normal occlusion: A mixed longitudinal study. American Journal of Orthodontics and Dentofacial Orthopedics. 2008;134(6):720.e1-.e7.	Fishman	USA	87	Both	8 to 18
Coelho ESMJ, Figueiredo AJ, Simoes F, Seabra A, Natal A, Vaeyens R, et al. Discrimination of u-14 soccer players by level and position. International Journal of Sports Medicine. 2010;31(11):790-6.	Fels	Portugal	128	Boys	13 to 14
Cole TJ, Rousham EK, Hawley NL, Cameron N, Norris SA, Pettifor JM. Ethnic and sex differences in skeletal maturation among the Birth to Twenty cohort in South Africa. Archives of Disease in Childhood. 2015;100(2):138-43.	TW3	South Africa	607	Both	9 to 20
Cunha P, Moura DC, Guevara Lopez MA, Guerra C, Pinto D, Ramos I. Impact of ensemble learning in the assessment of skeletal maturity. Journal of Medical Systems. 2014;38(9):87.	Own method	Portugal	887	Both	0 to 20
De Luca S, Mangiulli T, Merelli V, Conforti F, Velandia Palacio LA, Agostini S, et al. A new formula for assessing skeletal age in growing infants and children by measuring carpals and epiphyses of radio and ulna. Journal of Forensic and Legal Medicine. 2016;39:109-16.	Own system	Italy	204	Both	1 to 16
Dhar S, Dangerfield PH. Skeletal maturity in normal children from Liverpool, United Kingdom. Clinical Anatomy. 1992;5(6):458-65.	TW2	UK	273	Both	2 to 17
El-Bakary AA, Attalla SM, Hammad SM, El-Ashry RA, De Luca S, Ferrante L, et al. Age estimation in Egyptian children by measurements of carpals and epiphyses of the ulna and radius. Journal of Forensic Radiology and Imaging. 2014;2(3):121-5.	Cameriere	Egypt	257	4 to 18	2 to 18
Engstrom C, Engstrom H, Sagne S. Lower third molar development in relation to skeletal maturity and chronological age. Angle Orthodontist.	Unclear, 5 stages	Sweden	221	Both	possibly 8 to 21

1983;53(2):97-106.					
Figueiredo AJ, Goncalves CE, Coelho ESMJ, Malina RM. Youth soccer players, 11-14 years: maturity, size, function, skill and goal orientation. Annals of Human Biology. 2009;36(1):60-73.	Fels	Portugal	159	Boys	11- 14 years
Fishman LS. Maturational patterns and prediction during adolescence. Angle Orthodontist. 1987;57(3):178-93.	SMI	USA	2225 female, 1775 males	Both	9- 19 years
Fishman LS. Radiographic evaluation of skeletal maturation. A clinically oriented method based on hand-wrist films. Angle Orthodontist. 1982;52(2):88-112.	SMA method 4 stages	USA	170 female, 164 males	Both	3 months to adult
Flores-Mir C, Burgess CA, Champney M, Jensen RJ, Pitcher MR, Major PW. Correlation of skeletal maturation stages determined by cervical vertebrae and hand-wrist evaluations. Angle Orthodontist. 2006;76(1):1-5.	Demirjian & Hagg and Taranger	Peru	140	Both	9,5 to 16,5
Flores-Mir C, Mauricio FR, Orellana MF, Major PW. Association between growth stunting with dental development and skeletal maturation stage. Angle Orthodontist. 2005;75(6):935-40.	Hägg & Taranger	Peru	140	Both	10-17 years
Freitas D, Maia J, Beunen G, Lefevre J, Claessens A, Marques A, et al. Skeletal maturity and socio-economic status in Portuguese children and youths: the Madeira growth study. Annals of Human Biology. 2004;31(4):408-20.	TW2, TW3	Portugal	507	Both	8- 6 years
Freitas D, Malina RM, Maia J, Lefevre J, Stasinopoulos M, Gouveia E, et al. Short-term secular change in height, body mass and Tanner-Whitehouse 3 skeletal maturity of Madeira youth, Portugal. Annals of Human Biology. 2012;39(3):195-205.	TW3	Portugal	2856	Both	4-17 years
Freitas DL, Lausen B, Maia JA, Gouveia ER, Thomis M, Lefevre J, et al. Skeletal Maturation, Body Size, and Motor Coordination in Youth 11-14 Years. Medicine & Science in Sports & Exercise. 2016;48(6):1129-35.	TW3	Portugal	613	Both	11-14 years
Gelbrich B, Frerking C, Weiss S, Schwerdt S, Stellzig-Eisenhauer A, Tausche E, et al. Combining wrist age and third molars in forensic age estimation: how to calculate the joint age estimate and its error rate in age diagnostics. Annals of Human Biology. 2015;42(4):389-96.	Thiemann-Nietz	Germany	383	Both	8 -19 years
Guimarey L, Moreno Morcillo A, Orazi V, Lemos-Marini SHV. Validity of the use of a few hand-wrist bones for assessing bone age. Journal of Pediatric Endocrinology and Metabolism. 2003;16(4):541-4.	TW2	Brazil, Argentina	205	Both	0,9- 17,4 years
Hauspie R, Bielicki T, Koniarek J. Skeletal maturity at onset of the adolescent growth spurt and at peak velocity for growth in height: a threshold effect? Annals of Human Biology. 1991;18(1):23-9.	TW2	Poland	191	Boys	8- 19 years
Helm S. Relationship between dental and skeletal maturation in Danish schoolchildren. Scandinavian Journal of Dental Research. 1990;98(4):313-7.	TW2	Denmark	2744	Both	7- 14 years
Helm S. Skeletal maturity in Danish schoolchildren assessed by the TW2 method. American Journal of Physical Anthropology. 1979;51(3):345-52.	TW2	Denmark	3817	Both	7- 18 years
Himes JH, Huang Z, Haas JD, Rivera R, Pineda O. Serum alkaline phosphatase activity and skeletal maturation in Guatemalan adolescents. Annals of Human Biology. 1993;20(1):39-46.	TW2	Guatemala	873	Both	11- 25 years
Houston WJ. Relationships between skeletal ma-	TW2	UK	126	Both	8- 17 years

turity estimated from hand-wrist radiographs and the timing of the adolescent growth spurt. European Journal of Orthodontics. 1980;2(2):81-93.					
Huo AH, Peng Y, Zeng JJ, Yu T, Li DH, Hu D. The CHN radiographic atlas method for assessing skeletal age of hand and wrist in 1397 children and result analysis. [Chinese]. Chinese Journal of Radiology (China). 2013;47(12):1074-6.	CHN atlas	China	1397	Both	1 - 18 years
Ilich JZ, Hangartner TN, Skugor M, Roche AF, Goel PK, Matkovic V. Skeletal age as a determinant of bone mass in preadolescent females. Skeletal Radiology. 1996;25(5):431-9.	FELS	USA	456	Girls	8 -13 years
Jensen BL, Dahl E, Kreiborg S. Longitudinal study of body height, radius length and skeletal maturity in Danish boys with cleft lip and palate. Scandinavian Journal of Dental Research. 1983;91(6):473-81.	TW2	Denmark	85	Boys	6- 20 years
Johnson A, Doherty PJ, Freemont A. Investigation of growth, development, and factors associated with injury in elite schoolboy footballers: prospective study. BMJ. 2009;338:b490.	Fels	Uk	292	Boys	9- 16 years
Jones G, Ma D. Skeletal age deviation assessed by the Tanner-Whitehouse 2 method is associated with bone mass and fracture risk in children. Bone. 2005;36(2):352-7.	TW2	Australia	642	Both	9- 16 years
Joshi V, Yamaguchi T, Matsuda Y, Kaneko N, Maki K, Okano T. Skeletal maturity assessment with the use of cone-beam computerized tomography. Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology. 2012;113(6):841-9.	GARCIA's table	Japan	100	Both	3- 35 years
Katzmarzyk PT, Malina RM, Beunen GP. The contribution of biological maturation to the strength and motor fitness of children. Annals of Human Biology. 1997;24(6):493-505.	TW2	USA	740	Both	7- 12 years
Kemper HC, Post GB, Twisk JW. Rate of maturation during the teenage years: nutrient intake and physical activity between ages 12 and 22. International Journal of Sport Nutrition. 1997;7(3):229-40.	TW2	Netherland	200 longitudinal	Both	12- 22 years
Kimura K. Skeletal maturation in Japanese. A new analytical method (Japanese). Journal of the Anthropological Society of Nippon. 1972;80(4):319-36.	TW	Japan	598	Both	0 -18 years
Kimura K. Skeletal maturation of children in Okinawa. Annals of Human Biology. 1976;3(2):149-55.	TW & Kimura	Japan	264	Both	7- 15 years
Kimura K. Skeletal maturity and bone growth in twins. American Journal of Physical Anthropology. 1983;60(4):491-7.	TW2	Japan	179	Both	12- 18 years
Kimura K. Skeletal maturity of the hand and wrist in Japanese children by the TW2 method. Annals of Human Biology. 1977;4(4):353-6.	TW2	Japan	718	Both	0- 19 years
Kimura K. Skeletal maturity of the hand and wrist in Japanese children in Sapporo by the TW2 method. Annals of Human Biology. 1977;4(5):449-53.	TW2	Japan	258	Both	6- 18 years
Kumar V, Venkataraghavan K, Krishnan R, Patil K, Munoli K, Karthik S. The relationship between dental age, bone age and chronological age in underweight children. Journal of pharmacy and bioallied sciences. 2013;5:S73-9.	Demirjian, Bjork, Grave & Brown	India	100	Both	8- 14 years
Lai EH, Chang JZ, Jane Yao CC, Tsai SJ, Liu JP, Chen YJ, et al. Relationship between age at menarche and skeletal maturation stages in Taiwanese fe-	NTUH-SMI (hand) + CVMS (cer-	Taiwan	304	Girls	8- 19 years

male orthodontic patients. Journal of the Formosan Medical Association. 2008;107(7):527-32.	vical vertebra)				
Lai EH, Liu JP, Chang JZ, Tsai SJ, Yao CC, Chen MH, et al. Radiographic assessment of skeletal maturation stages for orthodontic patients: hand-wrist bones or cervical vertebrae? Journal of the Formosan Medical Association. 2008;107(4):316-25.	NTUH-SMI (hand) + CVMS (cervical vertebra)	Taiwan	709	Both	8 to 18 years
Lejarraga H, Guimarey L, Orazi V. Skeletal maturity of the hand and wrist of healthy Argentinian children aged 4-12 years, assessed by the TWII method. Annals of Human Biology. 1997;24(3):257-61.	TW2	Argentina	775	Both	4 to 12 years
Lequin MH, van Rijn RR, Robben SG, Hop WC, van Kuijk C. Normal values for tibial quantitative ultrasonometry in caucasian children and adolescents (aged 6 to 19 years). Calcified Tissue International. 2000;67(2):101-5.	Tanner,	Netherland	596	Both	6 to 20 years
Li CS, Li CY, Xi HJ, Ren F, Huang KQ, Wen YF, et al. Assessment of development of wrist skeletal age of Tibetan adolescent in Lhasa. [Chinese]. Chinese Journal of Clinical Rehabilitation. 2005;9(23):36-8.	Fels	China	1496	Both	7 to 21 years
Li CY, Ren F, Li CS, Huang KQ, Wen YF, Guo ZY, et al. Assessment of skeletal age of hand-wrist in Tibetan adoslescent of Lhasa with Fels method. [Chinese]. Chinese Journal of Clinical Rehabilitation. 2006;10(24):36-8.	Fels	China	1496	Both	7 to 21 years
Litsas G, Ari-Demirkaya A. Growth indicators in orthodontic patients. Part 1: comparison of cervical vertebral maturation and hand-wrist skeletal maturation. European Journal of Paediatric Dentistry. 2010;11(4):171-5.	Bjork ,Grave and Brown.	Turkey	393	Both	8 to 18 years
Litsas G, Ari-Demirkaya A. Growth indicators in orthodontic patients. Part 2: comparison of cervical bone age to hand-wrist skeletal age. Relationship with chronological age. European journal of paediatric dentistry : official journal of European Academy of Paediatric Dentistry. 2010;11(4):176-80.	Bjork ,Grave and Brown.	Turkey	393	Both	8 to 18 years
Little BB, Malina RM. Gene-environment interaction in skeletal maturity and body dimensions of urban Oaxaca Mestizo schoolchildren. Annals of Human Biology. 2007;34(2):216-25.	TW2	Mexico, USA	1398	Both	6 to 13 years
Liu B, Wang D, Wang Z. Comparison of skeletal development between rural and urban school-age children. [Chinese]. Zhongguo yi xue ke xue yuan xue bao. 1994;0(3):165-9.	Chinese method	China	1680	Both	7 to 18 years
Liu ZX, Cheng XG, Li XM, Yu W. Bone age of children and adolescent of X-ray film: Comparison of left- and right- hand. [Chinese]. Chinese Journal of Radiology (China). 2013;47(12):1070-3.	CHN left vs right hand	China	1380	Both	1 to 19 years
Maggio A, Flavel A, Hart R, Franklin D. Skeletal age estimation in a contemporary Western Australian population using the Tanner-Whitehouse method. Forensic Science International. 2016;263:e1-8.	TW	Australia	360	Both	0 to 25 years
Magnusson TE. Skeletal maturation of the hand in Iceland. Acta Odontologica Scandinavica. 1979;37(1):21-8.	Bjørk	Iceland	1426	Both	5 to >17 years
Mahajan S. Evaluation of skeletal maturation by comparing the hand wrist radiograph and cervical vertebrae as seen in lateral cephalogram. Indian Journal of Dental Research. 2011;22(2):309-16.	Fishman & cervical vertebrae	India	100	Both	8 to 18 years
Malina RM, Coelho ESMJ, Figueiredo AJ, Carling C, Beunen GP. Interrelationships among invasive and non-invasive indicators of biological maturation in adolescent male soccer players. Journal of Sports	Fels	Portugal	180	Boys	11 to 14 years

Sciences. 2012;30(15):1705-17.					
Malina RM, Dompier TP, Powell JW, Barron MJ, Moore MT. Validation of a noninvasive maturity estimate relative to skeletal age in youth football players. Clinical Journal of Sport Medicine. 2007;17(5):362-8.	Fels	USA	143	Boys	9 to 14 years
Malina RM, Himes JH, Stepick CD. Skeletal maturity of the hand and wrist in Oaxaca school children. Annals of Human Biology. 1976;3(3):211-9.	TW2	Mexico	394	Both	5 to 18 years
Malina RM, Little BB. Comparison of TW1 and TW2 skeletal age differences in American black and white and in Mexican children 6-13 years of age. Annals of Human Biology. 1981;8(6):543-8.	TW1 +2	USA, Mexico	2562	Both	6 to 13 years
Malina RM, Pena Reyes ME, Eisenmann JC, Horta L, Rodrigues J, Miller R. Height, mass and skeletal maturity of elite Portuguese soccer players aged 11-16 years. Journal of Sports Sciences. 2000;18(9):685-93.	Fels	Portugal	135	Boys	10 to 17 years
Malina RM, Pena Reyes ME, Figueiredo AJ, Coelho ESMJ, Horta L, Miller R, et al. Skeletal age in youth soccer players: implication for age verification. Clinical Journal of Sport Medicine. 2010;20(6):469-74.	Fels	Portugal, Spain	592	Boys	11 to 17 years
Malina RM. Skeletal maturation studied longitudinally over one year in American Whites and Negroes six though thirteen years of age. Human biology; an international record of research. 1970;42(3):377-90.	TW	USA	806	Both	4 to 14 years
Malo L, Lima S, Teixeira V, Canova F, Alves S. Skeletal maturation in a Portuguese population - comparison between the hand-wrist and cervical vertebral maturation. [Portuguese]. Revista Portuguesa de Estomatologia, Medicina Dentaria e Cirurgia Maxilofacial. 2014;55(2):102-9.	Grave & Brown	Portugal	285	Both	7 to 16 years
Mappes MS, Harris EF, Behrents RG. An example of regional variation in the tempos of tooth mineralization and hand-wrist ossification. American journal of orthodontics and dentofacial orthopedics : official publication of the American Association of Orthodontists, its constituent societies, and the American Board of Orthodontics. 1992;101(2):145-51.	Fishman & Moorrees	USA	585 tann, 295 hand	Both	12 and 13 years
Marak FK, Sangma WBC, Singh MS, Kharrubon B. A roentgenographic study for age estimation in boys and girls of North-Eastern region of India. International Journal of Medical Toxicology and Legal Medicine. 2008;10(2):34-9.	Unclear for wrist, elbow, knee, pelvis	India	200	Both	16 to 22 years
Marti Henneberg C, Vilardell Latorre E. Bone maturation in the infantile population (boys 8-17 years old and girls 6-16 years old) of Barcelona, Spain. Standard curves from a numeric method. [Spanish]. Medicina Clinica. 1975;64(2):73-8.	TW	Spain	1268	Both	6 to 17 years
Matsuoka H, Sato K, Sugihara S, Murata M. Bone maturation reflects the secular trend in growth. Hormone Research. 1999;52(3):125-30.	TW2	Japan, China	3123	Both	7 to 16 years
Mohammed RB, Kalyan VS, Tircouveluri S, Vegesna GC, Chirla A, Varma DM. The reliability of Fishman method of skeletal maturation for age estimation in children of South Indian population. Journal of Natural Science Biology & Medicine. 2014;5(2):297-302.	Fishman	India	330	Both	9 to 20 years
Mohammed RB, Reddy MA, Jain M, Singh JR, Sanghvi P, Thetay AA. Digital radiographic evalua-	Fishman	India	330	Both	8 to 18 years

tion of hand-wrist bone maturation and prediction of age in South Indian adolescents. Hand. 2014;9(3):375-83.					
Molinari L, Hermanussen M. The effect of variability in maturational tempo and midparent height on variability in linear body measurements. Annals of Human Biology. 2005;32(5):679-82.	TW3	Switzerland	232	Both	2 to 20 years
Murata M. Characteristics of pubertal growth in Japanese children from the standpoint of skeletal growth. Acta Paediatrica Japonica. 1992;34(2):236-40; discussion 40-2.	TW2	Japan	200	Both	7 to 18 years
Murata M. Population-specific reference values for bone age. Acta Paediatrica Supplement. 1997;423:113-4.	TW2	Japan	382	Both	1 to 20 years
Pasciuti E, Franchi L, Baccetti T, Milani S, Farronato G. Comparison of three methods to assess individual skeletal maturity. Journal of Orofacial Orthopedics. 2013;74(5):397-408.	Gianni's analysis	Italy	100	Both	6-18 years
Safer AN, Homel P, Chung DD. Lateral comparisons using Fishman's skeletal maturation assessment. Angle Orthodontist. 2015;85(3):408-12.	Fishman	USA	125	Both	8-20 years
Sahin Saglam AM, Gazilerli U. The relationship between dental and skeletal maturity. Journal of Orofacial Orthopedics. 2002;63(6):454-62.	Fishman	Turkey	422	Both	7-15 years
Schmeling A, Baumann U, Schmidt S, Wernecke KD, Reisinger W. Reference data for the Thiemann-Nitz method of assessing skeletal age for the purpose of forensic age estimation. International Journal of Legal Medicine. 2006;120(1):1-4.	Thiemann-Nitz	Germany	402	Both	10-18 years
Schmidt S, Nitz I, Schulz R, Schmeling A. Applicability of the skeletal age determination method of Tanner and Whitehouse for forensic age diagnostics. International Journal of Legal Medicine. 2008;122(4):309-14.	TW	Germany	92	Both	12-16 years
Schmidt S, Nitz I, Schulz R, Tsokos M, Schmeling A. The digital atlas of skeletal maturity by Gilsanz and Ratib: a suitable alternative for age estimation of living individuals in criminal proceedings? International Journal of Legal Medicine. 2009;123(6):489-94.	Gilsanz Ratib	Germany	180	Both	10-18 years
Shim J, Heo G, Lagravere MO. Correlation between three-dimensional morphological changes of the hyoid bone with other skeletal maturation methods in adolescents. Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology. 2013;116(4):511-7.	Fishman	Canada	62	Both	11-17 years
Shim JJ, Bogowicz P, Heo G, Lagravere MO. Interrelationship and limitations of conventional radiographic assessments of skeletal maturation. International orthodontics / College europeen d'orthodontie. 2012;10(2):135-47.	Fishman	Canada	62	Both	11-17 years
Singer R, Kimura K. Body height, weight, and skeletal maturation in Hottentot (Khoikhoi) children. American Journal of Physical Anthropology. 1981;54(3):401-13.	TW2	South West Africa	120	Both	3-17 years
Soegiharto BM, Cunningham SJ, Moles DR. Skeletal maturation in Indonesian and white children assessed with hand-wrist and cervical vertebrae methods. American Journal of Orthodontics and Dentofacial Orthopedics. 2008;134(2):217-26.	Fishman	Indonesia, USA	2167	Both	8-15 years
Takai S, Akiyoshi T. Skeletal maturity of Japanese children in Western Kyushu. American Journal of Physical Anthropology. 1983;62(2):199-204.	TW2	Japan	985	Both	4 -15 years

Takai S. [Smoothed skeletal maturity curve of Japanese children by Tanner-Whitehouse 2 (TW2) method and its application]. Kaibogaku Zasshi - Journal of Anatomy. 1990;65(6):436-47.	TW2	Japan	6351	Both	6-18 years
Tanner J, Oshman D, Bahhage F, Healy M. Tanner-Whitehouse bone age reference values for North American children.[Erratum appears in J Pediatr. 2012 Dec;161(6):1180]. Journal of Pediatrics. 1997;131(1):34-40.	TW2	USA	450	Both	8-16 Years
Uysal T, Ramoglu SI, Basciftci FA, Sari Z. Chronologic age and skeletal maturation of the cervical vertebrae and hand-wrist: Is there a relationship? American Journal of Orthodontics and Dentofacial Orthopedics. 2006;130(5):622-8.	Björk and Grave and Brown	Turkey	2003	Both	5-24 years
Uysal T, Sari Z, Ramoglu SI, Basciftci FA. Relationships between dental and skeletal maturity in Turkish subjects. Angle Orthodontist. 2004;74(5):657-64.	Björk and Grave and Brown	Turkey	500	Both	7-20 years
Valente-dos-Santos J, Coelho-e-Silva MJ, Duarte J, Pereira J, Rebelo-Goncalves R, Figueiredo A, et al. Allometric multilevel modelling of agility and dribbling speed by skeletal age and playing position in youth soccer players. International Journal of Sports Medicine. 2014;35(9):762-71.	Fels	Portugal	83	Bøys	11-15 years
van Lenthe FJ, Kemper HC, van Mechelen W. Skeletal maturation in adolescence: a comparison between the Tanner-Whitehouse II and the Fels method. European Journal of Pediatrics. 1998;157(10):798-801.	Fels, TW2	Netherland	60	Both	12-16 years
Vignolo M, Naselli A, Magliano P, Di Battista E, Aicardi M, Aicardi G. Use of the new US90 standards for TW-RUS skeletal maturity scores in youths from the Italian population. Hormone Research. 1999;51(4):168-72.	TW-RUS	Italy	1831	Both	8-17 years
Xi HJ, Roche AF. Differences between the hand-wrist and the knee in assigned skeletal ages. American Journal of Physical Anthropology. 1990;83(1):95-102.	Fels	China	4902	Both	2-17 years
Xu YC, Ye LY, Li K, Wang ZY, Ke Y, Zhang QC. Accuracy of age estimation in 14-year-old females by two skeletal age standards. [Chinese]. Fa yi xue za zhi. 2006;22(5):328-9, 32.	CHN	China	51	Girls	14 years
Yang YM, Lee J, Kim YI, Cho BH, Park SB. Axial cervical vertebrae-based multivariate regression model for the estimation of skeletal-maturation status. Orthodontics & Craniofacial Research. 2014;17(3):187-96.	SMI, FMI	Finland	121	Both	6-18 years
Zhang S, Liu L, Hua J, Liu G. The observation of difference between skeletal age and chronological age with hand and wrist in Chinese Han adolescent. [Chinese]. Chinese Journal of Forensic Medicine. 2009;24(1):18-20.	RUS-CHN	China	12414	Both	3-18 years
Zhang S, Liu L, Zhang J, Liu G. The RUS-CHN radiographic atlas method of assessing skeletal age for adolescent. [Chinese]. Chinese Journal of Forensic Medicine. 2009;24(4):249-53.	RUS-CHN	China	5472	Both	13-18 years
Zhang S, Ma Z, Han Y, Shen X, Liu G, Xu R. The effects of the differences of skeletal development on age estimation in children and adolescent between large and middling cities in China. [Chinese]. Chinese Journal of Forensic Medicine. 2009;24(2):99-102+3.	RUS-CHN	China	11635	Both	3-18 years
Zhang SY, Liu LJ, Han YS, Liu G, Ma ZG, Shen XZ, et al. [Reference values of differences between TW3-	TW3	China	9408	Both	1-14 years

C RUS and TW3-C Carpal bone ages of children from five cities of China]. Zhonghua Erke Zazhi. 2008;46(11):851-5.					
Zhang SY, Liu LJ, Wu ZL, Liu G, Ma ZG, Shen XZ, et al. Standards of TW3 skeletal maturity for Chinese children. Annals of Human Biology. 2008;35(3):349-54.	TW3	China	17 401	Both	2-20 years
Zhao XD, Hu Y, Pan SN, Li XF, Li XM, Cheng XG, et al. Evaluation of bone age of wrist-hand in adolescent of Shenyang and Beijing. [Chinese]. Chinese Journal of Radiology (China). 2013;47(12):1066-9.	CHN	China	1333	Both	4-18 years

Appendix 5: Studies excluded after full text assessment

Reference	Reason for exclusion
Avenarius DMF, Ording Muller LS, Eldevik P, Owens CM, Rosendahl K. The paediatric wrist revisited-findings of bony depressions in healthy children on radiographs compared to MRI. Pediatric Radiology. 2012;42(7):791-8.	Less than 50 subjects in relevant age range.
A. Erratum: Tanner-whitehouse bone age reference values for North American children (Journal of Pediatrics (1997) 131 (34-40)). Journal of Pediatrics. 2012;161(6):1180.	Not an empirical study published in full text format (abstracts, reviews, other)
A. EVALUATION of skeletal age in roentgenograms. Nutrition Reviews. 1958;16(4):101-2.	Not an empirical study published in full text format (abstracts, reviews, other)
Abdel-Kader HM. The potential of digital dental radiography in recording the adductor sesamoid and the MP3 stages. British Journal of Orthodontics. 1999;26(4):291-4.	Another objective than to compare age estimation using x-ray of the hand with known chronological age.
Acheson RM, Fowler G, Fry EI, Janes M, Koski K, Urbano P, et al. Studies in the Reliability of Assessing Skeletal Maturity from X-Rays. I. Greulich-Pyle Atlas. Human biology; an international record of research. 1963;35:317-49.	Less than 50 subjects in relevant age range.
Acheson RM, Vicinus JH, Fowler GB. Studies in the reliability of assessing skeletal maturity from x-rays. 3. Greulich-Pyle Atlas and Tanner-Whitehouse method contrasted. Human Biology. 1966;38(3):204-18.	Less than 50 subjects in relevant age range.
Acheson RM, Vicinus JH, Fowler GB. Studies in the Reliability of Assessing Skeletal Maturity from X-Rays. Ii. The Bone-Specific Approach. Human Biology. 1964;36:211-28.	Less than 50 subjects in relevant age range.
Aggarwal ML, Pathak IC. Roentgenologic study of epiphyseal union in Punjabi girls for determination of age. Indian Journal of Medical Research. 1957;45(2):283-9.	Another objective than to compare age estimation using x-ray of the hand with known chronological age.
Al Khal HA, Wong RW, Rabie AB. Elimination of hand-wrist radiographs for maturity assessment in children needing orthodontic therapy. Skeletal Radiology. 2008;37(3):195-200.	Another objective than to compare age estimation using x-ray of the hand with known chronological age.
Andersen E. Skeletal development as a measure of biological development. Acta Paediatrica Scandinavica. 1967;0:Suppl 177:73-4.	Not an empirical study published in full text format (abstracts, reviews, other).
Anderson M. Use of the Greulich-Pyle "Atlas of Skeletal Development of the Hand and Wrist" in a clinical context. American Journal of Physical Anthropology. 1971;35(3):347-52.	Not an empirical study published in full text format (abstracts, reviews, other).
Armengaud G. Radiological examination of the ossification of the hand in Spanish children. Electromedica. 1973;41(4):188-91.	Another objective than to compare age estimation using x-ray of the hand with known chronological age.
Ashizawa K. Interpretation errors in the estimation of bone maturation stages by an observer using the Tanner Whitehouse method. [French]. Bulletins et Memoires de la Societe d'Anthropologie de Paris. 1974;13(3):335-50.	Another objective than to compare age estimation using x-ray of the hand with known chronological age.
Bagherpour A, Pousti M, Adelianfar E. Hand skeletal maturity and its correlation with mandibular dental development. Journal of Clinical & Experimental Dentistry. 2014;6(3):e275-9.	Less than 50 subjects in relevant age range.
Bai WJ, Ning G, Qu HB, Sun XM, Xiang CF, Wu KM, et al. Comparison among three standards of TW2 to skeletal age determination in children with central precocious puberty. [Chinese]. Journal of Forensic Medicine. 2010;26(3):181-4.	A study population with chronic disease or developmental disorders.
Banik ND, Nayar S, Krishna R, Raj L, Gadekar NG. Skeletal maturation of Indian children. Indian Journal of Pediatrics. 1970;37(269):249-54.	The study population is not living persons between the ages 10-25 years
Bassed RB, Briggs C, Drummer OH. Age estimation using CT imaging of the third molar tooth, the medial clavicular epiphysis, and the spheno-occipital synchondrosis: a multifactorial approach. Forensic Science International. 2011;212(1):273.e1-5.	Another objective than to compare age estimation using x-ray of the hand with known chronological age.
Bassed RB, Briggs C, Drummer OH. The incidence of asymmetrical left/right skeletal and dental development in an Australian popula-	Another objective than to compare age estimation using x-ray of the hand with

tion and the effect of this on forensic age estimations. International Journal of Legal Medicine. 2012;126(2):251-7.	known chronological age.
Baumann U, Schulz R, Reisinger W, Heinecke A, Schmeling A, Schmidt S. Reference study on the time frame for ossification of the distal radius and ulnar epiphyses on the hand radiograph. Forensic Science International. 2009;191(1):15-8.	Another objective than to compare age estimation using x-ray of the hand with known chronological age.
Beek FJA. Current validation of the Greulich and Pyle atlas for the determination of skeletal age. [Dutch]. Nederlands Tijdschrift voor Geneeskunde. 2003;147(15):689-90.	Not an empirical study published in full text format (abstracts, reviews, other).
Belkin V, Livshits G, Otremski I, Kobyliansky E. Aging bone score and climatic factors. American Journal of Physical Anthropology. 1998;106(3):349-59.	Another objective than to compare age estimation using x-ray of the hand with known chronological age.
Benson J, Williams J. Age determination in refugee children. Australian Family Physician. 2008;37(10):821-5.	Not an empirical study published in full text format (abstracts, reviews, other).
Berdikulov GB. [X-ray data on the times of synostosis of the bones in the hand and distal portion of the forearm in girls and young women of Uzbek nationality from 11 to 19 years of age]. Sudebno-Meditsinskaia Ekspertiza. 1980;23(2):23-5.	Another objective than to compare age estimation using x-ray of the hand with known chronological age.
Beunen G, Cameron N. The reproducibility of TW2 skeletal age assessments by a self-taught assessor. Annals of Human Biology. 1980;7(2):155-62.	Another objective than to compare age estimation using x-ray of the hand with known chronological age.
Beunen G, Malina RM, Claessens AL, Lefevre J, Thomis M. Ulnar variance and skeletal maturity of radius and ulna in female gymnasts. Medicine & Science in Sports & Exercise. 1999;31(5):653-7.	Another objective than to compare age estimation using x-ray of the hand with known chronological age.
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Zhang GD. A study of skeletal age in 250 pairs of twins. [Chinese]. Zhonghua yu fang yi xue za zhi [Chinese journal of preventive medicine]. 1985;19(6):321-3.	Another objective than to compare age estimation using x-ray of the hand with known chronological age.
Zhang S, Zhang J, Liu L, Liu G. Nondiscernable epiphyseal line of radius and ulna as the indicator to estimate adolescent age of 18 years old. [Chinese]. Chinese Journal of Forensic Medicine. 2010;25(2):100-1.	Another objective than to compare age estimation using x-ray of the hand with known chronological age.
Zhang S, Zhang J. The age estimation for overweight, obesity and thinness in 7146 urban adolescents. [Chinese]. Chinese Journal of Forensic Medicine. 2010;25(4):228-31.	Another objective than to compare age estimation using x-ray of the hand with known chronological age.
Zhang SC. [A longitudinal study of bone age]. Chung-Hua Kou Chiang i Hsueh Tsa Chih Chinese Journal of Stomatology. 1991;26(2):99-102.	Less than 50 subjects in relevant age range.
Zhang SY, Liu G, Ma CG, Han YS, Shen XZ, Xu RL, et al. Automated determination of bone age in a modern chinese population. ISRN Radiology. 2013;2013:874570.	Another objective than to compare age estimation using x-ray of the hand with known chronological age.
Zhang SY, Tanaka T, Martin D, Liu G, Ma CG, Han YS, et al. Adult height prediction for Han children based on automated bone age determination. Hormone Research in Paediatrics. 2012;78:144.	Another objective than to compare age estimation using x-ray of the hand with known chronological age.
Zhang Y, Wang B. Observation of cervical vertebrae and estimation of their bone age. [Chinese]. Zhonghua kou qiang yi xue za zhi = Zhonghua kouqiang yixue zazhi = Chinese journal of stomatology. 1997;32(3):152-4.	Another objective than to compare age estimation using x-ray of the hand with known chronological age.
Zhang Z, Li K, Yu RJ, Zhang Q. Preliminary study on the applying value of two measurements for bone age in the cases of minors. [Chinese]. Fa yi xue za zhi. 2004;20(4):212-4.	Less than 50 subjects in relevant age range.
Zhao H, Dong XA, Zheng T, Qing SH, Deng ZH, Zhu GY. Skeletal age estimation of sternal end of clavicle in Sichuan Han nationality youth using thin-section computed tomography. [Chinese]. Journal of Forensic Medicine. 2011;27(6):417-20.	Another objective than to compare age estimation using x-ray of the hand with known chronological age.
Zhu GY, Fan LH, Zhang GZ, Ying CL, Lu X, Xia WT, et al. [Staging methods of skeletal growth by X-ray in teenagers]. Fa i Hsueh Tsa Chih Journal of Forensic Medicine. 2008;24(1):18-24.	Another objective than to compare age estimation using x-ray of the hand with known chronological age.
Zink P, Zink I, Reinhardt G. [Roentgen image of the hand as a principle for age determination in adolescents]. Archiv fur Kriminologie. 1986;178(1):15-24.	Another objective than to compare age estimation using x-ray of the hand with known chronological age.
Aicardi, G., et al., Assessment of skeletal maturity of the hand-wrist and knee: A comparison among methods. American Journal of Human Biology, 2000. 12(5): p. 610-615.	Another objective than to compare age estimation using x-ray of the hand with known chronological age.
Galescu, O.A., et al., Obesity and predicted height in children: A longitudinal analysis. Endocrine Reviews. Conference: 97th Annual Meeting and Expo of the Endocrine Society, ENDO, 2015. 36(no pagination).	Not an empirical study published in full text format (abstracts, reviews, other).
Hassan, N., et al., Age of fusion of the distal radial and ulnar epiphyses from hand radiographs-A study in Kashmiri population. Science & Justice, 2016. 56(6): p. 431-436.	Not relevant methods.
Sypek, S.A., et al., A holistic approach to age estimation in refugee children. Journal of Paediatrics & Child Health, 2016. 52(6): p. 614-20.	Another objective than to compare age estimation using x-ray of the hand with known chronological age.
Thodberg, H.H., et al., Automated determination of bone age from hand X-rays at the end of puberty and its applicability for age estimation. International Journal of Legal Medicine, 2016. 18: p. 18.	Another objective than to compare age estimation using x-ray of the hand with known chronological age.
Hsieh CW, Liu TC, Wang JK, Jong TL, Tiu CM. Simplified radius, ulna, and short bone-age assessment procedure using grouped-Tanner-Whitehouse method. Pediatrics International. 2011;53(4):567-75.	Another objective than to compare age estimation using x-ray of the hand with known chronological age.
Johnston FE. The use of the Greulich-Pyle method in a longitudinal growth study. American Journal of Physical Anthropology. 1971;35(3):353-7.	Another objective than to compare age estimation using x-ray of the hand with known chronological age.
Kadam SS, Viswanathan KG. Age estimation radiologically from epiphyseal union at wrist joint among subjects in Davanagere district. Indian Journal of Forensic Medicine and Toxicology. 2012;6(2):195-8.	Another objective than to compare age estimation using x-ray of the hand with known chronological age.

Sahni D, Jit I. Time of fusion of epiphyses at the elbow and wrist joints in girls of northwest India. Forensic Science International. 1995;74(1):47-55.	Another objective than to compare age estimation using x-ray of the hand with known chronological age.
Theintz GE, Howald H, Allemann Y, Sizonenko PC. Growth and pubertal development of young female gymnasts and swimmers: a correlation with parental data. International Journal of Sports Medicine. 1989;10(2):87-91.	Another objective than to compare age estimation using x-ray of the hand with known chronological age.
Napoli MM, Saraiva PA. [Bone age]. Revista do Hospital das Clinicas; Faculdade de Medicina Da Universidade de Sao Paulo. 1985;40(5):210-5.	Another objective than to compare age estimation using x-ray of the hand with known chronological age.
Geier M, Dahlmann H. [Differences in growth and development of patients with cleft lip and palate and normal subjects]. Fortschritte der Kieferorthopadie. 1988;49(5):444-53.	Another objective than to compare age estimation using x-ray of the hand with known chronological age.
Fu CA, Henson T, Bethard JD. Validation study of the Ubelaker and London atlases. American Journal of Physical Anthropology. 2014;153:122.	Not an empirical study published in full text format (abstracts, reviews, other).
Pechnikova M, Gibelli D, De Angelis D, de Santis F, Cattaneo C. The "blind age assessment": applicability of Greulich and Pyle, Demirjian and Mincer aging methods to a population of unknown ethnic origin. La Radiologia medica. 2011;116(7):1105-14.	Less than 50 subjects in relevant age range.
Gindhart PS. Growth standards for the tibia and radius in children aged one month through eighteen years. American Journal of Physical Anthropology. 1973;39(1):41-8.	Another objective than to compare age estimation using x-ray of the hand with known chronological age.
Giordano D, Leonardi R, Maiorana F, Scarciofalo G, Spampinato C. Epiphysis and metaphysis extraction and classification by adaptive thresholding and DoG filtering for automated skeletal bone age analysis. Conference proceedings : . 2007;0:6552-7.	Another objective than to compare age estimation using x-ray of the hand with known chronological age.

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Baransel Isir A, Buken B, Tokdemir M, Dulger HE, Erel O, Fedakar R. Assessing the age determination cases which have been analyzed at forensic medicine departments of 5 different region's universities in Turkey between years 1998-2005. [Turkish]. Turkiye Klinikleri Journal of Medical Sciences. 2009;29(2):304-13.
Berchel C. [Bone growth and skeletal maturation in children]. Soins; La Revue de Reference Infirmiere. 1977;22(9):3-6.
Bleha P, Havlik J, Borsky M, Pelech L. [Relationship between dental and bone maturation]. Ceskoslovenska Stomatologie. 1976;76(1):15-24.
Fragoso I, Massuca LM, Ferreira J. Effect of birth month on physical fitness of soccer players (Under-15) according to biological maturity. International Journal of Sports Medicine. 2015;36(1):16-21.
Groell R, Lindbichler F, Riepl T, Gherra L, Roposch A, Fotter R. The reliability of bone age determination in central European children using the Greulich and Pyle method. British Journal of Radiology. 1999;72(857):461-4.
Jain S. Estimation of age from 13 to 21 years. Journal of Forensic Medicine and Toxicology. 1999;16(1):27-30.
Jungmann A. [the Estimation of Age]. Harefuah. 1964;67:178-81.
Kangne RN, Sami SA, Deshpande VL. Age estimation of adolescent girls by radiography. Journal of Forensic Medicine and Toxicology. 1999;16(1):20-6.
Labrune M. [Bone age determination in children]. Soins - Gynecologie, Obstetrique, Puericulture, Pediatrie. 1984;0(36):9-12.
Sabino Prates N, Peters CF, Lopes E. Bone maturity of the hand and wrist and mandibular growth. [Portuguese]. Rgo. 1988;36(5):318-24.
Senguttuvan R, Dahdal DG, Chin C, Desoky S, Wheeler M. Study of concordance in bone age estimation between pediatric endocrinologists vs. Pediatric radiologists. Pediatric Radiology. 2015;45:S227-S8.
Taranger J, Karlberg J, Bruning B, Engstrom I. Standard deviation score charts of skeletal maturity and its velocity in Swedish children assessed by the Tanner-Whitehouse method (TW2-20). Annals of Human Biology. 1987;14(4):357-65.
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Urumqi. [Chinese]. Chinese Journal of Tissue Engineering Research. 2015;19(15):2341-5.

Ye YY, Wang CX, Cao LZ. Skeletal maturity of the hand and wrist in Chinese children in Changsha assessed by TW2 method. Annals of Human Biology. 1992;19(4):427-30.

Yogesh S, Bhavesh B, Sanjeev B. A prospective roentogenological study in Mewar region of Rajasthan to establish age group 16 to 18 years. Medico-Legal Update. 2013;13(2):17-20.

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Appendix 6: All analysed results

Difference in chronological age and skeletal age (Greulich & Pyle development stages) by chronological age intervals in boys

Figures A1-A6: The difference in chronological age (CA) and skeletal age (SA) (development stages from the Greulich & Pyle atlas) in the included studies for boys 14 to 19 years respectively, grouped according to year of chronological age.

CI: Confidence interval of the mean difference

Figure A1
Boys,
14 år

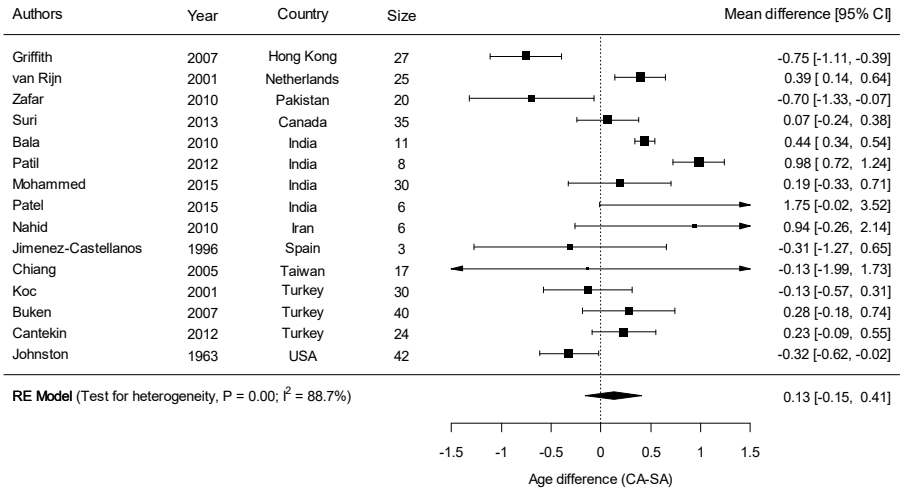


Figure A2
Boys,
15 years

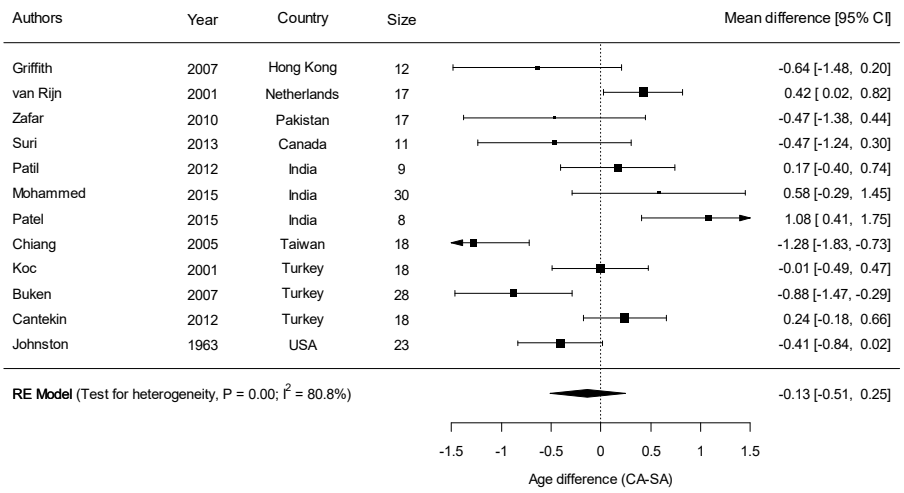


Figure A3
Boys,
16 years

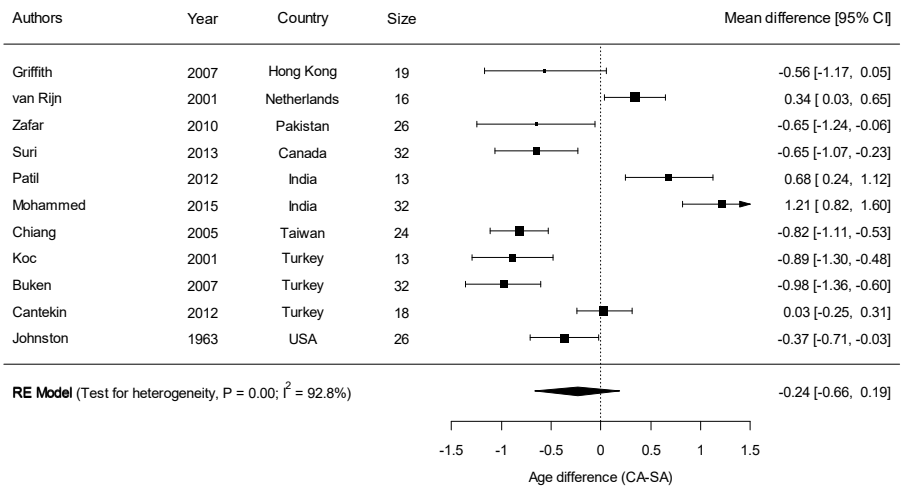


Figure A4
Boys,
17 years

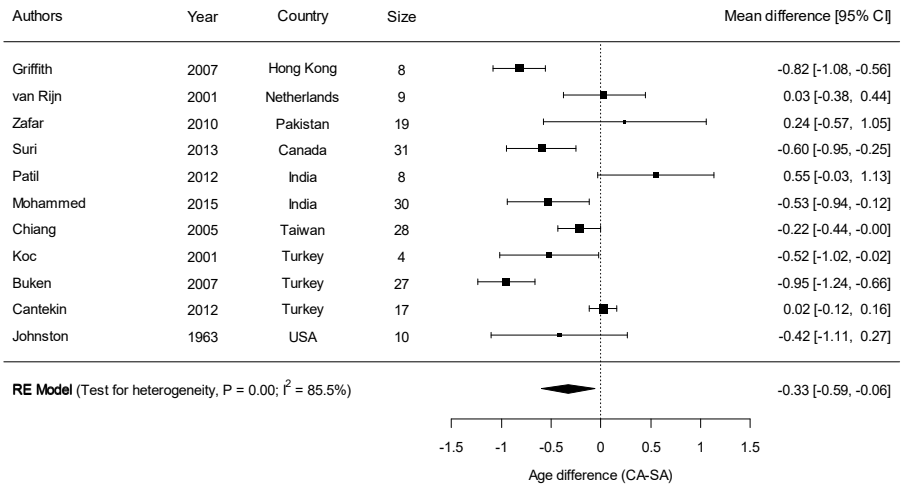


Figure A5
Boys,
18 years

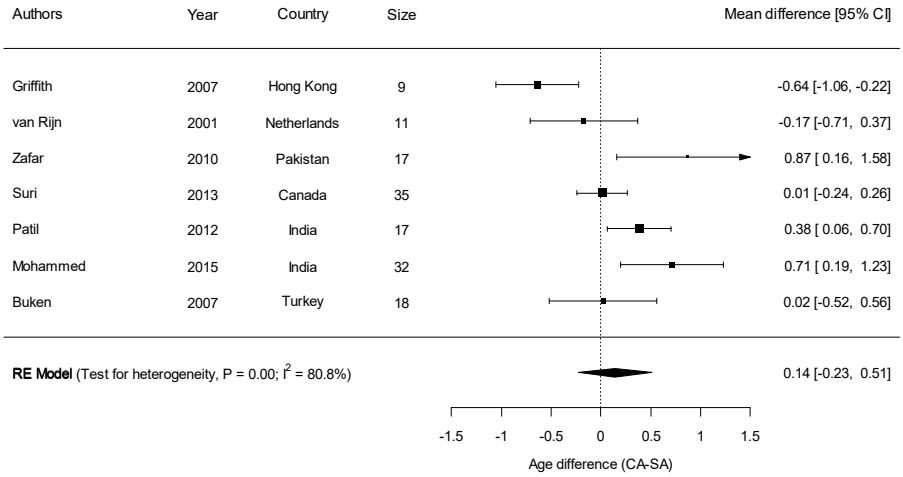
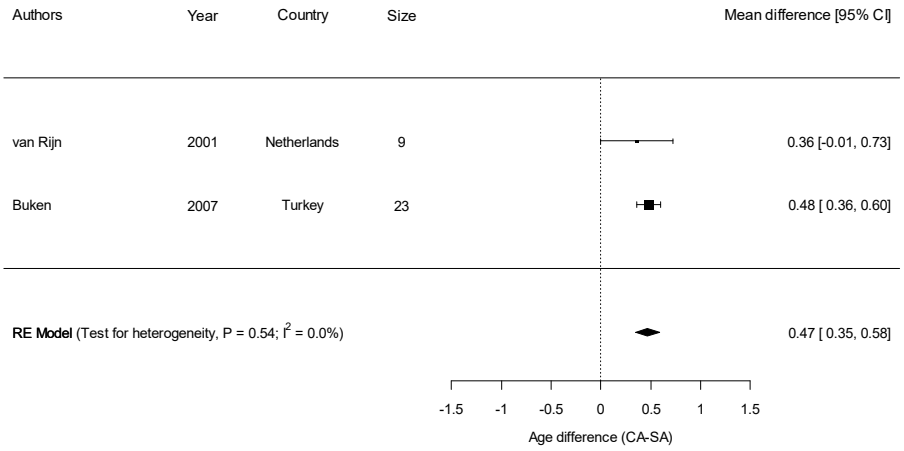


Figure A6
Boys,
19 years



Difference in chronological age and skeletal age (Greulich & Pyle development stages) by chronological age intervals in girls

Figures A7-A11: The difference in chronological age (CA) and skeletal age (SA) (development stages from the Greulich & Pyle atlas) in the included studies for girls 14 to 18 years respectively, grouped according to year of chronological age.

CI: Confidence interval of the mean difference

Figure A7
Girls,
14 years

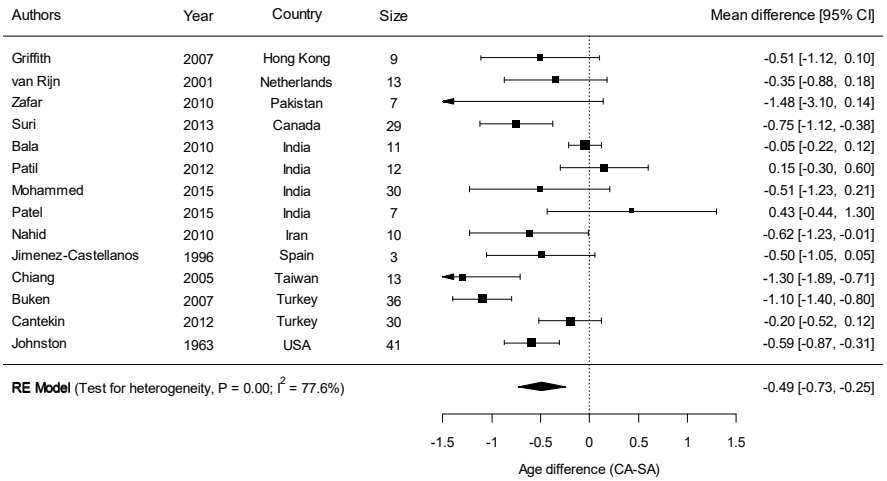


Figure A8
Girls,
15 years

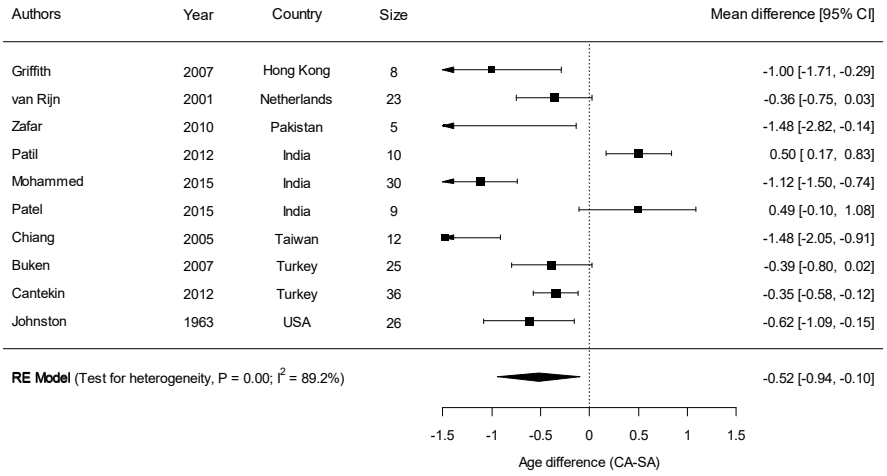


Figure A9
Girls,
16 years

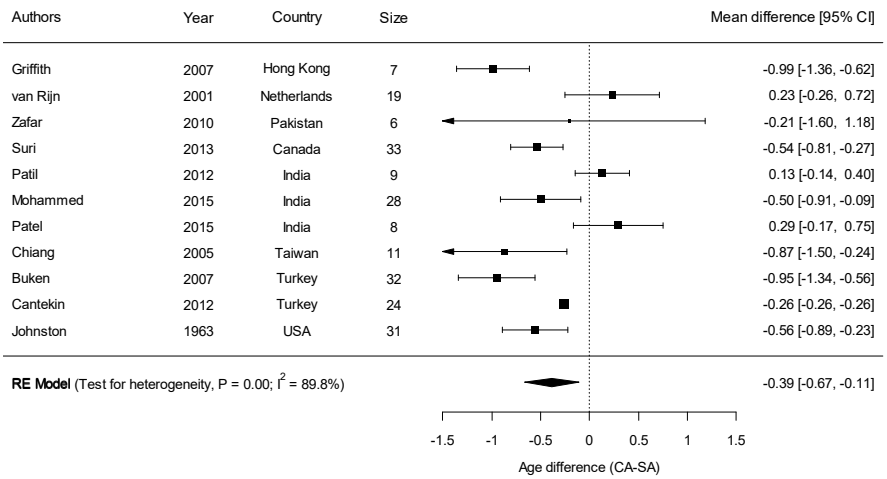


Figure A10
Girls,
17 years

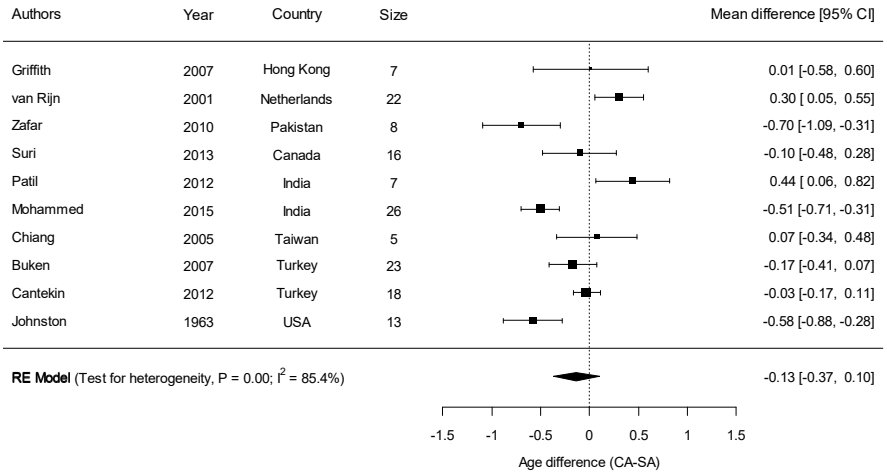
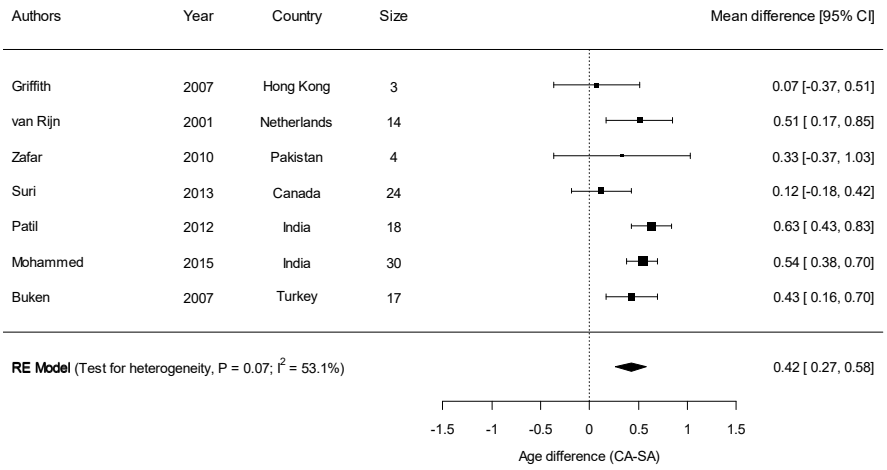


Figure A11
Girls,
18 years



Chronological age for boys in the development stages 10 years to 19 years from the Greulich & Pyle atlas

Figures A12-A23: Mean chronological age (CA) in the included studies for boys in development stages from 10 years to 19 years from the Greulich & Pyle atlas.

CI: Confidence interval of the mean difference

Figure A12

Boys, GP-stage 10 years

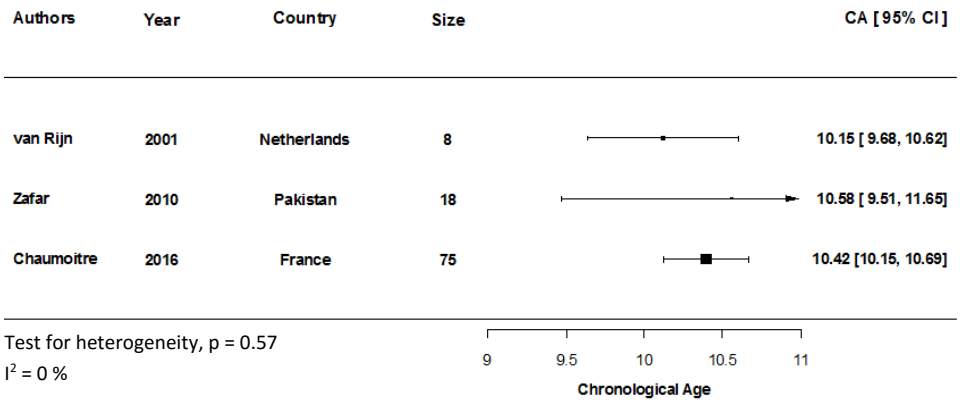


Figure A13

Boys, GP-stage 11 years

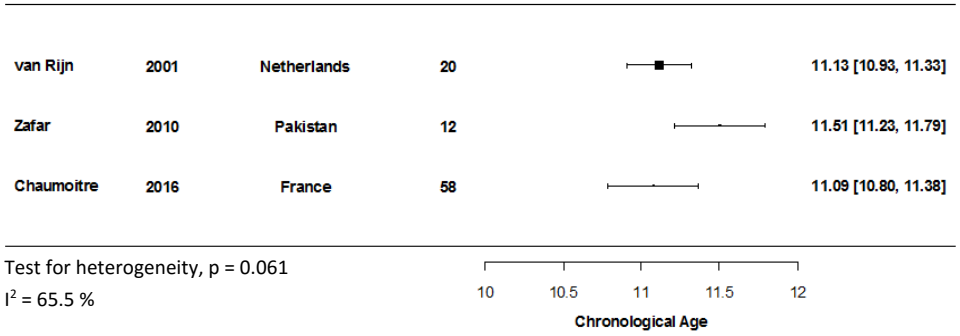


Figure A14

Boys, GP-stage 11.5 years

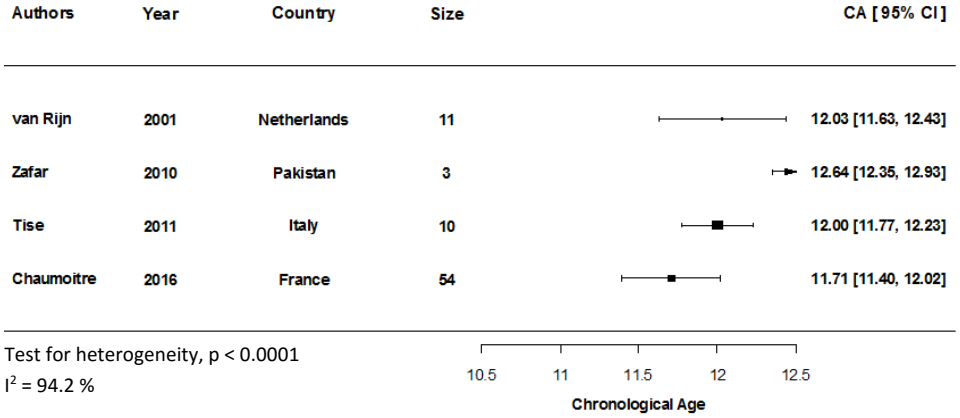


Figure A15

Boys, GP-stage 12.5 years

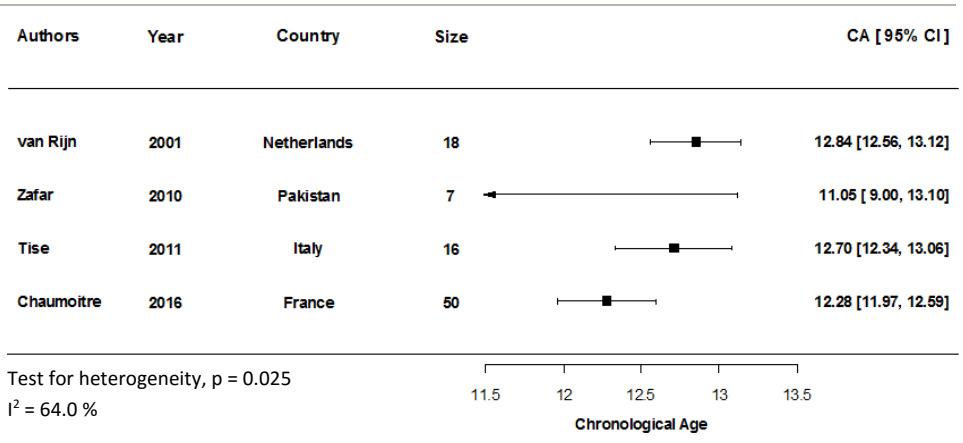


Figure A16

Boys, GP-stage 13 years

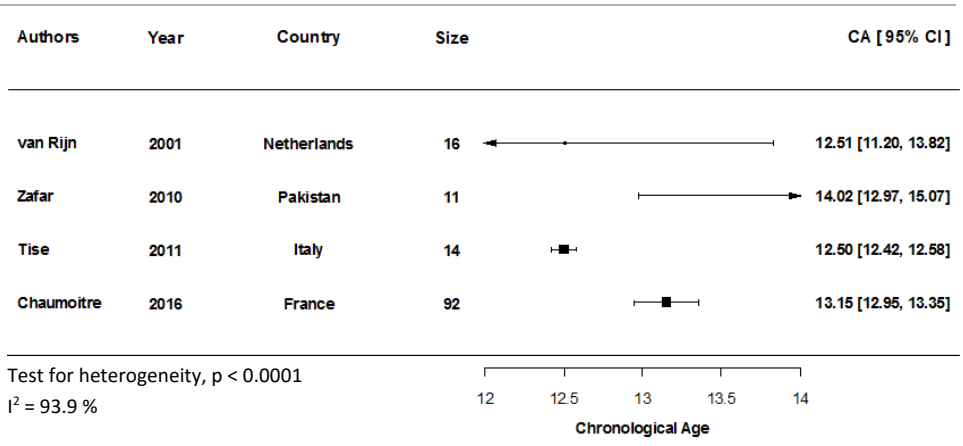


Figure A17

Boys, GP-stage 13.5 years

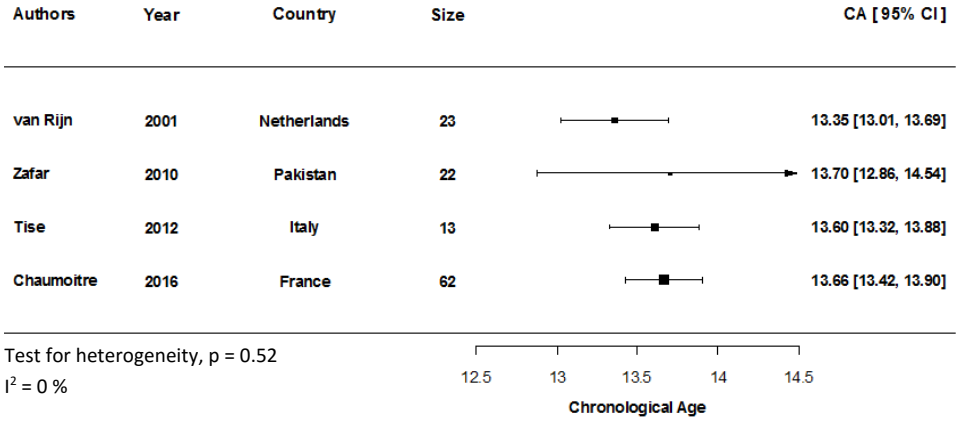


Figure A18

Boys, GP-stage 14 years

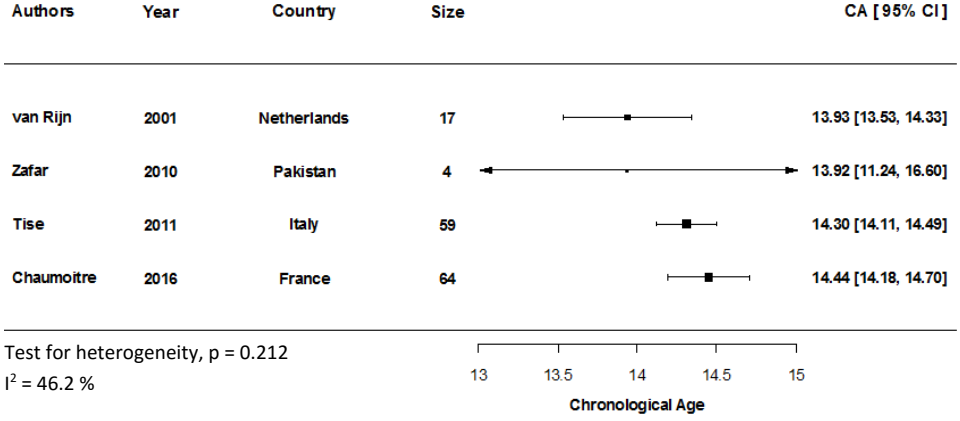


Figure A19

Boys, GP-stage 15 years

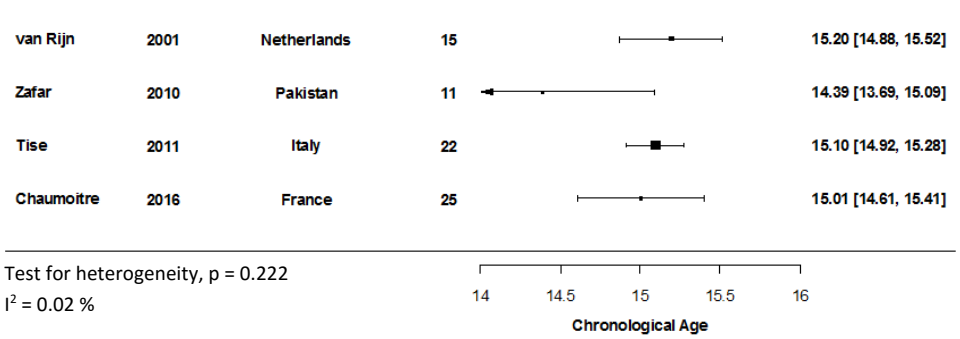


Figure A20

Boys, GP-stage 15.5 years

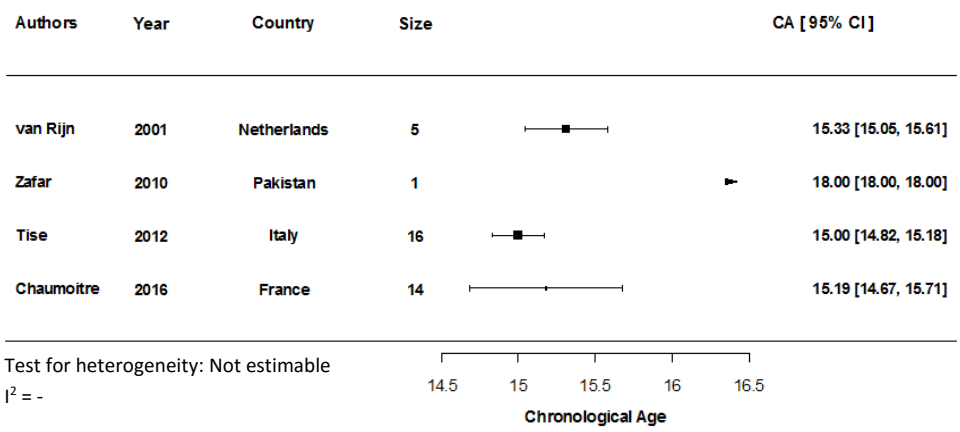


Figure A21

Boys, GP-stage 16 years

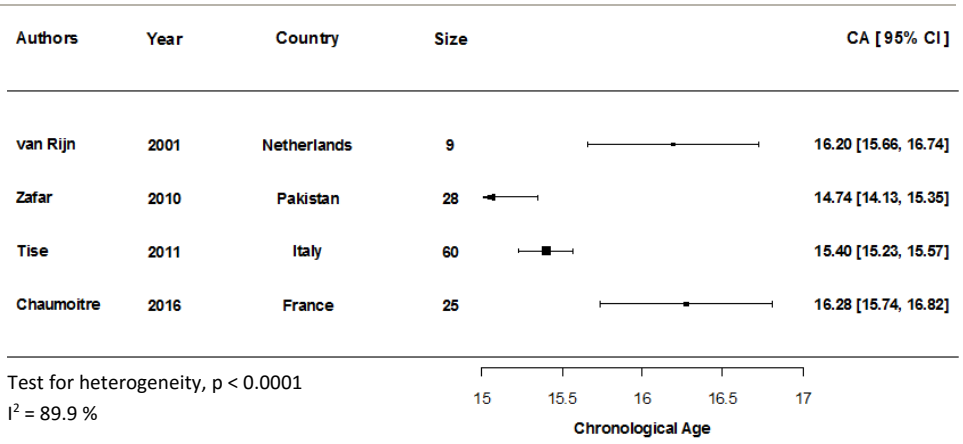


Figure A22

Boys GP-stage 17 years

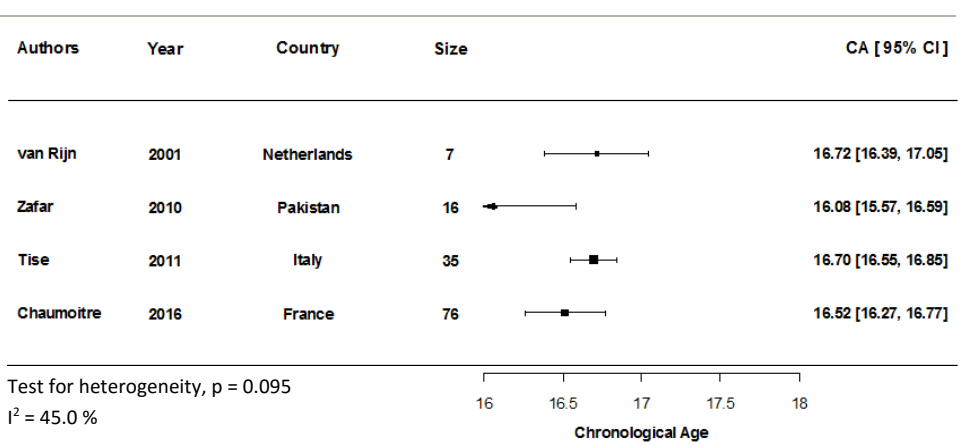


Figure A22

Boys GP-stage 18 years

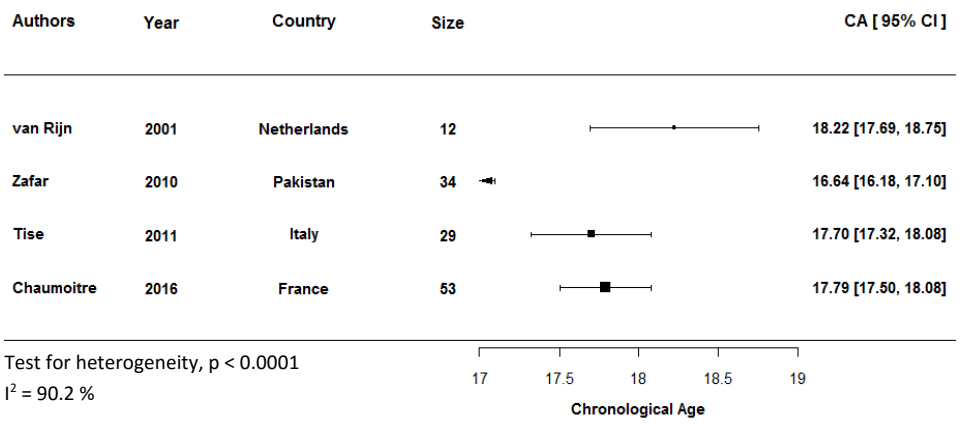
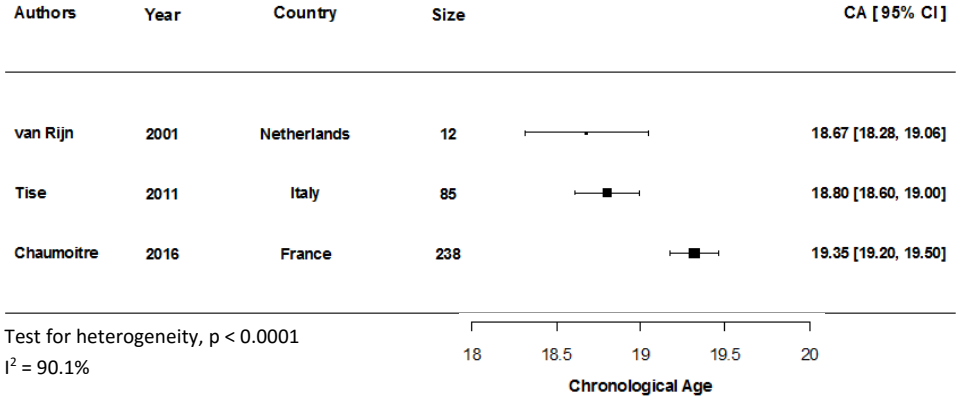


Figure A23

Boys, GP-stage 19 years



Chronological age for girls in the development stages 10 years to 18 years from the Greulich & Pyle atlas

Figures A24-A33: Mean chronological age (CA) in the included studies for girls in development stages from 10 years to 18 years from the Greulich & Pyle atlas.

CI: Confidence interval of the mean difference

Figure A24

Girls, GP-stage 10 years

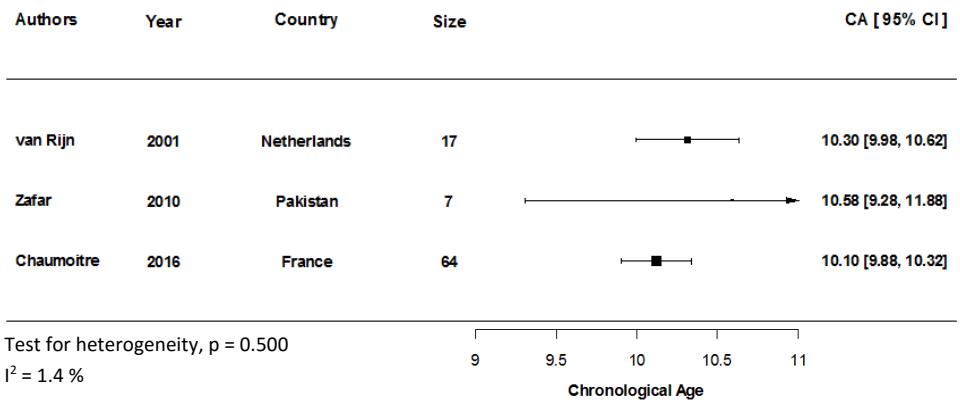


Figure A25

Girls, GP-stage 11 years

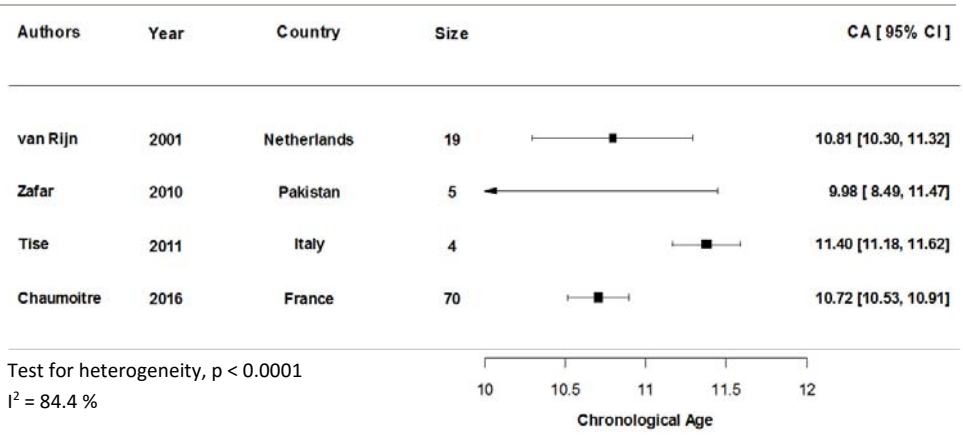


Figure A26

Girls, GP-stage 12 years

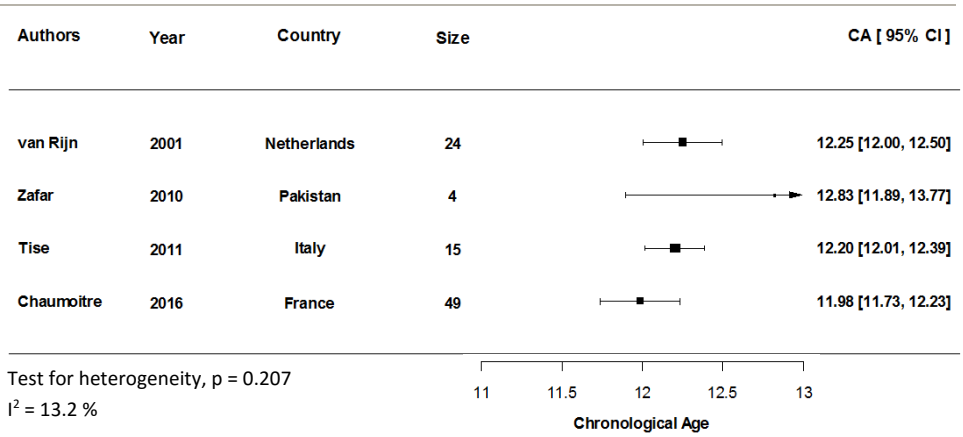


Figure A27

Girls, GP-stage 13 years

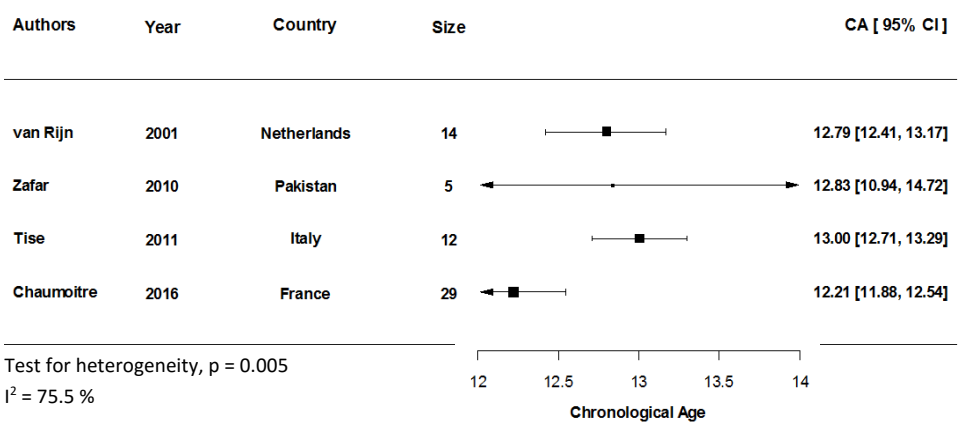


Figure A28

Girls, GP-stage 13.5 years

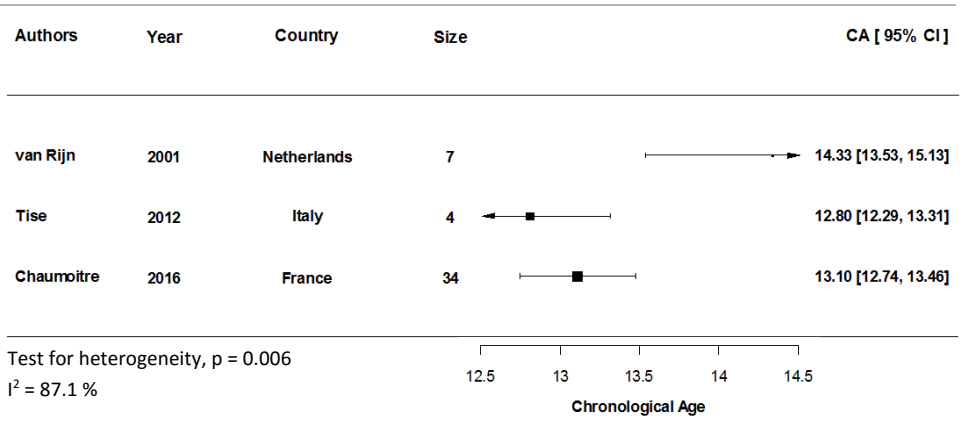


Figure A29

Girls, GP-stage 14 years

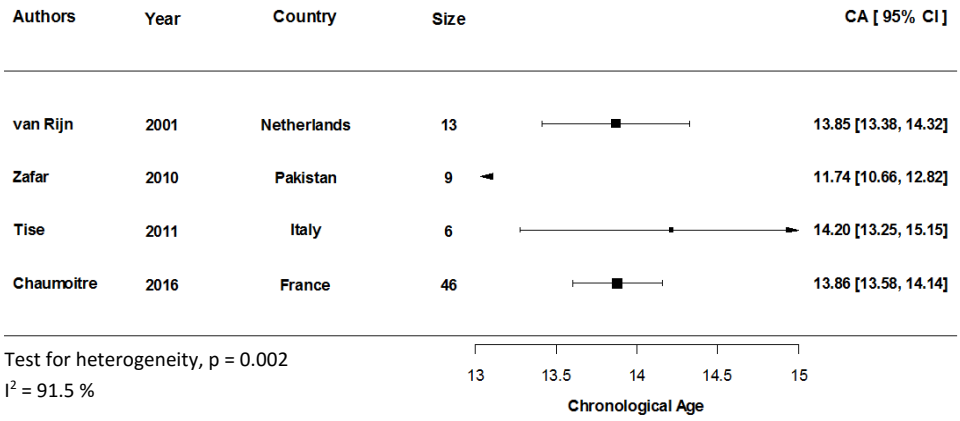


Figure A30

Girls, GP-stage 15 years

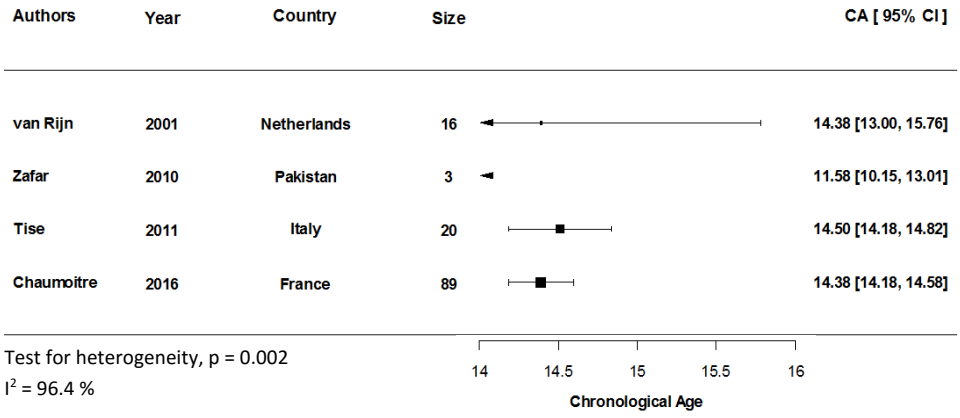


Figure A31

Girls, GP-stage 16 years

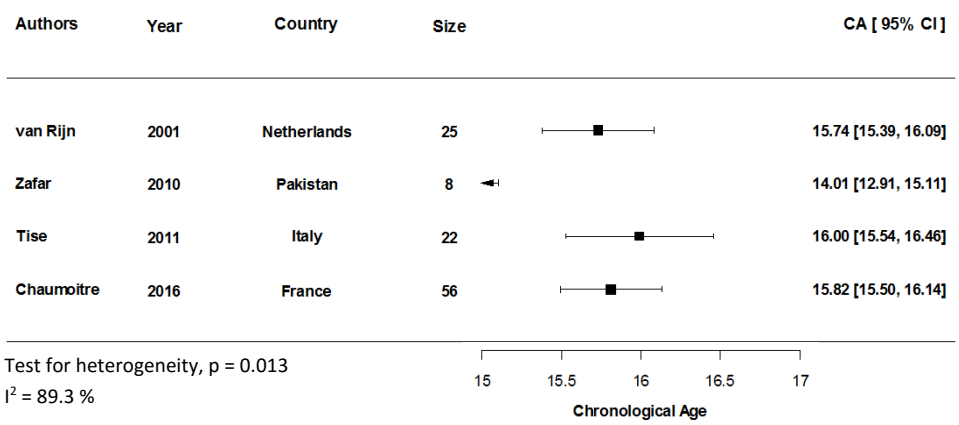


Figure A32

Girls, GP-stage 17 years

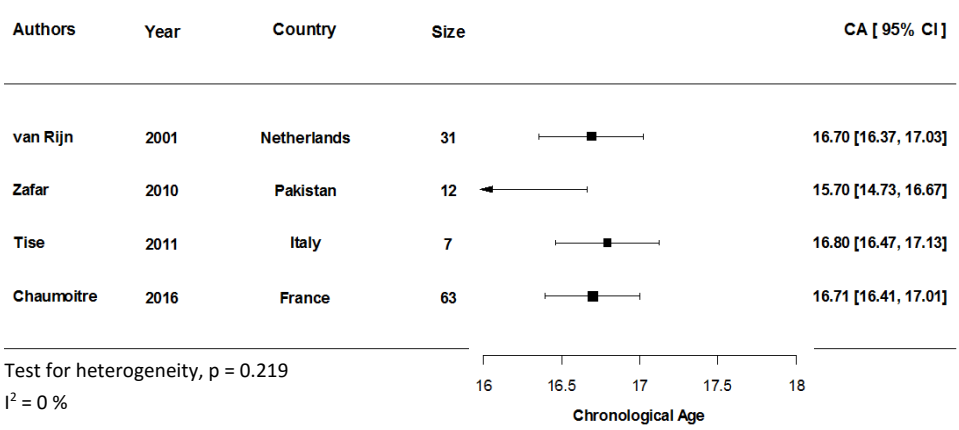
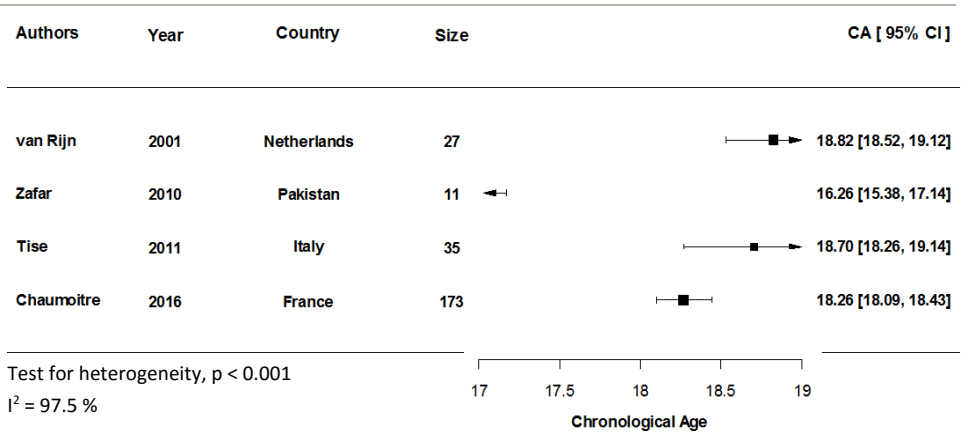


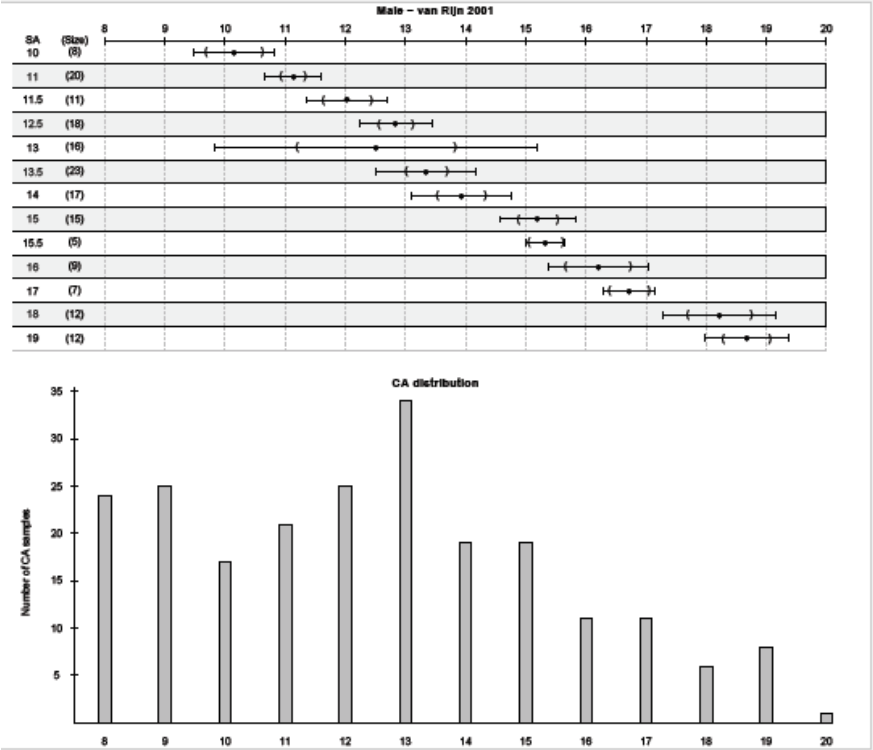
Figure A33

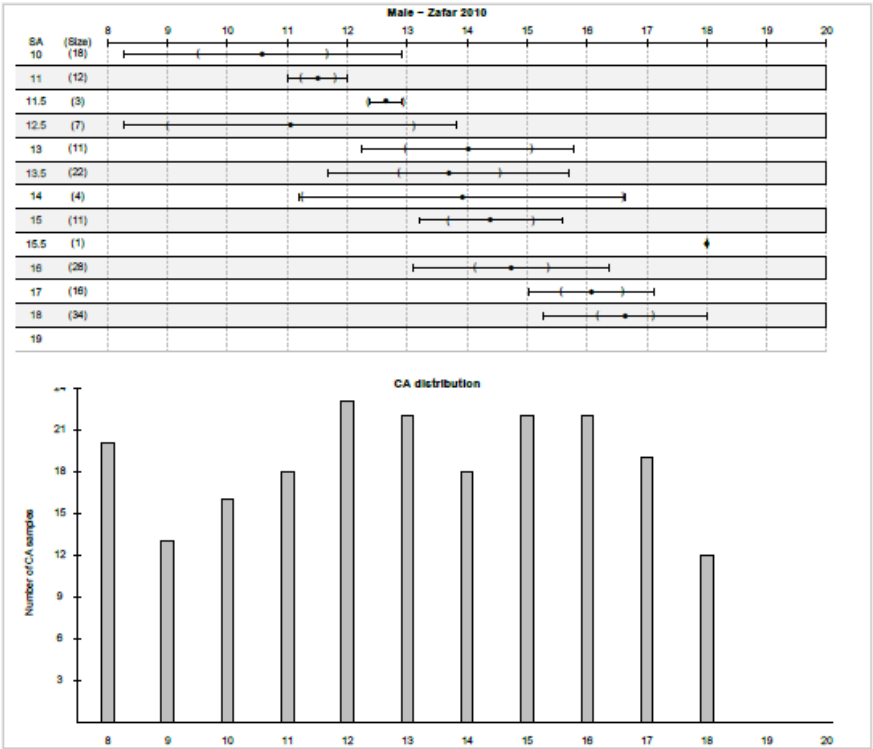
Girls, GP-stage 18 years

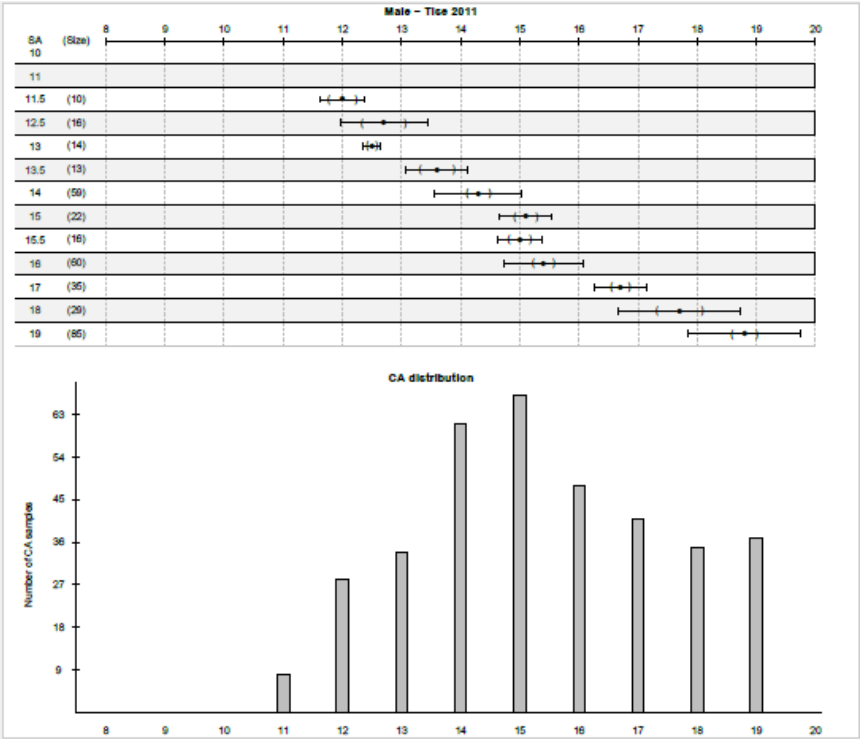


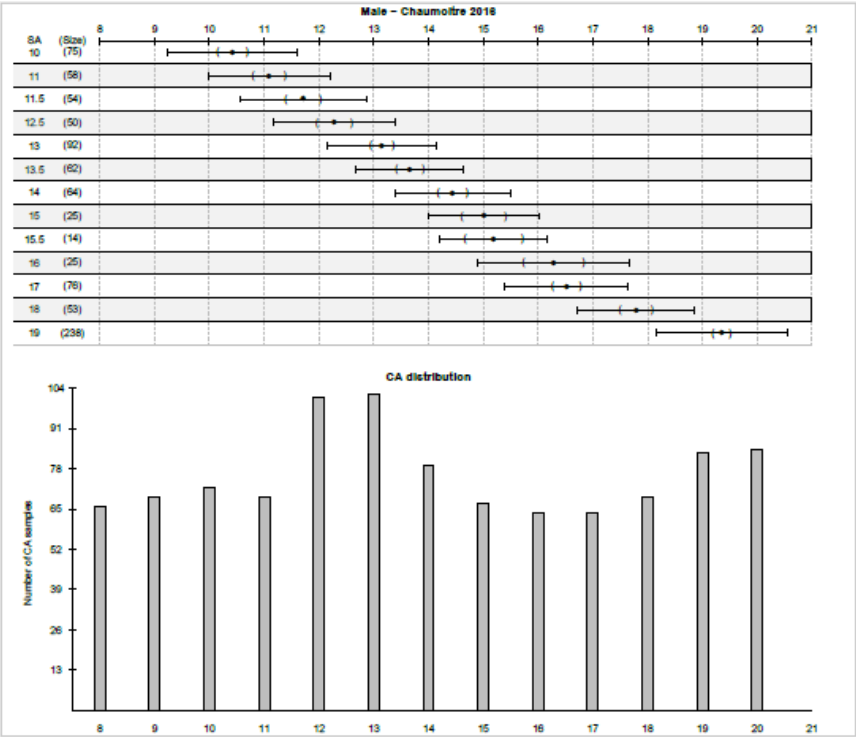
Mean chronological age by GP skeletal age categories alongside age distribution of included study participants, boys.

Figures A34-A37: Graphical representation of results for boys from the four studies presenting mean chronological age in GP skeletal age categories. The top part of the chart shows each GP skeletal age category, with the number of observations (left), mean chronological age (middle point) 95% confidence intervals for population means (brackets) and one standard deviation on each side (end of lines). The lower part of the figure shows the number of participants in each year of chronological age.



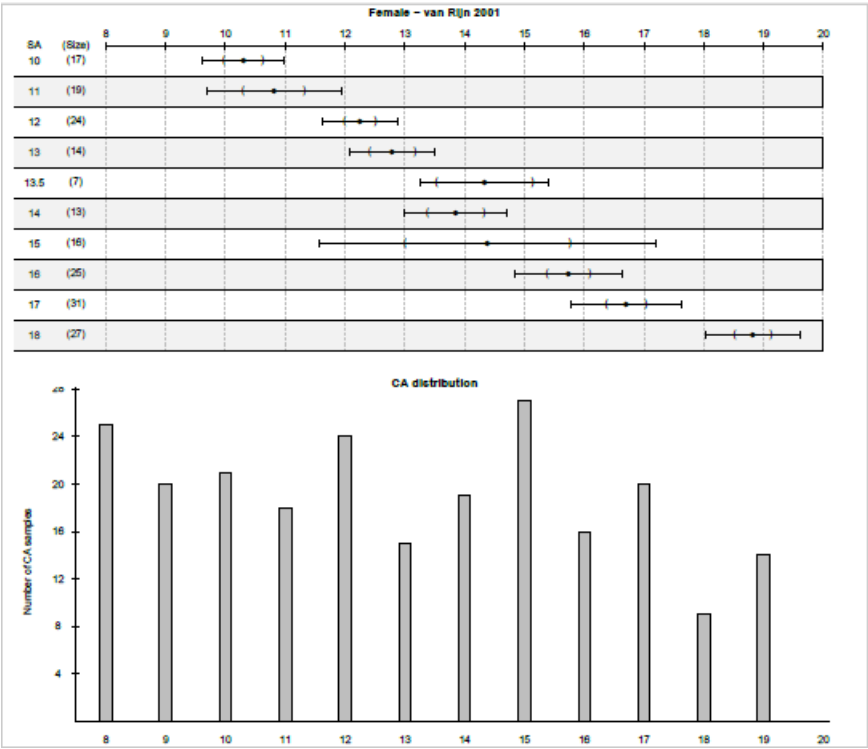


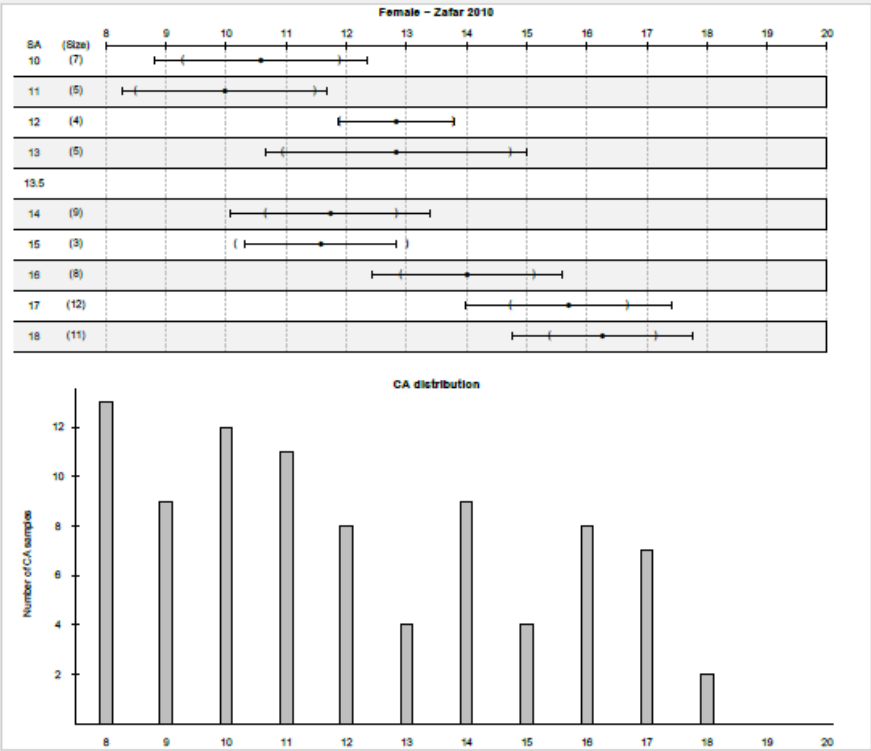

Male – Tise 2011
SA (Size)
10
11
11.5 (10)
12.5 (16)
13 (14)
13.5 (13)
14 (59)
15 (22)
15.5 (16)
16 (60)
17 (35)
18 (29)
19 (85)
CA distribution
Number of CA samples

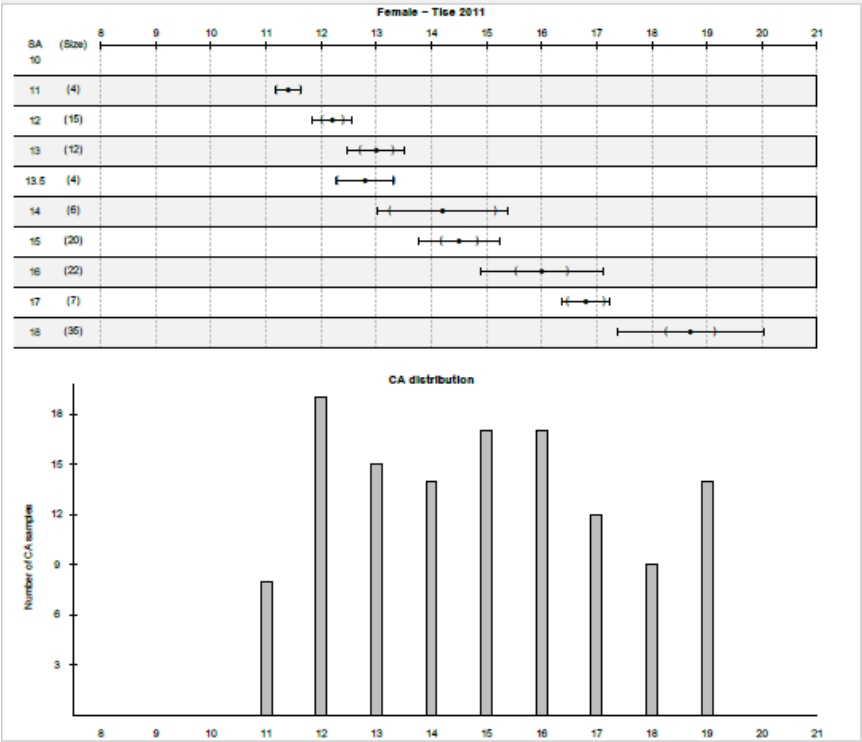

Male – Chaumoitre 2018
SA (Size)
10 (75)
11 (58)
11.5 (54)
12.5 (50)
13 (92)
13.5 (62)
14 (64)
15 (25)
15.5 (14)
16 (25)
17 (76)
18 (53)
19 (238)
CA distribution
Number of CA samples

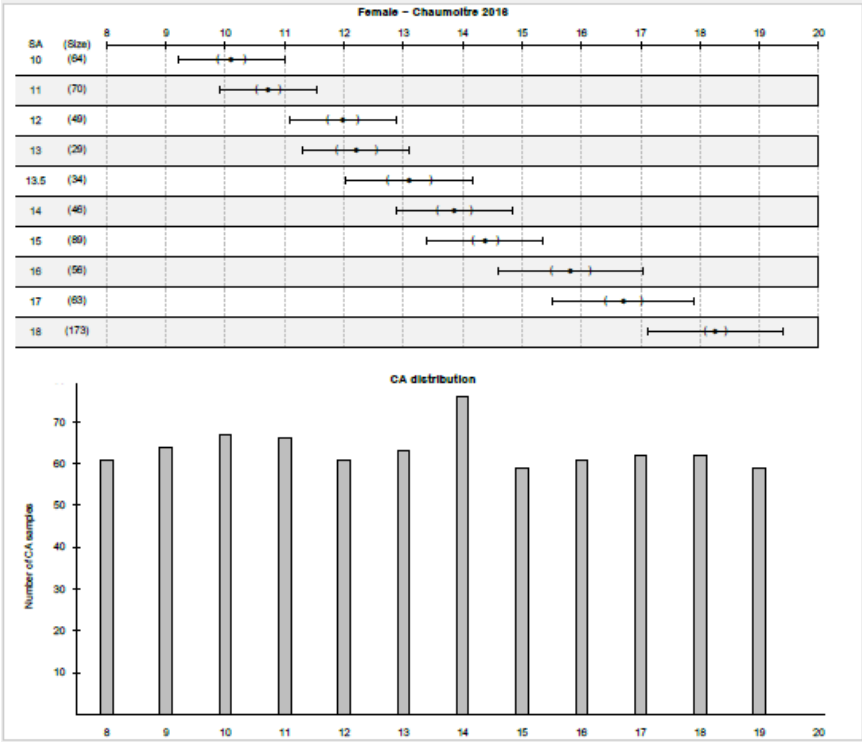
Mean chronological age by GP skeletal age categories alongside age distribution of included study participants, girls.

Figures A34-A37: Graphical representation of results for girls from the four studies presenting mean chronological age in GP skeletal age categories. The top part of the chart shows each GP skeletal age category, with the number of observations (left), mean chronological age (middle point) 95% confidence intervals for population means (brackets) and one standard deviation on each side (end of lines). The lower part of the figure shows the number of participants in each year of chronological age.






Female – Tise 2011
SA (Size)
10
11 (4)
12 (15)
13 (12)
13.5 (4)
14 (6)
15 (20)
16 (22)
17 (7)
18 (35)
CA distribution
Number of CA samples


Female – Chaumoitre 2018
SA (Size)
10 (64)
11 (70)
12 (49)
13 (29)
13.5 (34)
14 (46)
15 (89)
16 (56)
17 (63)
18 (173)
CA distribution
Number of CA samples

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