Aus der Klinik für Kinder- und Jugendmedizin,

Universitätsklinikum des Saarlandes, Homburg/Saar

Direktor: Prof. Dr. med. Michael Zemlin

Development of a new ultrasound device for determining maturity based on bone age assessment

Dissertation zur Erlangung des Grades eines Doktors der Medizin

der Medizinischen Fakultät

der UNIVERSITÄT DES SAARLANDES

2022

vorgelegt von

Ruth Lorna Dirksen

geboren am 17. November 1990

in England

Table of Contents

1 Summary

1.1 Abstract

1.1.1 Aim

The aim of this project was to develop and test an acceptable portable system to assess maturity, without the use of radiation, for use at international borders to detect underage victims of human trafficking. This study covers testing of the developed ultrasound device on young women, assessing the accuracy of the maturity categorisation given by the device, as well as assessing the usability and functionality of the device.

1.1.2 Materials and methods

The ultrasound device was used to measure the left ulna and radius epiphyseal plates in 148 young female participants, aged between 9-23 years (41% minors <18 years (n= 61), 59% adults ≥18 years (n=87)). The device consists of two ultrasound array transducers which travel along the forearm collecting reflection and transmission measurements from multiple pathways through the growth plates. The measurements were taken, and then assessed using a variety of machine learning methods, to categorise the individuals into minors or adults. Statistical analysis of each machine learning method was carried out and the most effective method was tested further for accuracy.

1.1.3 Results

Classical signal processing analysis of the ultrasound waves showed a difference between underage and adult epiphyseal plates. Using machine learning methods, correct age categorisation of the participants (minors <18 years, adults ≥18 years) was achieved with an F1 score of approximately 87%.

1.1.4 Conclusion

The novel use of ultrasound combined with machine learning techniques demonstrated in this study, provides a solid foundation for further progress in bone age assessment, including its use as a safe and quick screening tool to counter human trafficking.

1.2 Zusammenfassung auf Deutsch:

1.2.1 Ziel

Das Ziel unseres Projektes beinhaltet die Entwicklung und klinische Evaluation eines mobilen Systems, welches ohne Strahlenbelastung minderjährige Personen identifiziert. Endzweck ist die Prävention und Intervention bei Menschenhandel zum Zwecke sexueller Ausbeutung. Diese Studie stellt die Prüfung des entwickelten Ultraschallgerätes an junge Frauen dar, es werden Genauigkeit der Minder/Voll-jährigkeits Klassifikation und die Handhabung des Gerätes überprüft.

1.2.2 Methoden

Die Wachstumsfugen der Elle und Speiche von 148 jungen Frauen im Alter von 9 bis 23 Jahren (41% unter 18 (n=61), 59% über 18 Jahre (n=87)) wurden mit dem Ultraschallgerät gemessen. Das Gerät ermittelt sowohl Reflektions- als auch Transmissionsdaten in zahlreichen Bereichen über dem Unterarm, während die zwei Ultraschallelemente mechanisch entlang des Armes bewegt werden. Diese Messdaten werden durch Maschinelle Lernmethoden auf eine Weise analysiert, dass die Probandinnen in Minderjährig und Volljährig unterschieden werden können. Statistische Analysen der Ergebnisse jeder Maschinellen Lernmethode wurden durchgeführt und die Effektivste Methode weiter auf Genauigkeit untersucht.

1.2.3 Wesentliche Ergebnisse

Klassische Signalverarbeitungsmethoden zeigten eine Differenz zwischen den Messungen der minderjährigen und der erwachsenen Epiphysen. Mithilfe Maschineller Lernmethoden konnte dadurch mit einer Genauigkeit (F1-Score) von ca. 87% die korrekte Altersklasse ermittelt werden (Minderjährig <18 Jahre, volljährig ≥18 Jahre).

1.2.4 Schlussfolgerung

Die Nutzung von Ultraschall kombiniert mit maschinellen Lernmethoden zur Feststellung des Knochenalters stellt eine sichere und schnelle Screening-Methode dar. Diese Studie erweist sich als gute Grundlage für weitere Forschung in diesem Bereich, welcher auch im Kampf gegen Menschenhandel eine wichtige Rolle spielt.

2 Introduction

2.1 Background: Human trafficking

Between 2013 and 2014, 15,846 victims of human trafficking were reported within the European Union; 76% of these victims were female. The majority of human trafficked victims in Europe stem from other European countries, three of the five most common nations* share a border with Germany or Austria: Romania, Bulgaria, *The Netherlands, *Hungary, *Poland [11].

In Germany in 2018, 675 victims of human trafficking were identified, 25% of these were children, whilst 47.5% were under 21 years old. Of the identified children, 80% were between the ages of 14 and 17 years old, and 75% were girls [3].

2.2 The PRIMSA project

This study was one part of a larger international multi-disciplinary project funded by the German Department for Education and Development (Bundesministerium für Bildung und Forschung). The PRIMSA project (Prävention und Intervention bei Menschenhandel zum zweck Sexueller Ausbeutung – Prevention and intervention against human sex-trafficking) aims to combat human trafficking using a multi-disciplinary approach, including involvement from legal, medical, scientific and law-enforcement teams to provide a multi-pronged attack on this global issue [41]. As part of *PRIMSA Working Group 5,* our part within the project involved the development and testing of a technical instrument for use in identifying underage individuals falling victim to human trafficking across the German and Austrian national borders. The instrument designed needed to be portable, non-invasive and be able to determine if individuals are underage or have reached adult maturity. The creation of such a tool for non-invasive age assessment at international border control could help identify underage victims of human trafficking travelling under a false identity and allow them to be removed from this situation.

2.3 Existing methods to determine age

As current border control does not employ the use of a screening tool for age assessment other than the checking of passports and identification documents, we must consider normal markers of maturity and development of the adult body, and turn to the fields of forensic

medicine, paediatric endocrinology and sports medicine to explore existing methods of age determination.

2.3.1 Normal bone development

Each bone within the wrist and hand begins life as a cartilaginous structure at birth, developing and ossifying throughout the growth of the individual to later form the adult bone structure. The various bone centres found in each bone within the hand develop at different times in comparison to the bones around them, meaning that they become radio-opaque and appear on the x-ray at different stages. These timings are the basis for the standardised bone age assessment atlases [16] [37] and are influenced by various factors including, sex, ethnicity and the presence of certain medical conditions [46] (s. 5.2.4). At the end of growth and development the epiphyseal centres ossify and the growth plates fuse. Over time this fusion is consolidated by a further increase in bone density at the fused plate.

In women, the secondary ossification centres of radius and ulna close completely between ages 14 and 17 (radius), and 16 and 18 years (ulna); for men these ages ranges are from 16 to 20 years and 17 to 20 years (radius; ulna) [16]. This physiological phenomenon provides the foundation of this study in terms of maturity assessment based on the presence or absence of these growth plates when examined using ultrasound.

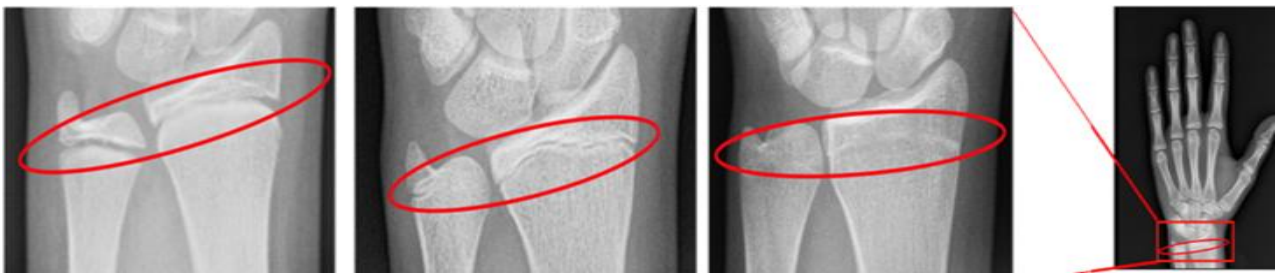

Figure 1 - Radiological bone age imaging showing ossification states in girls at 12, 15 and 18 years of age (from left to right) [16, 17]

Figure 2 - Depiction of the order of appearance of the individual carpal bones

“The usual sequence is capitate (1), hamate (2), triquetral (3), lunate (4), trapezium (5), trapezoid (6), navicular or scaphoid (7) and pisiform (8). The distal epiphysis of the radius ossifies before the triquetrum and that of the ulna before the pisiform." Image: Image of wrist bone development [14]**.**

2.3.2 Standardised methods in forensic medicine

In forensic medicine, accurate assessment of the age of living individuals is often required in order to provide the court with important information to inform legal decisions. The current standardised methods used for medical age assessment include medical history, physical examination and bone age assessment through the use of a wrist x-ray, orthodontic panorama x-rays, and, if indicated by complete formation of the hand bones on x-ray, a thin-slice CT or x-ray of the medial clavicular epiphyses [32] [33] [4].

2.3.3 Current gold standard for bone age determination in paediatric endocrinology

Outside the field of forensic medicine, radiological bone age determination is carried out regularly within the paediatric endocrinology setting for diagnostic and therapeutic purposes under strict clinical guidelines. The gold standard involves taking an x-ray of the left hand and wrist and comparing it to one of two atlases: the Greulich and Pyle atlas (GP Method) [16] or the Tanner and Whitehouse atlas (TW2 Method) [37]. The different bones within the hand and wrist are examined individually and collectively analysed according to the chosen atlas by an experienced medical practitioner. In endocrinology, the radiological bone age is then compared to the chronological age, a discrepancy between these two ages can be indicative of illness, for example an advanced bone age would support the diagnosis of precocious puberty requiring treatment in a child with pathologically early signs of puberty.

The wrist x-ray can also be used to detect subtle bone deformities associated with certain medical conditions, such as Ullrich-Turner Syndrome or SHOX Deficiency [5]. The radiological bone age can be used to predict adult final height, which is important for making medical treatment decisions and assessing treatment progress, for example in growth hormone deficiency treatment. Despite x-rays delivering only minimal radiation (0.0001 mSv for one hand x-ray [33]), well below the naturally-occurring yearly radiation exposure of approximately 5 mSv/ year, the use of ionising radiation required for this method, must be justified by a clear medical indication for the imaging [9].

2.3.4 Non-invasive techniques to assess bone age

The use of non-ionising radiation techniques in bone age assessment has previously been carried out using ultrasound and MRI scans.

Magnetic Resonance Imaging (MRI)

One study in 2018 charted the findings of progressive MRI scans of the knee joint in children creating an atlas of the developmental changes over time to assess the child's bone age [27]. MRI scans of the medial clavicular epiphysis have also been trialled in forensic medicine to replace the need for a CT scan, with promising results [34].

MRI scans are currently being trialled in sports medicine to determine the age of players within age-related tournaments [10]. In this field it is unethical to use ionising radiation to assess the players and so research into age assessment using MRI techniques has been carried out. Dvorak et. al. used MRI to assess the wrists of 496 14-19-year-old male adolescent football players developing a relatively reliable grading system based on bone fusion to assess bone maturity. A similar study by George, Nagendran and Azmi in Malaysia [13] showed a better correlation between the chronological age and bone age when using an MRI of the distal radius compared with a plain radiograph. The x-ray results tended towards an overrating of the skeletal maturity, documenting the individuals as older than their chronological age.

Dallora et al. used MRI examinations of the radius, distal tibia, proximal tibia, distal femur, and calcaneus alongside anthropological measurements to input into a machine learning model to classify young men and women into mature (≥18 years) and underage (<18 years) groups with accuracies of 0.9 (male) and 0.84 (female) [7].

Ultrasound

Bone age determining devices based on ultrasound rather than x-ray are few and far between [32]. One device currently on the market to measure bone age using ultrasound technology is the 'Sunlight BonAge', produced by the company 'BeamMed Ltd.' This device measures the speed at which the ultrasound waves travel through the different levels of calcification in the wrist bones and growth plates. The more calcified the bone, the faster the ultrasound waves can travel through it. Measuring the time between release and capture of the ultrasound waves on the distant side of the bone, allows the average wave speed through the calcifying bone to be calculated. As the level of calcification correlates with the age of the subject, the age can be determined by the speed of the ultrasound waves. With increasing age, the speed of the ultrasound waves increases. A formula is then used to calculate an age based on the speed of the waves and thus the level of growth plate calcification [25].

A second ultrasound device, the 'BAUS' device, from the company SonicBone, is also available on the market. This device takes static speed-of-sound measurements of the ultrasound waves through the wrist, metacarpals and phalanxes, calculating the bone age based on a formula taking into account the individual's sex. This device is portable and requires only 3 minutes per scan [28].

Both of these devices show a promising start for bone age assessment using ultrasound, however, they both measure one or multiple fixed points within the hand and forearm, using a formula to calculate the bone age based upon these measurements. This leaves significant room for error when aiming to screen for maturity based upon the definite presence of the radial and ulnar growth plates. The technique of measuring at the same point along the wrist of each individual does not allow for detection of the growth plate above or below the section of forearm measured. Both devices are aimed at a paediatric population to determine bone age in a growing child. This means that they have not been tested for an adult population and are unable to determine a bone age over 18 years of age [25] [28].

Anecdotally, we reviewed the BonAge device at the University of Saarland as part of the initial product development research. When informally trialled on a few female adult colleagues, the device proved unreliable for an adult population, reporting bone ages ranging from 13-16 years for colleagues over the age of 30 years old.

2.4 Study aims

The primary aim of this study is to test the developed ultrasound device on young females and assess its ability to determine the maturity status of these individuals.

The secondary outcome of this study is to assess the usability of the prototype device to determine its practicality for use as a screening tool and to highlight areas for improvement.

3 Materials and methods

3.1 Materials

3.1.1 The ultrasound device

The ultrasound device was designed and developed as part of *PRIMSA working group 5* by colleagues at the Fraunhofer Institute for Biomedical Technology (IBMT), Sankt Ingbert, Germany. The device was designed to collect ultrasound wave data from the left wrist of the participant. The data was recorded as raw ultrasound waves in the form of high-frequency measurements, technically referred to as “Amplitude measurements” (so called “A-Waves”), as opposed to ultrasound imagery. The PRIMSA technology was designed to collect various lengths of reflection and transmission ultrasound waves: reflection ultrasound waves being recorded on the same side of the device as emitted, having reverberated off the participant's wrist, transmission waves captured on the opposite side to emission, having passed through the participant's wrist. The device contains a motorised ultrasound probe which allows for measurements to be taken along multiple segments of the forearm, with data being individually recorded for each transducer. Each run of the device collects approximately 250 A-scans for that one participant [17].

The device connects to a computer system via WIFI, for this project a Microsoft Surface Tablet was used. This computer system is used to input the patient details, to start and stop the measurements and to store the data collected.

The development of the ultrasound device has been documented in detail in a paper published by the colleagues from the Fraunhofer Institution [17].

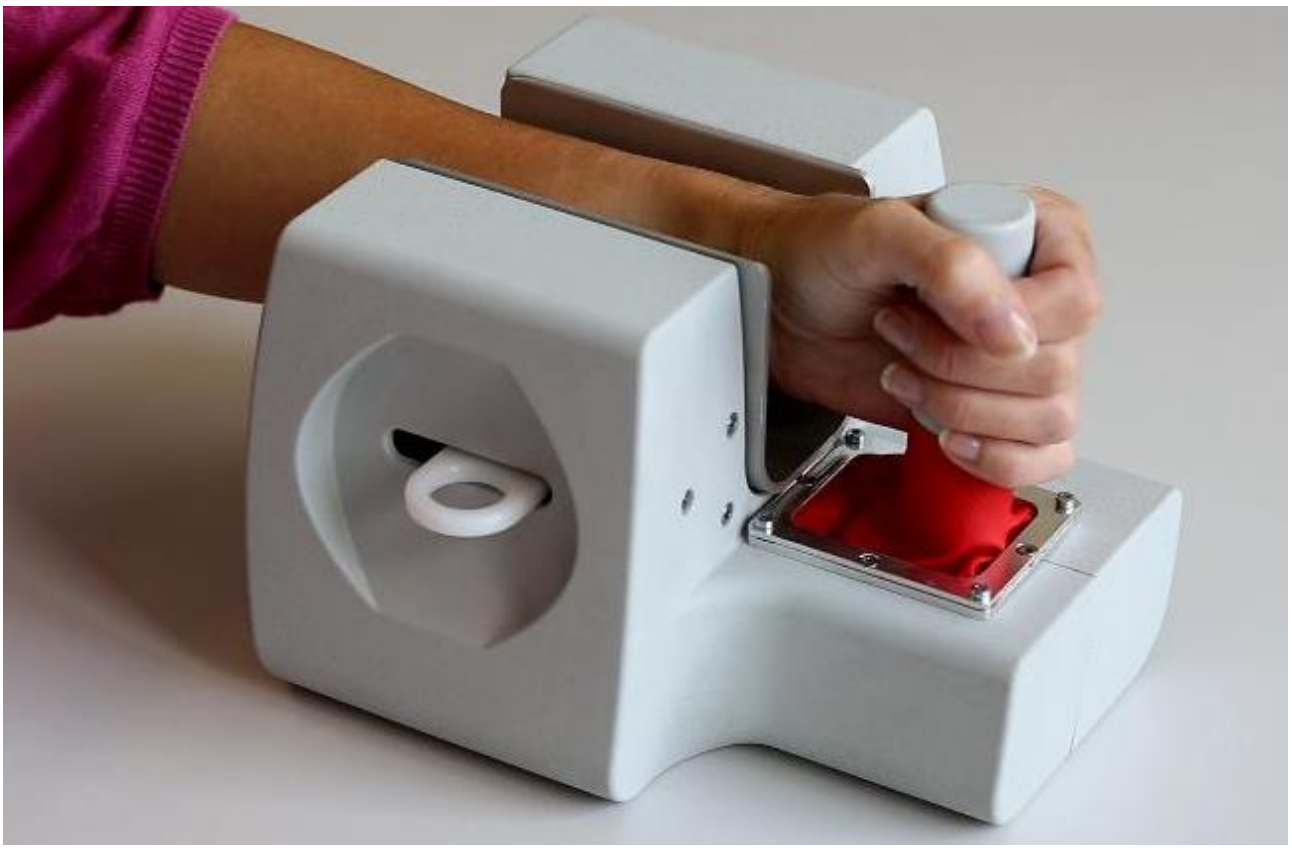

Figure 3 - The ultrasound device [2]

3.1.2 Device quality control and safety testing

Before use within this study the ultrasound device underwent the required quality control and safety testing to ensure that it could be used within hospital and community settings according to the EU regulations regarding medical devices.

The following technical certificates were acquired:

- electronic safety certificate: IEC 60601-1, IEC 62368
- electromagnetic compatibility: IEC 60601-1-2:2015, IEC 60601-1-2:2014 (Sections 7 and 8)
- acoustic testing: IEC 60601-2-37:2007 including A1:2015

3.2 Methods

3.2.1 Participants

Inclusion criteria

Participants were selected based on the following inclusion criteria:

1. Female
2. Aged 9 to 24 years

Exclusion criteria

Participants were excluded when any of the following criteria were met:

1. Existence of a previous fracture of the left hand, wrist or forearm.
2. The known existence of a medical condition known to affect bone age, when an x-ray for comparison was not available. Medical conditions including: Precocious puberty, delayed puberty, growth hormone deficiency, congenital adrenal hyperplasia, previous radio- or chemotherapy, previous high-dose steroid therapy, Ullrich-Turner syndrome, Down syndrome, transgender individuals undergoing/ previous hormone therapy, tall stature individuals undergoing hormone therapy, non-treated hyper- or hypothyroidism (where serum TSH levels from the previous year were abnormal or not available for assessment), severe obesity (BMI >40 kg/m^2).
3. Unviable ultrasound scan or insufficient ultrasound data (s.3.2.6).

3.2.2 Participant recruitment

Paediatric endocrinology patients

Patients meeting the inclusion criteria were recruited from the paediatric endocrinology clinic in the University of Saarland Hospital (UKS) in Homburg, Germany from December 2017 to July 2018. The majority of recruitment took place in person at the time of routine follow up appointments in the clinic. Further patients were invited via telephone to attend the clinic for

an ultrasound when their next routine appointment was not scheduled within the 7-month time frame of their last radiological bone age assessment.

Local healthy volunteers

Further participants meeting the inclusion criteria were recruited via written invitation. The invitation targeted healthcare students contacted through the university email, and school students contacted in letter form, both with permission and support from the responsible university department heads and school headteachers. The target participation age span was reduced to ages 14 to 24 for the healthy volunteers. The exclusion of younger children in the invitation took place after the initial studies showed difficulties with narrow underarm size, common in younger children. Participation was non-mandatory, and no incentive was provided.

Appendix 9.1 Letter of invitation for healthy volunteers

3.2.3 Participant demographics

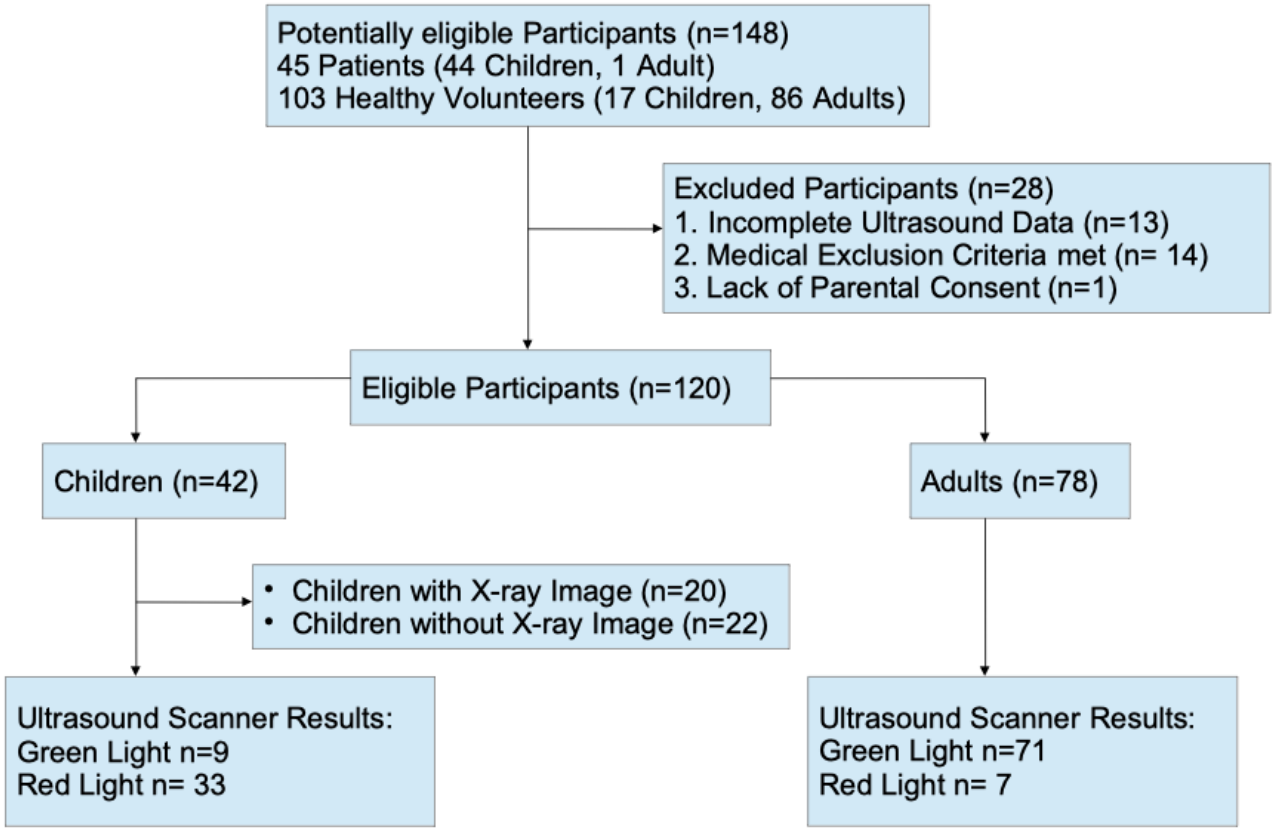

Figure 4 - STARD 2015 flow diagram of study participants

	Underage Cohort <18		Mature Cohort ≥ 18	
	Mean / Total	**Range**	**Mean / Total**	**Range**
Total (n)	42		78	
Age (years)	13.8	9.2 – 17.9	20.5	18.1 – 23.9
Number of patients	26		0	
Radiological bone age available	20		0	
Bone age incongruent with age category	0		-	
Height (cm)	154.9	130 - 180	166.3	154 - 184
Height percentile	36.9	0 – 98	40.3	2 – 99
Weight (kg)	52.3	28 – 103	60.9	45 – 92
Weight percentile	52.7	0 – 100	52.3	2 – 100
BMI (kg/m^2)	21.4	14 – 40	22	17 – 33
BMI percentile	61.1	0 – 100	53	1 – 100
White European ethnicity (ethnicity reported)	16	of 20	27	of 31
Questionnaire A	0		47	
Questionnaire B	17		26	

Table 1 - Participant demographics

3.2.4 Study procedure

Sequence of events for each participant

1. Participant recruitment and consent
2. ± health and demographics questionnaire
3. Height and weight measurement
4. Ultrasound examination
5. ± radiological bone age assessment (when clinically indicated)

3.2.5 Participant consent

The participants, and the legal guardians of participants under 18 years of age, gave formal consent for the study, both verbally and in written form, to one of the medical team. They received a copy of the consent form for their own records as well as an information flyer about the study and the wider PRIMSA project. Tailored information and consent forms were used for parents of underage participants with or without an x-ray, as well as for mature participants with or without an x-ray.

During the course of the study, participants, or legal guardians, could withdraw their participation consent at any time.

Examples of the consent forms and participant information sheets are included in the appendices:

Appendix 9.2 Study information sheet for parents of participants with an x-ray (German)

Appendix 9.3 Study information sheet for underage participants without an x-ray (German)

Appendix 9.4 Parental consent form for underage participant (German)

Appendix 9.5 Consent form for mature participant (German)

Health and demographics questionnaire

The medical details of the initial patients were taken, with permission, from their medical records. As the study progressed a health questionnaire was introduced to gather this information. This questionnaire was later extended to include further medical and demographic details. In total, 30 did not receive a questionnaire, 47 participants received Questionnaire A (Appendix 9.6), whilst 43 participants received Questionnaire B (Appendix 9.7).

3.2.6 Measurements

Height

The participant's height was measured on a calibrated medical stadiometer by a trained medical professional, with measurements being documented to the nearest 1 mm.

Weight

The participant's weight was measured on a calibrated medical weighing scale by a trained medical professional, with measurements being documented to the nearest 100 g.

Body Mass Index (BMI)

The BMI was calculated using the measured height and weight (kg/m^2).

Height, weight and BMI percentiles

For analytical purposes, the height, weight and BMI were converted into the correct percentile for the age of the participant using the Kromeyer-Hauschild growth charts online [19] [15].

For participants over the age of 18 the percentiles were calculated based on a 17 year 11-month-old girl as percentiles for adults were not available.

For percentiles found to be in the extreme (<1 or >99) the numbers were rounded to allow for numerical analysis <1 was rounded down to 0, and >99 up to 100.

Radiological bone age

A radiological bone age assessment is often required as part of the endocrine assessment of a patient in the endocrinology clinic.

Participants requiring a radiological bone age assessment as part of their medical treatment in the endocrinology clinic were asked for permission to use this data to compare with their ultrasound data.

The radiological bone age assessment consisted of an AP x-ray of the left hand and wrist compared to the Greulich and Pyle Atlas by an experienced paediatric endocrinology consultant, blinded to age and height of the individual. For participants with a recorded radiological bone age, the statistical analysis used bone age to match to the ultrasound measurements instead of chronological age.

The majority of the x-rays were taken in the UKS paediatric radiology department on the same day as the ultrasound scan. However, some patients brought a current x-ray on CD taken in an external radiology practice. These images had to be taken within 7 months of the ultrasound scan to be included within the study.

No non-medically indicated x-rays were performed on healthy individuals.

Ultrasound scan

The ultrasound scans were completed to the following protocol:

1. Disinfection of the ultrasound device with medical equipment disinfection wipes.

2. Turn the ultrasound device on and calibrate.

3. Apply ultrasound gel to the ultrasound plates.

4. Pull the moveable ultrasound plate back so that the participant can insert their hand and wrist into the device and take hold of the hand grip.

5. Ensure correct hand position – tight hold of the hand grip, thumb on top of the grip with thumb nail facing upwards, wrist pushed toward the ultrasound probe so lying flat against it. Provide appropriate elbow support for the participant.

6. Photograph hand position – one aerial view photograph and one lateral view photograph.

7. Start device and observe the scan on the computer device; actively encourage the participant to give feedback on any discomfort during the process.

8. End of scan – pull back the moveable ultrasound probe to allow the participant to remove their arm, allow the participant to clean the gel off their arm with the paper towels provided.

9. Thank the individual for their participation and clean the ultrasound device.

All ultrasound measurements were overseen by one of the team in order to troubleshoot for any problems or discomfort.

Troubleshooting

1. The most common problem occurring during the ultrasound scans was insufficient battery life. When this occurred, the device would stop measuring. The participant's hand would be removed from the device, the battery replaced, and the protocol from step 2 repeated, including recalibrating the device and retaking the positioning photos.

2. Hand positioning problems

    1. Arm diameter too wide for the device: the scan had to be discontinued when the motorised ultrasound probe was unable to move sufficiently along the forearm due to increased pressure from the underarm.

    2. Arm diameter too small for the device: the scan could not be carried out if the ultrasound probes were not able to make good surface contact with both sides of the underarm despite sufficient ultrasound gel.

    3. The arm was not sitting correctly to allow for a good ultrasound reading – as seen by the waves depicted on the monitor. The participant's arm was adjusted, and the scan repeated.

After a maximum of 3 failed attempts at measuring, the participant would be thanked for their participation and no further measurements would be carried out. The details explaining why

the measurement had failed were then noted and the participant was removed from the study.

Figure 5 – The ultrasound device in use

Image reproduced with permission from Hewener, H., Fraunhofer Institute.

Photographs of the hand position

During the ultrasound scanning process, photographs were taken of the positioning of the participant's hand for quality control purposes. Both an aerial and a lateral photograph of the ultrasound device and underarm of the participant were taken before the scan. The photographs did not include the rest of the individual's body or face and were anonymised using the participant's study number.

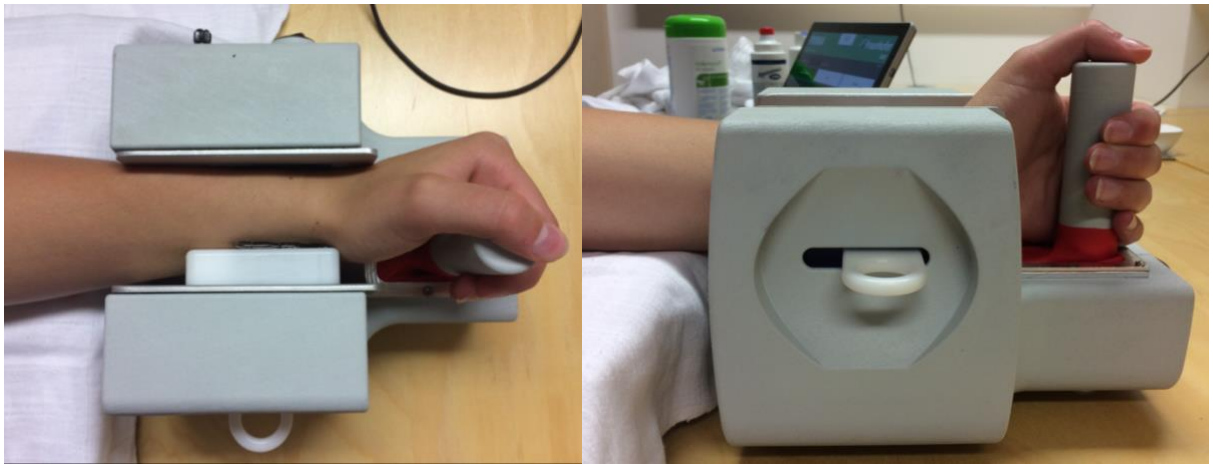

Figure 6 - Aerial and lateral photographs of the ultrasound device in use

Images by author.

3.3 Database and data protection

Each participant was allocated a study number based on the date on which they received their ultrasound scan. The anonymised data (questionnaire responses, anthropological measurements and bone age assessment results) was then entered into a Microsoft Excel spreadsheet before being transferred into SPSS for analysis.

The patient questionnaires and consent forms were filed in original paper form and kept securely.

The ultrasound data was recorded directly from each scan and stored anonymously under the participant's study number. Once the ultrasound data had been analysed to provide a categorisation for the participant (underage or mature) this was entered under the corresponding study number into the Excel spreadsheet.

3.4 Ethical approval

Ethical approval for the study was granted on 18.04.2016 by the Saarland Medical Ethics Board under the reference number 255/15.

Extended ethical approval to include healthy volunteers was granted on 30.01.2018.

3.5 Methods of analysis

3.5.1 Microsoft software and EndNote X9

Microsoft Word was used to write this paper, and Microsoft Excel was used for the data collection.

EndNote X9 was used in the generation of this paper and bibliography.

3.5.2 Statistical software

The statistical data analysis was carried out using the SPSS Statistics Programme (IBM SPSS Advanced Statistics 25.0).

3.5.3 Analysis techniques

Reliability assessment and means of variability

The reliability of the hand ultrasound device results were assessed by calculation of the accuracy, sensitivity, specificity, positive predictive value and negative predictive value.

Blyth-Still-Casella confidence intervals were calculated for each of these values using StatXact Version 10.

Statistical significance assessment

Logistical regression was used to determine the statistical significance of the ultrasound device results. This technique was also used to calculate p-values for each of the recorded potential confounding factors, where enough data variables were collected. The probability used to define significance was $p<0.05$.

The probability of the ultrasound device showing green (adult maturity) at age 18 years

Logistical regression was used to calculate the required constants (B0 and B1) to complete the following formulas to calculate the probability of the ultrasound device showing green (Pa) based on the age (A) of the individual. This was then displayed in the form of a graph (s.4.5.).

Formula 1: N(a)= B0 + A(B1)

Formula 2: Pa= e^N(a) / 1+e^N(a)

3.5.4 Photographs of the ultrasound device during data collection

The photographs taken during the ultrasound measurements were used in the analysis when assessing the outliers, to ensure that the hand position was correct during the scans.

4 Results

4.1 Detection of the growth plate

The first assessment of the ultrasound wave data collected involved determining whether the device was able to detect a difference in the readings between mature adults and underage minors. This assessment and the subsequent programming using different machine learning techniques was carried out by our colleagues from the IBMT. They were able to detect a difference in the amount of ultrasound wave dispersion and plotted this change, comparing it to the age of the participant, as seen here in figure 7. There was a clear trend to be seen when comparing the participant's age to the level of wave dispersion in their cumulative ultrasound scan data [17].

The most significant indicator of underage status was the variability within the ultrasound signals during transducer movement over the epiphysis: more variability correlates to a younger chronological age.

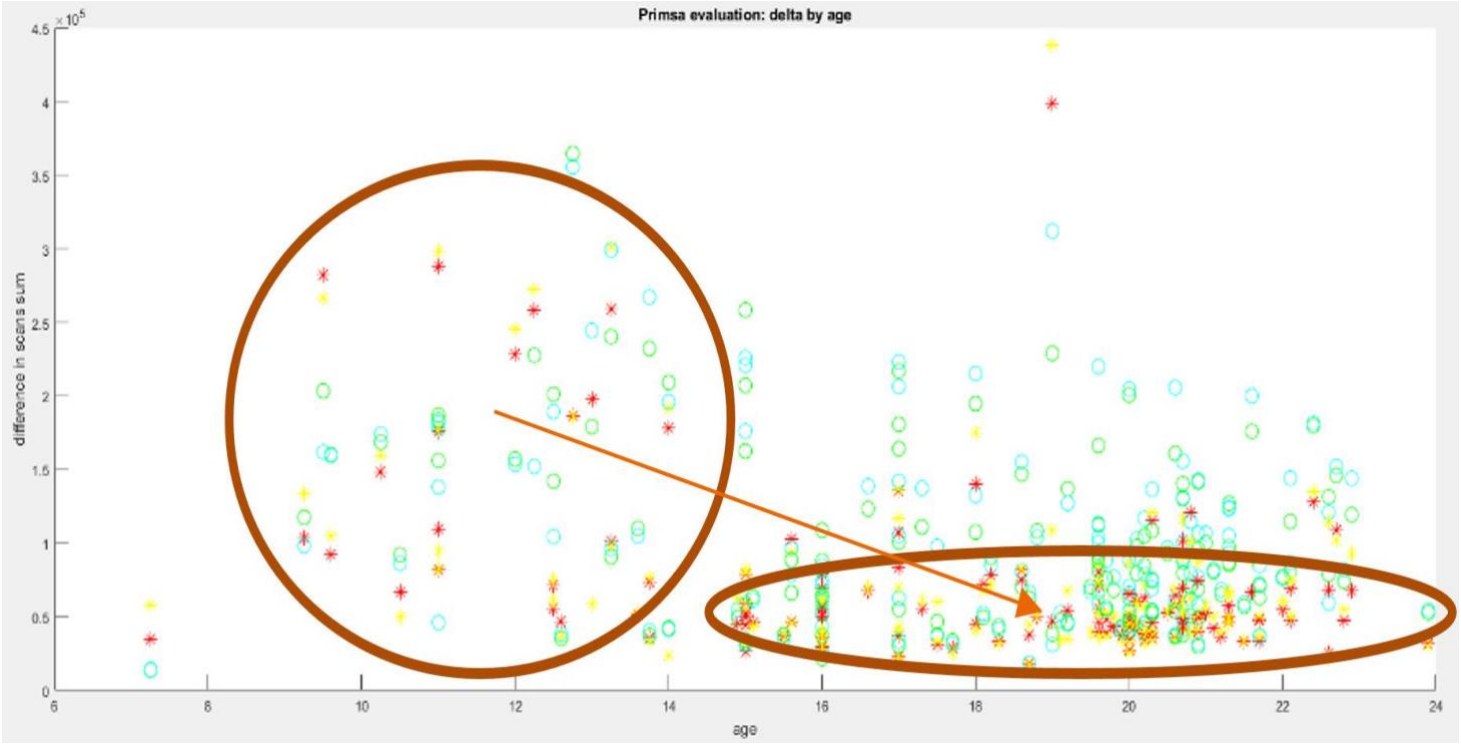

Figure 7 - Difference in ultrasound scan sum in relation to delta by age [17]

4.2 Machine learning techniques

Having established the presence of a trend within the data, my colleagues at the Fraunhofer Institution ran the data using various machine learning techniques in order to find the best technique for analysis. The different techniques trialled included: dynamic time warping distance, artificial neural networks (fully convolutional networks, multilayer perceptrons, residual networks and radial basis function neural networks) and gradient boosting machines (XGBoost, LightGBM and CatBoost). The 'CatBoost with 10,000 Iterations' proved to be the most effective technique for the data [2]. This technique was then used to analyse the various different A-Scan signals recorded by the ultrasound device. Figure 8 shows the results of the CatBoost technique for each individual set of signals with the success rate displayed as an f1 score for each participant in the final row. The f1 score for each participant is calculated based upon the ultrasound device's ability to correctly classify the individual into 'red' (underage <18 years old) or 'green' (mature ≥18 years old) when compared with the 'truth' (as determined by the bone age, when available, or chronological age).

In figure 8 the f1 scores above 0.8 are highlighted in green, those between 0.7-0.8 in yellow and those below 0.7 in red for each participant (one row) using each set of signals (one column). In the final row the cumulative f1 scores are displayed, showing the 'b3_transmission3_nonTruncated' signals (column 13) as having provided the most accurate results (highlighted in blue).

Participant	Age	Truth	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
1103	9.3	0	0,44	0,56	0,64	1	0	1	0,4	0,08	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0,8
1102	9.5	0	1	1	1	1	0,48	1	0,08	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
2201	9.6	0	0,96	1	1	0,88	0	1	1	1	1	1	0,92	0,28	0,24	0,88	0,96	0,84	0,8	1	0,96	1	0,88	0,08	1	0,16
1105	10.3	0	1	0,76	1	0,48	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
1304	10.5	0	0,32	1	0,88	0,72	0,64	1	0,96	1	0,44	0,96	0,12	0,04	1	1	0,96	1	0,12	1	0,48	0,6	0,96	1	0,48	1
1203	11.0	0	1	0	1	0,2	1	0,96	1	1	0,84	0,96	0,88	0,68	0,92	1	0,04	1	1	0,8	1	0,92	1	1	1	1
1204	11.0	0	0,24	0,6	0,76	0,88	0,96	0,96	1	0,72	0,96	1	1	1	1	1	0,96	1	1	1	1	0,84	1	1	1	1
1207	11.0	0	0,76	0	1	1	1	0,04	1	1	0,2	0,84	0,36	0,6	1	1	0,68	0,48	0,88	1	0,96	0,12	1	0,96	0,96	0,96
1205	12.0	0	0,48	1	0,76	1	0,68	1	1	1	1	1	1	1	1	1	1	1	0,84	1	1	1	1	1	1	1
1308	12.3	0	1	1	1	1	0,92	0,84	1	1	0,68	0,84	0,88	1	1	0,92	0,96	0,92	1	1	1	1	1	1	1	1
1509	12.5	0	1	0,68	0,44	0,64	1	1	1	0,96	0,32	0,48	0,08	0,68	1	0,96	0,84	0,64	0,56	0,08	0,4	0,64	0,48	0,56	0,68	0,68
1512	12.5	0	0,84	0,56	1	0	1	0,56	1	1	1	1	1	0,76	1	1	1	1	1	1	1	0,72	1	1	0,96	0,92
2103	12.6	0	1	1	1	1	1	1	1	1	0,96	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0,96
1206	12.8	0	0,88	0,6	1	0,12	1	0	1	0,96	0,8	0,44	1	1	0,96	0,76	1	0,88	1	0,64	0,84	1	1	1	1	1
1108	13.0	0	1	1	0,72	1	1	1	0,56	1	1	1	1	1	1	1	1	1	1	1	0,96	1	1	1	1	1
1101	13.3	0	0,96	0,36	0	1	1	0,96	1	1	0,92	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
1510	13.3	0	0,6	0	0,96	0,92	0,76	0,04	1	0,6	1	0,44	0,96	0,68	0,92	0,24	1	0	0,76	0,68	0,84	0,6	0,96	0,88	0,8	0
2001	13.6	0	1	1	1	1	1	1	0,84	0,72	1	1	1	1	1	1	1	1	1	1	1	0,96	1	1	1	0,32
1301	13.8	0	0,64	0,16	0	1	0,36	1	0,28	1	1	1	0,84	1	1	1	0,92	1	1	1	0,92	1	1	1	0,84	1
1302	14.0	0	0	0	1	1	0,96	1	0,44	0	0	0,64	0,32	1	0,68	1	1	0,12	0,6	0,08	0,4	1	1	0,4	0,4	0
1305	14.0	0	0,28	0	0,48	1	1	1	1	1	0	0,76	0	0,96	1	1	1	1	1	1	0,4	1	1	1	1	1
1907	14.9	0	0	0,04	0,96	0,72	0	0,72	0	0	0	0	1	0,64	0	0	0	0	0,04	0,24	0,44	0,96	0	0	0	0
1010	15.0	0	1	1	0,16	0,64	1	1	1	1	0,96	0,84	0,96	0,68	0,28	0	0,36	0,88	0,92	0,88	0,96	0,72	0,92	0,8	0,32	0
1104	15.0	0	0,2	1	1	1	1	0	1	0,52	0,84	1	1	1	0,16	1	1	1	0,56	1	1	1	1	0,52	0	0,92
1201	15.0	0	1	0	0	1	1	1	0,8	1	1	1	1	1	1	1	1	1	0,6	0,88	0,92	0,48	0,96	1	0,56	1
1202	15.0	0	1	0	1	1	0,08	0,4	1	1	0,72	0,92	1	1	1	1	0,88	1	0,48	0,96	1	1	1	0,88	0,88	0
1511	15.0	0	0	0,28	0	0,8	1	0,64	0,72	0	0,28	0,84	0	0,92	0,92	1	0,12	1	0,6	0,72	0	0,88	0,48	1	0	0,48
2003	15.0	0	1	1	1	1	0,44	1	1	0,92	0,52	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
1903	15.1	0	0	0,64	0,48	0,2	0	0,2	0,36	0	0,2	0,44	0,8	0,6	0,04	0	0,96	0,08	0,84	0,92	0,8	0	0	0,12	0,36	0,2
1904	15.5	0	0	1	1	1	0	0	1	1	0,76	1	1	1	1	0,56	1	1	1	1	1	1	1	0,4	1	1
1913	15.6	0	1	1	0,48	1	0	0	0	0,08	0,28	1	0,84	1	0	0	0,12	0,36	0,28	0,56	0,96	1	0	0	0	0
1916	15.6	0	0	0,84	0	0	0,96	1	0	0	0	0,48	0,64	0,84	0,88	0,68	0,92	0,52	0	0	0,8	1	0,84	1	0,8	1
1901	16.0	0	0	1	0	1	0,96	1	1	1	0,8	0,32	1	1	1	1	0,92	1	1	0,4	1	1	1	0,88	0,08	1
1905	16.0	0	0,32	0,92	0,84	0,52	0,92	1	0	0	0,2	0	0,56	0,2	1	0,04	0	0	0,36	0,08	0,32	1	1	0,44	0,04	0
1906	16.0	0	1	1	0	0,56	0	0	0	0	0	0,16	1	0,72	0,6	0	0,48	0	0,76	0,92	0,8	0,6	0	0	0	0
2100	16.0	0	0	0	0,92	0,08	0	0	0	0,2	0,08	0,76	0,72	0,24	0,8	0,4	0,44	1	0,08	0,64	0,36	0,88	0	0,04	0,04	1
1912	16.6	0	0	0	0	0,12	0,88	1	0	0	0	0	0	0,12	0,64	0,28	0	0	0	0	0	0	1	0,72	0	0
1503	17.0	0	0,36	0,16	0,12	0	0,72	0,88	1	1	0,6	0,68	0,44	0,08	1	1	0,8	1	0,08	0,88	0,32	0,52	1	1	0,88	1
1507	17.0	0	0,44	0	0,48	0,44	0	0,36	0,04	0	0	0	0	0,08	0	0,04	0	0	0	0,04	0	0,08	0,08	0,04	0	0
1909	17.3	0	0	0,64	1	0,64	0	0,92	1	0,72	1	0,56	0,88	0,96	0,08	0,08	0,16	0,12	0,6	0,24	0,8	0,92	0	0	0,96	1
2002	17.5	0	0	1	1	1	1	1	0,96	1	1	0,92	1	1	1	1	1	1	1	0,96	1	1	1	1	1	0,88
1910	17.7	0	0,56	0	0	0,32	0	0	0	0,2	0,72	0,04	0,44	0,64	0	0	0	0	0,08	0	0,04	0,4	0	0	0	0,08
1504	18.0	1	0	0,48	0,44	0,12	0	0,56	0	0	0,32	0,76	0,96	0,88	0,6	0,08	0,6	0	0,32	0,56	1	0,96	0,48	0,36	0,8	0,52
1714	18.0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0,8	1	1	1	1	0,76	0,84	0,64
2102	18.1	1	1	1	0	0	0,24	0	1	0,92	1	1	0	0,16	1	0,92	1	0,76	1	1	0,08	0,88	0,48	1	1	0,96
1617	18.2	1	0,6	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
1911	18.3	1	0	0,28	0	0	1	1	0,92	1	0	0	0	0	1	1	0,12	0,48	0	0	0	0	1	1	0,64	0
1702	18.6	1	1	1	1	1	1	1	1	1	0,96	0,96	1	1	1	1	1	1	0,84	0,64	1	1	1	1	1	1
1713	18.6	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0,96	1	0	1	0	1
1812	18.7	1	1	1	1	1	0,96	0,88	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
1704	18.8	1	1	1	0,92	0	1	1	1	1	0,88	1	0,92	1	1	1	1	0,64	1	1	1	0,76	1	1	0,72	0,76
1502	19.0	1	0,4	0	0	0,24	0	0	0	0	0	0	0	0,36	0,56	0	0,04	0,08	0,44	0,12	0,36	0,24	0,56	0	0,96	0,04
2101	19.0	1	1	1	1	0,64	1	1	0,4	0	0,96	1	1	1	0,96	1	1	0	0	0,72	0,32	0	0	0	0	0
1611	19.1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
1607	19.2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
1616	19.2	1	1	0,88	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
2004	19.5	1	0,24	1	0,12	0,56	0	0	1	1	0	0,84	0	0	0,32	0	0,52	1	0,08	0	0,16	0,2	0	0,04	0,04	0,92
1606	19.6	1	1	1	0,48	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0,96	1	1	1	1	1
1618	19.6	1	0,96	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0,68	1	1	1	1	1	1	1

Participant	Age	Truth	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
1716	19.6	1	1	0,96	1	1	0,52	1	1	1	0,96	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
1806	19.6	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
1811	19.6	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
1615	19.7	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
1603	19.8	1	1	1	0,56	1	1	1	0,76	1	1	1	1	1	1	1	0,88	1	1	0,76	1	1	1	1	1	1
1628	19.9	1	1	1	0,6	0,52	1	1	0,08	0,16	1	1	1	1	1	1	0,12	0,48	1	1	1	0,72	1	1	0	0,04
1505	20.0	1	0,72	0,92	0,32	0,8	0,68	0	0	0	0,96	0,88	1	0,96	0,28	1	0,4	0,76	0,84	1	1	1	0,92	1	0,92	0,68
1506	20.0	1	0	1	0	0	0,88	0,2	0	0,04	0,08	0,04	0,08	0,2	0,24	0,04	0	0	0,36	0,12	0,92	0,76	0,48	0,6	0,56	0,76
1609	20.0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
1610	20.0	1	1	1	0,88	0,8	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
1712	20.0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
1715	20.0	1	1	1	0,28	0	1	1	1	1	1	1	0,92	0,36	1	1	1	1	1	1	0,96	0,72	1	1	1	1
1810	20.0	1	0,12	0	1	1	1	1	1	1	0,24	0	0,96	0,76	1	0,76	1	1	0	0	0,84	0,92	1	1	0,52	0,36
1624	20.1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
1707	20.1	1	1	1	1	1	1	1	1	1	1	0,96	1	1	1	1	1	1	1	1	1	1	1	1	1	1
1619	20.2	1	0,92	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
1631	20.2	1	1	1	1	1	1	1	1	1	0	0,44	1	1	1	1	1	1	1	0,64	1	1	1	1	1	1
1802	20.2	1	1	0,68	1	1	1	1	1	0,92	1	1	1	1	1	0,92	1	1	1	1	1	1	0,68	0,4	1	1
1602	20.3	1	0,76	0,48	1	1	0,92	1	1	0,96	1	1	1	1	1	1	1	1	1	1	0,36	1	1	1	1	1
1612	20.3	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
1801	20.3	1	1	1	1	1	1	0,92	1	1	1	1	1	1	1	0,92	0,84	0,96	1	0,68	0,72	1	1	0,88	1	1
1614	20.5	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
1605	20.6	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0,88	1	1	1	1	1	1	1
1703	20.6	1	1	1	0,92	0,08	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
1805	20.6	1	1	1	1	1	1	1	1	1	1	1	1	0,96	1	1	1	1	1	1	1	1	1	1	1	1
1621	20.7	1	1	1	1	1	1	1	1	1	1	1	0,96	1	1	1	1	1	1	1	1	1	1	1	1	1
1623	20.7	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0,88	1	1	1	1	1	1	1
1625	20.7	1	1	0	1	0,76	1	1	1	1	1	1	1	1	1	1	1	1	1	0,96	1	1	1	1	0,04	0,96
1705	20.7	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0,88	1	1	1	1	1	0,88	0,8
1804	20.7	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
1814	20.7	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
1608	20.8	1	1	1	1	1	1	1	1	1	1	0,88	1	1	1	1	1	1	1	0,96	1	1	1	1	1	1
1620	20.8	1	0,84	1	1	1	1	1	1	1	0	0,32	1	0,76	1	1	1	1	0,6	0,2	0,96	1	1	1	1	1
1719	20.8	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
1627	20.9	1	0,96	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
1629	20.9	1	1	1	1	1	1	1	1	0,4	0,96	0,96	1	1	1	1	1	1	0,72	1	1	1	1	1	0,96	1
1630	20.9	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0,68	1	1	1	1	1	1
1710	20.9	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0,72	0,88
1711	20.9	1	0,96	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
1501	21.0	1	0,24	0,12	0	0	0	0	0	0	0,04	0	0	0	0,48	0	0	0	0	0	0	0,24	0	0,48	0	0
1626	21.1	1	1	0,84	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0,92	1	1	1	1	0,96	1
1622	21.2	1	0,08	0,92	1	1	1	1	1	1	1	1	1	1	0,36	1	0,88	0,44	1	0,8	1	1	1	1	0,68	0
1706	21.3	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
1708	21.3	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
1718	21.3	1	1	1	1	0,96	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0,96	1	1
1915	21.3	1	0	0,52	0,92	0	0	0	1	1	0	0,32	0,52	0	0	0,28	0,04	0,48	0,4	0	1	0	0	0	1	1
1604	21.5	1	0	0	0,88	0,88	0	0	1	1	0,96	0,36	1	0,4	0,68	0,12	0,56	0,08	0,64	0,8	1	0,68	0	0,12	0,96	0,84
1709	21.6	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0,84
1803	21.7	1	0,96	0	0	0,88	1	1	1	0,96	1	0,72	1	1	1	1	1	1	1	1	1	1	1	1	1	1
1816	21.7	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0,84
1908	21.7	1	0	0	0	0	0	0	0	0	0,04	1	0	0,04	0,12	0	0,04	0	0,04	0,08	0	0	0,04	0	0	0
1821	22.0	1	1	1	0,24	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
1701	22.1	1	1	1	1	1	1	1	1	1	0,8	1	1	1	1	1	1	1	0,92	1	1	1	0,68	1	1	1
1813	22.1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
1819	22.4	1	1	0,84	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0,88	1	1
1815	22.6	1	1	1	1	1	1	1	1	1	1	1	0,92	1	1	1	1	1	1	1	0,8	1	1	1	1	1
1822	22.6	1	1	1	0	0	1	1	1	1	1	0,32	1	0	1	1	1	1	1	1	0,96	0	1	1	1	1
1818	22.7	1	0	0,36	1	1	1	0,96	1	1	0,96	1	1	1	1	1	1	1	1	0,96	1	1	1	1	1	1
1824	22.8	1	1	1	1	1	0,88	0,8	1	1	1	1	1	1	1	1	1	1	0,92	1	1	1	1	1	1	1
1823	22.9	1	1	1	1	1	1	0,16	1	0,04	1	1	1	1	1	1	1	1	1	1	1	1	0,96	1	0,92	1
1820	23.9	1	1	1	1	1	0,92	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
F1 Score			0.74	0.76	0.76	0.78	0.80	0.81	0.82	0.79	0.78	0.83	0.85	0.84	0.86	0.83	0.83	0.82	0.80	0.81	0.85	0.86	0.84	0.83	0.79	0.79

Key to figure 8		
Machine learning type abbreviation:		**Explanation**:
1	b3_reflection1_nonTruncated	Complete A-Scan Reflection signals from the 1st Ultrasound Probe, using 3-cycle burst excitation signals.
2	b5_reflection1_nonTruncated	Complete A-Scan Reflection signals from the 1st Ultrasound Probe, using 5-cycle burst excitation signals.
3	b3_reflection2_nonTruncated	Complete A-Scan Reflection signals from the 2nd Ultrasound Probe, using 3-cycle burst excitation signals.
4	b5_reflection2_nonTruncated	Complete A-Scan Reflection signals from the 2nd Ultrasound Probe, using 5-cycle burst excitation signals.
5	b3_reflection3_nonTruncated	Complete A-Scan Reflection signals from the 3rd Ultrasound Probe, using 3-cycle burst excitation signals.
6	b5_reflection3_nonTruncated	Complete A-Scan Reflection signals from the 3rd Ultrasound Probe, using 5-cycle burst excitation signals.
7	b3_reflection4_nonTruncated	Complete A-Scan Reflection signals from the 4th Ultrasound Probe, using 3-cycle burst excitation signals.
8	b5_reflection4_nonTruncated	Complete A-Scan Reflection signals from the 4th Ultrasound Probe, using 5-cycle burst excitation signals.
9	b3_transmission1_nonTruncated	Complete A-Scan Transmission signals from the 1st Ultrasound Probe, using 3-cycle burst excitation signals.
10	b5_transmission1_nonTruncated	Complete A-Scan Transmission signals from the 1st Ultrasound Probe, using 5-cycle burst excitation signals.
11	b3_transmission2_nonTruncated	Complete A-Scan Transmission signals from the 2nd Ultrasound Probe, using 3-cycle burst excitation signals.
12	b5_transmission2_nonTruncated	Complete A-Scan Transmission signals from the 2nd Ultrasound Probe, using 5-cycle burst excitation signals.
13	b3_transmission3_nonTruncated	Complete A-Scan Transmission signals from the 3rd Ultrasound Probe, using 3-cycle burst excitation signals.
14	b5_transmission3_nonTruncated	Complete A-Scan Transmission signals from the 3rd Ultrasound Probe, using 5-cycle burst excitation signals.
15	b3_transmission4_nonTruncated	Complete A-Scan Transmission signals from the 4th Ultrasound Probe, using 3-cycle burst excitation signals.
16	b5_transmission4_nonTruncated	Complete A-Scan Transmission signals from the 4th Ultrasound Probe, using 5-cycle burst excitation signals.

17	b3_transmission1_nonTruncated_FFTs	Fast Fourier Transformed A-Scan Transmission signals from the 1st Ultrasound Probe, using 3-cycle burst excitation signals.
18	b5_transmission1_nonTruncated_FFTs	Fast Fourier Transformed A-Scan Transmission signals from the 1st Ultrasound Probe, using 5-cycle burst excitation signals.
19	b3_transmission2_nonTruncated_FFTs	Fast Fourier Transformed A-Scan Transmission signals from the 2nd Ultrasound Probe, using 3-cycle burst excitation signals.
20	b5_transmission2_nonTruncated_FFTs	Fast Fourier Transformed A-Scan Transmission signals from the 2nd Ultrasound Probe, using 5-cycle burst excitation signals.
21	b3_transmission3_nonTruncated_FFTs	Fast Fourier Transformed A-Scan Transmission signals from the 3rd Ultrasound Probe, using 3-cycle burst excitation signals.
22	b5_transmission3_nonTruncated_FFTs	Fast Fourier Transformed A-Scan Transmission signals from the 3rd Ultrasound Probe, using 5-cycle burst excitation signals.
23	b3_transmission4_nonTruncated_FFTs	Fast Fourier Transformed A-Scan Transmission signals from the 4th Ultrasound Probe, using 3-cycle burst excitation signals.
24	b5_transmission4_nonTruncated_FFTs	Fast Fourier Transformed A-Scan Transmission signals from the 4th Ultrasound Probe, using 5-cycle burst excitation signals.
F1 Scores:		
1	Score > 0.8	
0	Score < 0.7	
0.8	0.7 ≤ Score ≤ 0.8	

Figure 8 - Testing the different signals collected using the CatBoost technique with 10,000 Iterations

Figure courtesy of the Fraunhofer Institution.

4.2.1 The ultrasound device classification results

Figure 9 shows the results of the most accurate method, the CatBoost technique, for the 'b3_transmission3_nonTruncated' signals. This is a depiction of the ultrasound device classification result for each individual compared with the ‘truth’ (again determined by the bone age, when available, or chronological age). Where the f1 score for that individual was higher than 0.5 in every testing of the ultrasound device then the result was classified as correct, for example, an adult testing with an f1 score of 0.8 would be classified correctly as an adult and thus the box is highlighted green (green light for adult status). For f1 scores of less than 0.5 the result was classified falsely by the ultrasound device, for example, an adult testing with an f1 score of 0.48 would be classified incorrectly as underage with a red highlighted box (red light for underage status).

Age (years)	9.3	9.5	9.6	10.3	10.5	11.0	11.0	11.0	12.0	12.3
Truth	0	0	0	0	0	0	0	0	0	0
Device Result	0	0	1	0	0	0	0	0	0	0
Age (years)	12.5	12.5	12.6	12.8	13.0	13.3	13.3	13.6	13.8	14.0
Truth	0	0	0	0	0	0	0	0	0	0
Device Result	0	0	0	0	0	0	0	0	0	0
Age (years)	14.0	14.9	15.0	15.0	15.0	15.0	15.0	15.0	15.1	15.5
Truth	0	0	0	0	0	0	0	0	0	0
Device Result	0	1	1	1	0	0	0	0	1	0
Age (years)	15.6	15.6	16.0	16.0	16.0	16.0	16.6	17.0	17.0	17.3
Truth	0	0	0	0	0	0	0	0	0	0
Device Result	1	0	0	0	0	0	0	0	1	1
Age (years)	17.5	17.7	18.0	18.0	18.1	18.2	18.3	18.6	18.6	18.7
Truth	0	0	1	1	1	1	1	1	1	1
Device Result	0	1	1	1	1	1	1	1	1	1
Age (years)	18.8	19.0	19.0	19.1	19.2	19.2	19.5	19.6	19.6	19.6
Truth	1	1	1	1	1	1	1	1	1	1
Device Result	1	1	1	1	1	1	0	1	1	1
Age (years)	19.6	19.6	19.7	19.8	19.9	20.0	20.0	20.0	20.0	20.0
Truth	1	1	1	1	1	1	1	1	1	1
Device Result	1	1	1	1	1	0	0	1	1	1
Age (years)	20.0	20.0	20.1	20.1	20.2	20.2	20.2	20.3	20.3	20.3
Truth	1	1	1	1	1	1	1	1	1	1
Device Result	1	1	1	1	1	1	1	1	1	1
Age (years)	20.5	20.6	20.6	20.6	20.7	20.7	20.7	20.7	20.7	20.7
Truth	1	1	1	1	1	1	1	1	1	1
Device Result	1	1	1	1	1	1	1	1	1	1
Age (years)	20.8	20.8	20.8	20.9	20.9	20.9	20.9	20.9	21.0	21.1
Truth	1	1	1	1	1	1	1	1	1	1
Device Result	1	1	1	1	1	1	1	1	0	1
Age (years)	21.2	21.3	21.3	21.3	21.3	21.5	21.6	21.7	21.7	21.7
Truth	1	1	1	1	1	1	1	1	1	1
Device Result	0	1	1	1	0	1	1	1	1	0
Age (years)	22.0	22.1	22.1	22.4	22.6	22.6	22.7	22.8	22.9	23.9
Truth	1	1	1	1	1	1	1	1	1	1
Device Result	1	1	1	1	1	1	1	1	1	1

Key	
Classification: red (<18 years)	0
Classification: green (≥18 years)	1

Figure 9 - The classification results for each participant using the CatBoost technique for the 'b3_transmission3_nonTruncated' signals, colour-coded to represent the classification of each individual by the ultrasound device

4.3 Reliability assessment and means of variability of the ultrasound device

4.3.1 Accuracy

The overall likelihood of the participant being correctly categorised by the ultrasound device: 0.87 [0.80, 0.92].

4.3.2 Sensitivity

The sensitivity of the ultrasound device in detecting underage status lies at 0.79 [0.64, 0.89].

This means that there is a 79 % likelihood that an underage individual is correctly classified with a red light by the ultrasound device.

4.3.3 Specificity

The specificity of the ultrasound device in detecting underage status lies at 0.91 [0.83, 0.96].

This means that there is a 91 % likelihood that an adult is correctly classified with a green light by the ultrasound device.

4.3.4 Positive predictive value (PPV)

The positive predictive value is 0.83 [0.68, 0.92].

This defines the relative frequency of underage girls in the total number of participants classified with a red light by the ultrasound device.

4.3.5 Negative predictive value (NPV)

The negative predictive value is 0.89 [0.80, 0.94].

This defines the relative frequency of adult women in the total number of participants classified with a green light by the ultrasound device.

4.4 Statistical significance assessment

4.4.1 P-value

The ultrasound device effectively categorised the participants into underage or mature. This result was shown to be statistically significant with a p value $<10^{-3}$.

4.4.2 Identification of confounding factors

The following potential confounding factors were statically assessed to measure their influence on the ultrasound device categorisation: height, weight and BMI, and their respective percentiles. Height proved not be statistically significant. However, weight and BMI, and their percentiles, proved to have a statistically significant influence on the outcome, with p values of 0.004 for both factors.

Factor	**P Value**
Height	0.353
Weight	0.004
BMI	0.004

Table 2 - Confounding factors and their p values

4.5 Probability of being classed as an adult

Using logistical regression, the probability of being classified as an adult and receiving a green light from the ultrasound device was calculated for a woman of 18 years old at 0.70.

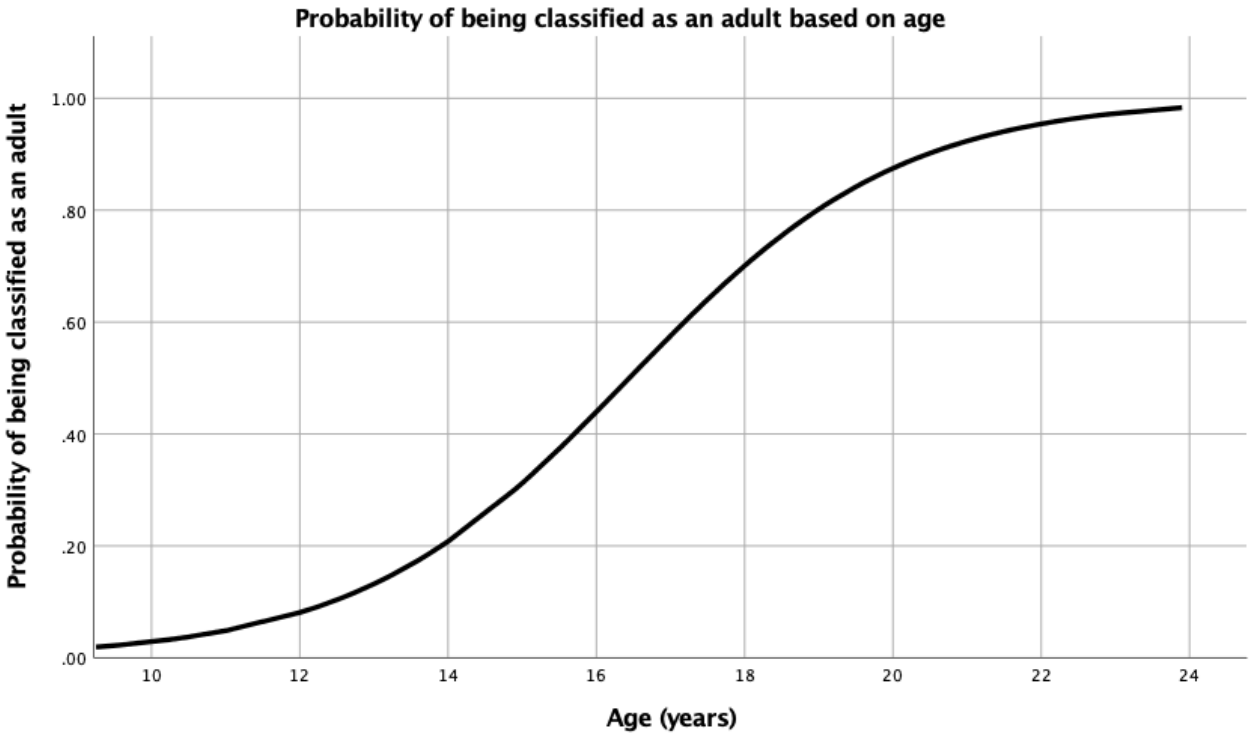

Figure 10 - The probability of being classified by the ultrasound device as an adult based upon the age in years

5 Discussion

Firstly, I would like to explore the facts and figures behind the wider project supporting this study, as well as the reasoning behind the choices made towards the project outcome of creating a portable, non-invasive screening tool for use in the fight against human trafficking on the international borders. This will include consideration of other techniques for age assessment beside bone age assessment and ultrasound, whilst also highlighting the conditions causing potential discrepancy between chronological and bone age.

Secondly, I will assess the achievement of the primary objective addressed in this study, before going on to outline the features of other similar devices available on the medical market and make a comparison with our device.

Finally, I will consider the secondary objective, usability and practicality in the field, looking at the limitations of our device and planned improvements. I will then explore the limitations of this study. In conclusion, I will discuss the implications this study has for the field of ultrasound in medicine and forensics, including the further research planned and required in this area.

5.1 Human trafficking statistics

In 2018, only 17 % of victims of human trafficking for prostitution were identified by the police on their own initiative, a further 38 % were identified by the police after some form of tip-off. The remaining 45 % were identified when the victim presented themselves to the police or to another trained individual [3].

According to the European Commission, “Early identification of victims is crucial to promptly assist, support and protect victims of trafficking in human beings and enables police and prosecution authorities to better investigate and punish traffickers. Frontline officers, such as border guards, police officers, social workers and inspector services are crucial in this respect. The involvement of civil society organisations in the identification of victims and their referral for support is a challenge, just as the lack of training of professionals in cross-border victims’ support cases.” [12].

As stated by the German Federal Criminal Office, “During the first contact with an underage victim, it is usually difficult to identify a case of exploitation because either the victim does

not recognise themselves to be a victim, they are threatened into silence by the perpetrator, or they are ashamed of what has happened to them. The victims are often unwilling or unable to press charges because they are afraid of the police and the legal consequences or they are prevented by the physical and psychological abuse they have endured." [3].

Looking at this data and comments from the experts, we see that very few victims of human trafficking are identified by the police without insider-knowledge or the victim themselves coming forward. With the likelihood of underage victims coming forward being lower than that of adults, it is clear why an intervention to improve the detection of underage victims by the police is necessary. Creating a screening tool that can be deployed easily on the borders aims to provide the border control staff with another 'tip-off' as to which individuals may be being trafficked, as well as providing trafficked individuals with an opportunity to reveal their situation in a safe environment. Tools such as the American 'Trafficking Victim Identification Tool' [40], with or without an additional detailed medical and physical examination could then be employed to further screen those women and girls flagged up by the ultrasound device categorisation.

5.2 Assessing existing methods of age determination and their appropriateness for this project

In order to develop an appropriate assessment tool, we looked at possible methods for medical age assessment and explored the suitability of these techniques for a portable non-invasive device.

5.2.1 Existing methods in forensic medicine and paediatric endocrinology

The current standardised methods used for medical age assessment include medical history, physical examination and bone age assessment through the use of wrist x-ray, orthodontic panorama x-rays, and, if indicated by complete formation of the hand bones on x-ray, a thin-slice CT or x-ray of the medial clavicular epiphyses [33].

Medical history and physical examination

The medical history should include questions about developmental milestones, illness and medications that could have influenced growth and puberty, as well as a detailed family

history including information about ethnicity and poverty markers. In section 5.2.4., I discuss medical conditions and medications that can influence growth and puberty.

The physical examination should be conducted by a trained physician and include anthropometric data, such as height, weight, BMI, as well as an assessment of pubertal development using a tool such as Tanner staging [20] [21]. The physical examination should also take into account any physical features in keeping with endocrine or other disorders, for example goitre, exophthalmos, virilisation in girls, syndromic features (e.g. Down Syndrome) [33].

Both a medical history and physical examination require an appropriate space, sufficient time and a trained professional, as well as the participant's consent. This is, therefore, not feasible for use as a quick screening tool at the border.

Invasive bone age assessment techniques

Wrist x-ray

This method is used in both forensic medicine and paediatric endocrinology as discussed in the introduction. The x-rays are compared with a standardised atlas such as the Greulich and Pyle or Tanner and Whitehouse atlases. The GP-Method takes a subjective, qualitative approach in comparing the x-ray image with a picture atlas [16]. On the other hand, the TW2-Method takes a more systematic approach, using a score-system to assess the development of 20 different bones within the hand and wrist [37]. The TW2-Method is more flexible and precise in comparison to the GP-Method, using a mathematical basis for the analysis. However, this method is much more time consuming and, therefore, rarely used in clinical practice [23]. For both methods an experienced clinician, usually a trained radiologist or paediatric endocrinologist, is required to assess the x-ray. For this study the GP method was chosen as this is the method routinely used by the clinicians in Homburg University Medical Centre and required no additional training or alteration to the daily clinical practice.

The average discrepancy between the bone age and chronological age in healthy individuals has been shown to differ based on the sex, ethnicity and age group of the individual. The maximum range for girls occurs at age thirteen years where a bone age discrepancy of up to fourteen months is considered within the normal limits [16].

Computerised assessment of x-rays is becoming more popular, one example being the BoneXpert from Visiana, which analyses digital x-rays using both the GP-Method and the TW2-Method more time efficiently than a clinician [22] [38]. These tools are however still relatively expensive (financial quote on 06.03.2018 for BoneXpert: 1,000 Analysis for 6,750 Euro) which is why the traditional method using the manual GP atlas was chosen.

Orthodontic panorama x-rays

The stage of dental development seen in orthodontic panorama x-rays are compared to a standardised chart, such as Schour and Massler [24] or the teeth are rated on a standardised scale, such as in the Demirjian and Goldstein's method [8]. Rai et al. found a strong correlation between the dental maturity and the skeletal bone age in their study of 150 healthy children aged 5 to 15 years [29].

An orthodontic panorama x-ray delivers a dose of 0.026 mSv effective radiation [33].

Thin-slice computer tomography (CT) of medial clavicular

Schmeling et al. provided studies into the time frame for ossification of the medical clavicular epiphyseal cartilage in conventional radiography (PA and additional lateral view chest x-rays), categorising the development into 5 separate stages [31]. Further studies have shown the reliability of thin-slice CT of the medial clavicular to be superior to plain x-ray [35]. Wittschieber et al. used a combination of the Schmeling et al. 5 Stages and the Kellinghaus et al. sub-stages [18] to report thin-slice CT images narrowing the age estimation of individuals compared to the x-ray estimations [43] [44]. It is worth noting that a thin-slice CT of the medial clavicular is only performed during forensic age estimation of individuals around the age of 17 years and older, when the ulnar and radial epiphyses are closed on wrist x-ray. The amount of radiation required for this CT scan is around 0.4 mSv, 400 times the dosage of radiation required for one wrist x-ray [33].

If there is no medical indication for these invasive tests, then a clear legal indication must be present, and the examination authorised by the court of law. Current scenarios in which authorisation for an x-ray to assess age without a medical indication may be given under German law include: criminal proceedings for defendants, family court proceedings, legal procedures relating to residency or eligibility for social benefits. In order to protect vulnerable young people during legal proceedings Schmeling et al. conclude that the 'minimum-age

concept' is appropriate when using the current above-listed techniques to assess an individual's chronological age for legal reasons in order to prevent the erroneous classification of minors as legal adults [33].

As x-ray and CT examinations not only involve the use of ionising radiation, but also require legal authorisation when not being used for specific medical purposes, they are inappropriate for consideration when designing a screening tool for wide use among the general public at border control. The machinery required is also too large and requires too much energy to be used in the development of a portable screening tool.

The use of hand x-rays taken for medical purposes in this study, however, serves as a quality control mechanism for participants with potential discrepancies between their chronological and radiological bone age due to medical conditions.

5.2.2 Experimental methods of age determination

DNA methylation

During the natural ageing process DNA changes occur. Some of these changes include methylation of the DNA at certain locations within the genome [42]. Weidner et al. used this epigenetic age-signature to estimate the biological age of an individual from their blood to within 5 years of their chronological age. Similarly, Zbiec-Piekarska et al. were able to correctly predict chronological age to within 7 years from blood samples examining DNA methylation of the ELOVL2 marker [45].

Obtaining DNA for examination raises possible ethical and legal complications, including permission from individuals for obtaining and storing their DNA. The resulting wide age span reported, the invasiveness of the test and the time required to achieve the results rule this method out as a screening tool for border control.

Combining methods using artificial intelligence

Using machine learning techniques to combine various methods of age assessment in order to improve the outcome accuracy has been trialled by Dallora, et al. in 2020 combining MRI assessment of multiple regions of interest (radius, distal tibia, distal femur and calcaneus) with anthropological details (height and weight), as well as self-reported physical

examination, lifestyle and ethnicity information (Tanner stage, level of physical activity, parental origin and childhood residency type). This study looked at various machine learning techniques to process this data in order to categorise individuals into adult vs. minor and then to approximate into one of 8 age categories between ages 14 to 21 years. Classification of the individuals as adult or minor produced accuracies of 0.90 and 0.84 for male and female subjects respectively [7]. These results are similar to the accuracy achieved with our ultrasound device.

This study compliments our use of artificial intelligence within the screening tool demonstrating the success of an artificial network in dividing individuals into adult and underage categories based upon their anthropological data and MRI scan results. Completing multiple MRI scans alongside a questionnaire is, however, not an appropriate technique for a screening tool due to the time, cost and practicality.

ECG assessment using artificial intelligence

ECG traces are known to demonstrate sex and age-related changes. Attia et al. used convolutional neuronal networks to assess 12-lead ECGs to predict sex and age in a large adult population. Sex was correctly classified with an accuracy of 90.4 % whilst age could be determined to the nearest 7 years in healthy individuals whilst inaccuracies (>7 years discrepancy) were linked to individuals with a higher incidence of cardiovascular comorbidities. Children were not assessed in this study [1].

This study provides an interesting concept using ECG, which is a non-invasive, cheap, quick and a relatively easy to learn technique, alongside artificial intelligence to determine age. The resulting accuracy of ± 7 years in adults, and the lack of data in children, however, renders the technology as insufficient for a screening tool aimed at determining adult maturity. The practicalities of performing 12-lead ECGs at border control are also not in keeping with the ease-of-performance desired in a quick screening tool.

5.2.3 Non-invasive techniques to assess bone age

Magnetic resonance imaging (MRI)

MRI techniques as noted in the introduction, show promising results in terms of accuracy for bone age assessment when assessing adolescents [10]. This technique can also be applied to the wrist and compared with plain radiographs. The use of MRI, however, requires very expensive and large equipment, in the form of an MRI scanner, which also requires a large and reliable power source in order to function. The surroundings must be appropriate for the scanner, including no loose metal or sensitive magnetic devices nearby. The idea of creating an efficient, portable, economical MRI scanner for the use at border control does not appear to be feasible.

Ultrasound

Ultrasound proved to be the most appealing technology for the development of a screening tool for age determination because it is non-invasive, requires a low-power input and is safe to use.

5.2.4 Medical conditions known to affect bone age

To create an effective screening tool which assesses chronological age based on the bone age of an individual it is important to understand the difference between bone age and chronological age and how these can be affected.

There are various medical conditions that can be diagnosed based upon the discrepancy between chronological and bone age. There are also certain metabolic states and medications which are known to affect an individual's bone age. It is important to be aware of these conditions in order to recognise their potential effects on the outcome of this study.

The medical conditions and medications associated with an accelerated bone age are:

Endocrine conditions	Constitutional tall stature Hyperthyroidism Precocious puberty Premature adrenarche
Oncological conditions	Ovarian tumour Leydig cell tumour Germ cell tumour Testicular tumour Brain tumour
Syndromes	McCune-Albright syndrome Sotos syndrome Beckwith-Wiedemann syndrome
Other medical conditions	Brain malformations (leading to precocious puberty) Obesity
Medications and supplements	Oestrogen Oral contraceptives Testosterone preparations Lavender (oestrogen-like effect) Tea tree oil (oestrogen-like effect)

Table 3 - Medical conditions and medications associated with accelerated bone age [6]

The physiology underlying the majority of these conditions results from the premature presence of adult sex hormones (oestrogen and testosterone) which accelerates the bone maturation process.

The medical conditions and medications associated with a delayed bone age are:

Endocrine conditions	Constitutional delay of growth and puberty Hypothyroidism Growth hormone deficiency Panhypopituitarism Hypogonadism Cushing disease
Chronic Illnesses	Congenital heart disease Chronic kidney disease Juvenile idiopathic arthritis Inflammatory bowel disease Coeliac disease Cystic fibrosis Severe asthma Immunodeficiency states – including HIV infection, active tuberculosis Anorexia
Syndromes	Trisomy 13, 18 and 21 Ullrich-Turner syndrome Klinefelter syndrome Russell-Silver syndrome
Other medical conditions	Malnutrition Neglect and abuse
Medications and supplements	Glucocorticoids Amphetamine and dextroamphetamine GnRH analogues Aromatase inhibitors

Table 4 - Medical conditions and medications associated with delayed bone age [6]

In this study participants with these conditions were accounted for by use of a recent hand x-ray to verify their appropriate bone age category.

5.3 Achievement of objectives

Primary aim: to test the developed ultrasound device on young females and assess its ability to determine the maturity status of these individuals.

This study has shown that the ultrasound device would correctly identify 87% of female individuals as adult or underage. 79% of underage girls would be correctly classified red by the ultrasound device whilst 89% of adults would be correctly classified green. The 1-NPV for maturity detection is 11%.

Theoretical data in real world terms:

The study results can be interpreted to apply them to the real-world scenario of human trafficking and the implementation of the ultrasound device for screening purposes on international borders. Currently, of those individuals testing as green, 11% would in fact be underage, thus having been falsely classified as adults. This 1-NPV percentage is important when assessing this screening tool as it identifies the proportion of false negatives, in other words, the number of underage girls who would go undetected when screened using the ultrasound device currently. With further input of data into the machine learning algorithm this number would be expected to reduce, ensuring that fewer girls are falling through the screening system.

5.4 Comparison with existing ultrasound devices

The two other ultrasound devices currently on the medical market for the assessment of bone age are the Sunlight BonAge [25] and the BAUS [28], both have a similar but fundamentally different desired outcome when compared to our device. Both these devices aim to provide an accurate bone age assessment in children based on the ultrasound measurements. Both have been trialled and compared against the radiological bone age assessment using the Greulich and Pyle atlas method. Both devices show promising results within the small participant numbers tested. However, in order to provide a bone age assessment with an age in years and months as the outcome, both devices have only been tested in children under the age of 18 years old. There is no data for adults who should no longer have an open growth plate.

The key features of each device are listed for comparison in the following table:

Device	Manufacturer	Measurement Location	Ultrasound Probe & Data collection	Time per Scan	Analysis Method	Outcome	Accuracy
BonAge	Sunlight Medical Ltd., Israel	Distal radial and ulna epiphysis	• Static Probe • Transmission Data • Speed of sound	5 min	Sex- and ethnicity-based algorithm	Bone age in years and months	1.0±0.8 years
BAUS	SonicBone, Israel	1. Distal radius and ulna secondary ossification centres 2. Distal metacarpal epiphyses 3. Along the proximal third phalanx shaft, growth plate, and epiphysis	• Static Probe • Transmission Data • Speed of sound (m/sec) and ATN (decay rate).	3 min	Sex-based 'conversion equation' (according to data retrieved from the analysis of 100 subjects, including SOS, ATN, and the manual reading by the GP method)	Bone age in years and months.	No significant difference between GP bone age and BAUS bone age.
Our device	IBMT St. Ingbert, UKS Homburg, Germany	Distal radial and ulna epiphysis	• Moving Probe • Transmission and reflection data • Speed of sound	1 min	Machine learning	Green light ≥18years Red light <18years	87%

Table 5 - Comparison of ultrasound devices assessing bone age currently on the market [25, 28]

Below I consider each feature in turn and compare the different devices. Any comparison I make will be in the context of the principal aim of this study to create a screening device to provide a robust indication of maturity.

5.4.1 Measurement location

Both our device and the BonAge device take measurements at the wrist, accounting for the radial and ulnar epiphyseal plates [25]. The BAUS takes three separate measurements from the wrist, metacarpals and phalanges. The gold standard for radiological bone age assessment, Greulich and Pyle, takes into account each of the bones within the hand and wrist [16]. The radial and ulnar epiphyses are used for the initial generalised year rating before the other hand bones are examined to more accurately pinpoint the bone age to within months. It is, therefore, worth considering how accurately a bone age assessment of purely the radial and ulnar bones fairs in comparison to one of the long and short bones of the wrist as well as the finger bones. This is demonstrated in the BAUS study, the bone age using all three parameters appears to be more accurate than the measurements taken only from the radius and ulnar bones ($p= 0.20$, $p= 0.47$) [28].

When attempting to assess maturity, however, it is sufficient to assess the radial and ulnar epiphyses, as an accuracy in terms of months above or below 18 years of age is not required. For this reason, our device only takes one set of measurements.

5.4.2 Ultrasound probe and data collected

Both the BonAge and BAUS devices use static ultrasound probes, requiring accurate placement of the participants wrist (± fingers) in the device [25] [28]. Mentzel, et. al. commented regarding the Sunlight BonAge device, “since imaging is not included in the ultrasonic measurement, the path of ultrasound waves is not known in detail.” [25]. As our participants range in age and size, it is expected that the distance of the radial and ulnar epiphyses from the surface anatomy of the ulnar process will vary for each individual.

By using a motorised probe, we are able to measure along the forearm, thus extending the bony field measured, and reducing errors in detection of the growth plate, such as the growth plate being missed.

All three devices measure ultrasound transmission data, through the bone or growth plate. Our device additionally measures the reflection ultrasound data. By recording not only the transmission but also the reflection data, the device is able to measure the speed of sound travelling perpendicularly through the bone and growth plate, whilst also measuring the number of ultrasound waves reflecting back off the bone and growth plate surface. The data has shown that this reflection data is key in the robust detection of a growth plate. The younger the participant, and therefore the wider the growth plate, the higher the change in reflection wave data. The assumption here being that more multi-directional reflection occurs where the bone transitions at the edge of the growth plate, this can be detected by the change in reflection waves.

5.4.3 Time per scan

Our ultrasound device requires approximately one minute for the four motorised cycles along the forearm recording the ultrasound measurements. The Sunlight BonAge requires around 5 minutes per measurement [25]. The SonicBone BAUS takes measurements at three different anatomical sites, requiring a stated three minutes per scan [36]. Although the time frame required for measurements using each of these devices is short, the quicker a screening tool can achieve its results the more effective its implementation.

5.4.4 Analysis method

The BonAge device measures the speed of sound of the ultrasound waves before analysing the data with a set algorithm programmed based upon the participants sex and ethnicity, with ethnicity-based algorithms available for Caucasian and Chinese individuals [25]. The BAUS measures speed of sound, as well as the decay rate of the ultrasound waves, analysing the data using an algorithm incorporating both these measurements alongside the participant’s sex. No adjustments are made for ethnicity [28].

Our device measures both the transmission and reflection ultrasound waves using machine learning to analyse the data. By using machine learning the system is able to learn from each participants' data set, allowing the potential for improved detection rates as the data pool increases, and reducing systemic bias inherent in the use of static algorithms.

Our Colleagues from the IBMT, Sankt Ingbert, first explored classical signal processing to analyse the ultrasound data but this provided only limited success. They applied

dimensionality reduction techniques to the individual A-scans confirming the initial finding that classical signal processing of individual scans through the bone, or growth plate, were insufficient to achieve a robust outcome from the one scan. The team then trialled various machine learning techniques to identify a more effective way of analysing the various A-scans from each subject. The machine learning methods tested include: fully convolutional networks, multilayer perceptrons, residual networks (ResNets) and radial basis function neural networks [2]. Out of these techniques, a ResNet approach proved most accurate with an F1-score of 84 %.

5.4.5 Outcome

As the outcome of their ultrasound scan, both the BonAge and BAUS devices generate a bone age in years and months. Our device does not provide a calculated bone age but instead provides a red or green light. This traffic light system is designed to be universally understood and allow its use and interpretation by non-healthcare staff with little training required.

5.4.6 Accuracy

Both the BonAge and BAUS devices show accuracy levels similar to those for a calculated bone age using the GP x-ray method. This can be up to two years difference in relation to the chronological age to two standard deviations.

5.4.7 Similarities

All three of the ultrasound devices share the following similarities: assessment of the radial and ulnar epiphyses using ultrasound, no ionising radiation, no medical expertise required.

5.5 Overall assessment of the ultrasound device

After one introductory session from the IBMT colleagues, the device proved easy to use. The correct initial positioning of the hand and wrist required a little practise to achieve, however, was easily mastered, relying on the ultrasound demarcation and obvious anatomical structures of the wrist to aid positioning. The measurements were then quickly taken by pressing the ‘start’ button on the touch-screen mobile computer device after having typed in the participant’s identification number. The ultrasound wave depictions on the tablet showed

clearly if the device was taking a reading or if there was a troubleshooting problem, whilst the motor noise and movement of the ultrasound probes relayed information about the functioning of the ultrasound device. The small blue light within the ultrasound device displayed the battery status clearly. After completion of the measurements the computer device prompted the user to save the data and then the next participant's measurements could then be taken.

The ultrasound device and its accompanying tablet are easily portable and can be lifted with one hand. It proved easy to clean with a small towel or tissue to remove excess ultrasound gel and could then be disinfected with appropriate disinfection wipes. The battery itself proved a little awkward to remove, this will be further discussed in the next section on battery life.

In conclusion, the device proved to be portable, easy to set up and to use with clearly marked buttons for each step and troubleshooting indicators. The possible improvements and shortcomings are discussed in the next section.

5.6 Ultrasound device improvements

Secondary outcome: to assess the practicality of the prototype device and to highlight areas for improvement.

During the use of the ultrasound device, various areas for improvement were identified and further work has since been carried out to address these areas before the next study.

5.6.1 Physical improvements

Battery life

The battery life of the prototype device is too short. The battery is rechargeable, however, on some occasions multiple battery changes were required during a measurement session. On average one charged battery would provide the energy for at least 5 scans. The battery itself was also slightly tricky to remove from the casing, requiring unscrewing of one screw (manually, no screwdriver required) to access the battery. The device does have a small light indicating that the battery has charge, although this does not indicate the level of charge

remaining. This would be a useful addition in order to be able to change an almost empty battery before a scan rather than having the battery run out mid-scan.

Casing size

The mobile metal casing attached to the ultrasound probes was created to be the same length as the body of the device itself. When moving, especially when scanning overweight participants, the metal casing would hit the larger part of the wrist and be obstructed from moving further back along the forearm. This occurred for a number of overweight participants causing the study to be aborted in these cases as the measurements could not be completed. This metal casing can easily be shortened to improve the range of the device allowing for the measurement of larger individuals (s. figure 11).

Elbow support

The device is designed to be small and compact to increase its portability. When measuring the individuals, however, it became apparent that an interchangeable elbow support is required to help the individual to maintain the correct wrist positioning comfortably for the duration of the measurements.

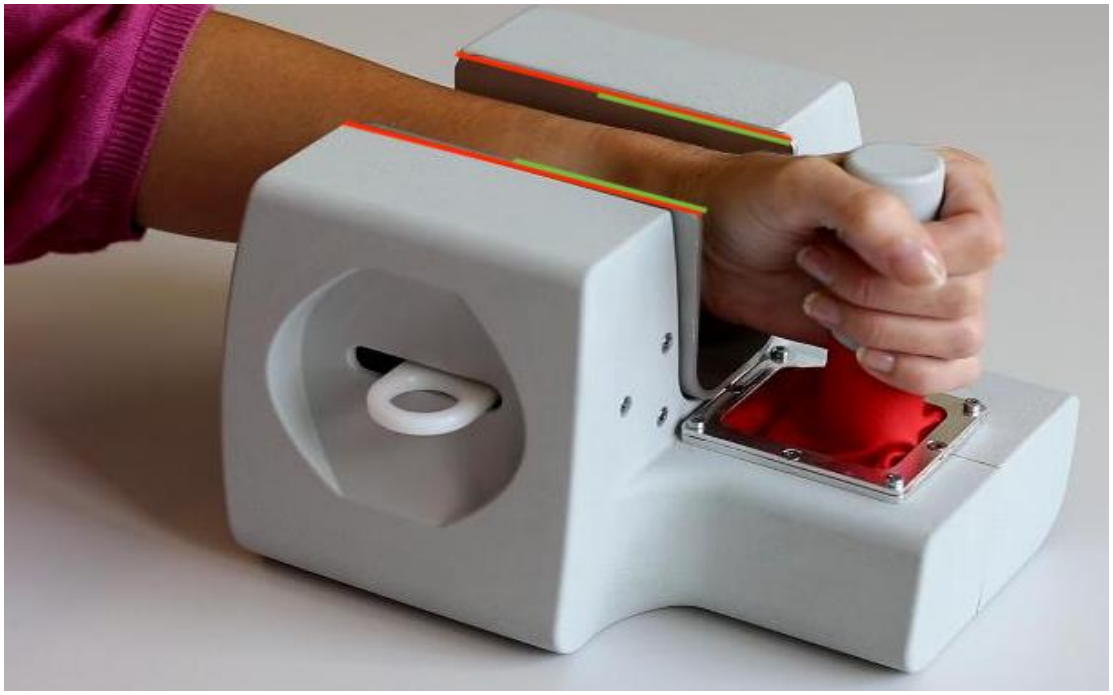

Figure 11 - The ultrasound device current casing size highlighted in red, planned reduced size highlighted in green [2]

5.6.2 System improvements

Amber traffic light

It is very difficult to enforce a strict binary classification system for a variable, such as age, which is a continuum. The borderline cases, such as 17.5-year-old girls who were classified by the device as adults, or 18.2-year-old women who received a red light (underage classification), have a significant influence on the overall results. In order to improve the accuracy of the classification and to reduce the number of underage individuals being falsely classified as adults it could be helpful to introduce an amber light to the traffic light system. This amber light would signify those individuals who do not clearly fall into one of the two groups, underage or adult. This would reduce the number of underage girls who are classified as adults with certainty, allowing for a buffer of 'inconclusive'. These individuals could then potentially be further questioned or examined to better ascertain their maturity status through a second screening process, rather than being given a direct green light.

5.7 Study limitations and improvements

5.7.1 Methodological limitations

Sample size

The sample size for this study was kept relatively small due to time and geographical constraints. As a pilot study, it was important to quickly ascertain the functional capabilities of the new ultrasound device in order to allow for further development and pave the way for further studies. Access to only one ultrasound device, and the limited battery life, meant that the number of participants was restricted during each session.

5.7.2 Study population

Patients and healthy volunteers

Geographical constraints played a role in the ability to recruit patients with a current x-ray of the left hand. The ethical permission for the study was granted by the Saarland medical ethics board for the state of Saarland. With the university medical centre being the only paediatric endocrinology department in Saarland, the pool of patients was limited. For this reason, the study was later extended to cover healthy volunteers without a confirmatory

bone age x-ray, allowing for an increase in participants, especially those in the 'mature' category.

The distribution of patients to healthy volunteers in each age category is disproportional as the paediatric endocrine department only treats patients up to the age of 18 years before their care is transitioned into the separate adult department. This may produce selection bias within the study population.

Ethnicity

The study population consisted mainly of white European girls and women in keeping with the relatively monomorphic population of Saarland, bearing in mind not all ethnicities were elicited. Although this population is not world representative, with only single representatives for some ethnicities (e.g., black African), it is relatively accurate for white European girls and women who, in 2018, accounted for 72,6 % of the female individuals trafficked into Europe [3].

However, 20,2 % of trafficked individuals were of African nationality [3]. These women were not well represented within this cohort. For this reason, further study including individuals from every continent and ethnicity is required.

Questionnaire inconsistencies

During the study the need for a questionnaire detailing past medical history arose with the introduction of healthy volunteers. For the original patient participants, the medical history was taken, with consent, from the medical notes during the regular medical appointment. For the first healthy volunteers, questionnaire A was developed, it was designed to include key necessary background information for the participants, without compromising compliance by making the questionnaire too long. After further consideration questionnaire B was introduced for the later participants. Questionnaire B was more comprehensive than version A. These improvements provided more background information about the participants, however, the late introduction meant that minimal analysis of this information (for example, participant ethnicity) was possible. This comprehensive collection of information should be included in further studies.

Confounding factors

The analysis showed weight and BMI to be potentially significant confounding factors in the ultrasound classification results. This is unsurprising as children grow with increasing age, meaning that adults should be heavier than children. Surprisingly, however, this did not appear to be the case for the participant's height. Another potential explanation would be that children with a higher weight and BMI are more likely to have an advanced bone age compared to their healthy counterparts due to the increased metabolism and sex hormones. This would mean that overweight children are more likely to be overestimated, leading them to be falsely classified as adults. The study population groups had similar mean height and weight percentiles, though the underage group had a higher average BMI percentile compared to the adult group, despite the average BMI being very similar for both groups. The relevance of confounding due to weight and BMI would need to be assessed during further studies with a larger study population.

There is, however, the potential that this confounding factor could prove beneficial for the assessment of maturity as providing the ultrasound programme with this data (height, weight and BMI of the individual) could improve the accuracy of the outcome. This would be interesting to assess in the future either as an additional part of the screening at the border for all participants, or possibly as part of a second examination for the participants registering in the ‘amber’ category.

Bone age vs. chronological age

The underlying assumption that bone age and chronological age correlate sufficiently to be used interchangeably is well established in current medical and legal age determination strategies [26]. Of the 20 individuals who provided a current x-ray examination for this study, all of them showed a bone age congruent with the chronological age classification of the individual, despite these being individuals with medical conditions known to cause acceleration or delay in bone age. For this study, ethical approval was only granted for the use of medically indicated x-ray studies on patients. This means that the congruency between the bone age of healthy individuals in relation to their chronological age could not be investigated. Should ethical approval be granted for further studies including a larger population with x-ray imaging it would be interesting to see how the ultrasound changes relate comparatively to x-ray changes and chronological age.

In this study medical conditions potentially altering the bone age were accounted for by use of x-ray, however, in normal use as a screening tool this would not be the case.

5.8 Implications for the field of ultrasound in medicine and forensics

5.8.1 Paediatric endocrinology

In paediatric endocrinology an x-ray of the left hand to determine bone age is a routine examination required for the diagnosis of many common paediatric conditions. This initial x-ray provides important information, not only regarding the child's bone age but also allowing detection of various bony abnormalities pathognomonic for certain conditions (e.g., SHOX gene mutations, Turner Syndrome, skeletal dysplasia). For this reason, I do not expect ultrasound to completely replace the radiological bone age assessment in practise. However, once this diagnostic has been completed and a diagnosis has been made it is important to record the bone age of certain patients on a yearly basis, for example, children with a growth hormone deficiency on replacement therapy. This treatment monitoring could be done by ultrasound if the ultrasound device is able to be developed further to robustly determine a bone age in years, saving these children the yearly dose of radiation.

5.8.2 Forensics

Age assessment is required in many fields within forensic and legal diagnostics. The ability to assess age more accurately using non-invasive methods has ethical and legal implications, which also need to be appropriately considered before their implementation in fields such as: age determination of asylum seekers, legal-age assessment in criminal proceedings, age confirmation of individuals in sporting events. Due to the ethical implications, the European Academy of Paediatrics strongly advised doctors in 2016 “not to participate in the process of age determinations in minor asylum seekers stating they are minors” [30]. Further study would be required to investigate the limitations and to improve the accuracy of the ultrasound device before such highly ethically difficult uses for the device should be considered.

5.9 Further studies

5.9.1 KLEVUS

Klinische Evaluation eines neuen Verfahrens der Volljährigkeitsbestimmung mittels Ultraschall - clinical evaluation of a new method of maturity assessment using ultrasound

The extended project began on the 01.01.2019 with a national multi-centre study testing the newly improved ultrasound device. The study extends the use of the device to include male participants and is also focusing on participants of various ethnicities in order to provide robust data for all ethnicities, for maximal efficacy at international borders [39]. The majority of human trafficking victims are white European women; however, the male and ethnic minority should also be allowed to benefit from this technology if possible.

The large sample size planned in this study is important to improve the data bank upon which the machine learning system can improve its accuracy. The more data presented to the device, the more accurate the final outcome.

5.9.2 Real world data

The desired final outcome of identifying more victims of human trafficking at international borders and ultimately reducing human trafficking altogether must be looked at once the device has been further tested on more individuals, as in the KLEVUS study. This study has only addressed the potential of the device to correctly identify individuals as underage or mature adults.

A real-world data study is required, after implementation of the device in its designed role as part of security checks at international borders, to assess the efficacy of the device in relation to the current human trafficking statistics.

A few ideas to be considered from real-world data include:

1. The possibility that implementation of the device at international borders deters human traffickers.

2. A potential increase in self-reporting of human trafficking at the border regardless of the bone scan result.

3. Potential avoidance techniques to falsify ultrasound results introduced by the perpetrators of human trafficking, such as hormone therapy to accelerate growth plate fusion.

4. The practicalities of implementing extra screening at border control in terms of delays and disruption.

The device should act as a screening tool meaning that it is important to ensure that police and border enforcement officers continue to practise their powers of discernment when suspecting a potential human trafficking victim and are supported to take the appropriate action regardless of the ultrasound device reading.

5.10 Conclusion

Human trafficking presents a current international legal and social problem which needs to be addressed further. The development and preliminary testing of this portable ultrasound device to determine the maturity of women and young girls has shown promising results in terms of accuracy and practicality. Further studies are required to assess its use on a wider population as well as real-world studies to assess the potential for reduction in human trafficking.

6 References

1. Attia ZI, Friedman PA, Noseworthy PA, Lopez-Jimenez F, Ladewig DJ, Satam G, Pellikka PA, Munger TM, Asirvatham SJ, Scott CG, Carter RE, Kapa S (2019) Age and Sex Estimation Using Artificial Intelligence From Standard 12-Lead ECGs. Circ Arrhythm Electrophysiol 12:e007284

2. Brausch L, Dirksen R, Risser C, Schwab M, Stolz C, Tretbar S, Rohrer T, Hewener H (2022) Classification of Distal Growth Plate Ossification States of the Radius Bone Using a Dedicated Ultrasound Device and Machine Learning Techniques for Bone Age Assessments. Applied Sciences 12:3361

3. Bundeskriminalamt (2019) Menschenhandel und Ausbeutung 2018. Bundeskriminalamt, Wiesbaden.

4. Bundeszahnärztekammer (2018) Die zahnärztliche forensische Altersdiagnostik bei Lebenden mit besonderer Würdigung röntgenologischer Verfahren. Bundeszahnärztekammer, Berlin.

5. Child CJ, Kalifa G, Jones C, Ross JL, Rappold GA, Quigley CA, Zimmermann AG, Garding G, Cutler GB, Jr., Blum WF (2015) Radiological Features in Patients with Short Stature Homeobox-Containing (SHOX) Gene Deficiency and Turner Syndrome before and after 2 Years of GH Treatment. Horm Res Paediatr 84:14-25

6. Creo AL, Schwenk WF, 2nd (2017) Bone Age: A Handy Tool for Pediatric Providers. Pediatrics 140(6):e20171486

7. Dallora AL, Kvist O, Berglund JS, Ruiz SD, Boldt M, Flodmark CE, Anderberg P (2020) Chronological Age Assessment in Young Individuals Using Bone Age Assessment Staging and Nonradiological Aspects: Machine Learning Multifactorial Approach. JMIR Med Inform 8:e18846

8. Demirjian A, Goldstein H, Tanner JM (1973) A New System of Dental Age Assessment. Human Biology 45:211-227

9. Deutschen Gesellschaft für Kinderendokrinologie und Diabetologie (2016) Kleinwuchs. [AWMF-Register No. 174/004]. Available at: https://www.awmf.org/leitlinien/detail/ll/174-004.html (Accessed: 03.08.2020)

10. Dvorak J, George J, Junge A, Hodler J (2007) Age determination by magnetic resonance imaging of the wrist in adolescent male football players. Br J Sports Med 41:45-52

11. European Parliament (2017) Human trafficking: nearly 16,000 victims in the EU. Available at: http://www.europarl.europa.eu/news/en/headlines/society/20171012STO85932/human-trafficking-nearly-16-000-victims-in-the-eu (Accessed: 13.08.2020)

12. European Union: European Commission Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions on the EU Strategy on Combatting Trafficking in Human Beings 2021-2025. COM(2021) 171 final. Available at: https://ec.europa.eu/home-affairs/sites/default/files/pdf/14042021_eu_strategy_on_combatting_trafficking_in_human_beings_2021-2025_com-2021-171-1_en.pdf (Accessed: 04.08.2021)

13. George J, Nagendran J, Azmi K (2012) Comparison study of growth plate fusion using MRI versus plain radiographs as used in age determination for exclusion of overaged football players. Br J Sports Med 46:273-278

14. Gilsanz V, Ratib O (2005). Hand Bone Age. In A Digital Atlas of Skeletal Maturity (Springer-Verlag), pp. 97

15. Gräfe D (2008-2020) Ped(z) Kinderarzt Rechner. Available at: https://www.pedz.de/de/bmi.html (Accessed: 13.08.2020)

16. Greulich WW, Pyle SI (1959) Radiographic atlas of skeletal development of the hand and wrist. 2nd ed. Stanford University Press, Stanford

17. Hewener H, Risser C, Brausch L, Rohrer T, Tretbar S (2019) A mobile ultrasound system for majority detection. Paper presented at: 2019 IEEE International Ultrasonics Symposium. IEEE, Glasgow

18. Kellinghaus M, Schulz R, Vieth V, Schmidt S, Pfeiffer H, Schmeling A (2010) Enhanced possibilities to make statements on the ossification status of the medial clavicular epiphysis using an amplified staging scheme in evaluating thin-slice CT scans. Int J Legal Med 124:321-325

19. Kromeyer-Hauschild K, Wabitsch M, Kunze D, Geller F, Geiß HC, Hesse V, von Hippel A, Jaeger U, Johnsen D, Korte W, Menner K, Müller G, Müller JM, Niemann-Pilatus A, Remer T, Schaefer F, Wittchen HU, Zabransky S, Zellner K, Ziegler A, Hebebrand J (2001) Perzentile für den Body-mass-Index für das Kindes- und Jugendalter unter Heranziehung verschiedener deutscher Stichproben. Monatsschrift Kinderheilkunde 149:807-818

20. Marshall WA, Tanner JM (1969) Variations in pattern of pubertal changes in girls. Arch Dis Child 44:291-303

21. Marshall WA, Tanner JM (1970) Variations in the pattern of pubertal changes in boys. Arch Dis Child 45:13-23

22. Martin DD, Neuhof J, Jenni OG, Ranke MB, Thodberg HH (2010) Automatic determination of left- and right-hand bone age in the First Zurich Longitudinal Study. Horm Res Paediatr 74:50-55

23. Martin DD, Wit JM, Hochberg Z, Sävendahl L, van Rijn RR, Fricke O, Cameron N, Caliebe J, Hertel T, Kiepe D, Albertsson-Wikland K, Thodberg HH, Binder G, Ranke MB (2011) The use of bone age in clinical practice - part 1. Horm Res Paediatr 76:1-9

24. Massler M, Schour I, Poncher HG (1941) Developmental pattern of the child as reflected in the calcification pattern of the teeth. American Journal of Diseases of Children 62:33-67

25. Mentzel HJ, Vilser C, Eulenstein M, Schwartz T, Vogt S, Böttcher J, Yaniv I, Tsoref L, Kauf E, Kaiser WA (2005) Assessment of skeletal age at the wrist in children with a new ultrasound device. Pediatr Radiol 35:429-433

26. Ontell FK, Ivanovic M, Ablin DS, Barlow TW (1996) Bone age in children of diverse ethnicity. American Journal of Roentgenology 167:1395-1398

27. Pennock AT, Bomar JD, Manning JD (2018) The Creation and Validation of a Knee Bone Age Atlas Utilizing MRI. J Bone Joint Surg Am 100:e20

28. Rachmiel M, Naugolni L, Mazor-Aronovitch K, Koren-Morag N, Bistritzer T (2017) Bone Age Assessments by Quantitative Ultrasound (SonicBone) and Hand X-ray Based Methods are Comparable. Isr Med Assoc J 19:533-538

29. Rai V, Saha S, Yadav G, Tripathi AM, Grover K (2014) Dental and skeletal maturity-a biological indicator of chronologic age. J Clin Diagn Res 8:ZC60-64

30. Sauer PJ, Nicholson A, Neubauer D, Advocacy and Ethics Group of the European Academy of Paediatrics (2016) Age determination in asylum seekers: physicians should not be implicated. Eur J Pediatr 175:299-303

31. Schmeling A, Schulz R, Reisinger W, Muhler M, Wernecke KD, Geserick G (2004) Studies on the time frame for ossification of the medial clavicular epiphyseal cartilage in conventional radiography. Int J Legal Med 118:5-8

32. Schmeling A, Grundmann C, Fuhrmann A, Kaatsch HJ, Knell B, Ramsthaler F, Reisinger W, Riepert T, Ritz-Timme S, Rosing FW, Rotzscher K, Geserick G (2008) Criteria for age estimation in living individuals. Int J Legal Med 122:457-460

33. Schmeling A, Dettmeyer R, Rudolf E, Vieth V, Geserick G (2016) Forensic Age Estimation. Deutsches Ärzteblatt International 113:44-50

34. Schmidt S, Ottow C, Pfeiffer H, Heindel W, Vieth V, Schmeling A, Schulz R (2017) Magnetic resonance imaging-based evaluation of ossification of the medial clavicular epiphysis in forensic age assessment. Int J Legal Med 131:1665-1673

35. Schulz R, Muhler M, Mutze S, Schmidt S, Reisinger W, Schmeling A (2005) Studies on the time frame for ossification of the medial epiphysis of the clavicle as revealed by CT scans. Int J Legal Med 119:142-145

36. SonicBone Medical Ultrasound System for Bone Age Assessment (BAUSTM) Replacing the Conventional X-Ray-Based Methods. Available at: https://sonicbonemedical.com/the-solution-baus/ (Accessed: 13.08.2020)

37. Tanner JM, Whitehouse RH, Marshall WA (1975) Assessment of skeletal maturity and prediction of adult height (TW2 Method). Academic Press, London

38. Thodberg HH, Kreiborg S, Juul A, Pedersen KD (2009) The BoneXpert method for automated determination of skeletal maturity. IEEE Trans Med Imaging 28:52-66

39. Universität des Saarlandes Pädiatrische Endokrinologie Klevus. Available at: https://www.klevus.de (Accessed: 14.08.2021)

40. Vera Institute of Justice (2014) Screening for Human Trafficking: Guidelines for Administering the Trafficking Victim Identification Tool (TVIT). [NCJ No. 246713].

Available at: https://www.ojp.gov/pdffiles1/nij/grants/246713.pdf (Accessed: 13.08.2021)

41. Völschow Y Prävention und Intervention bei Menschenhandel zum Zweck sexueller Ausbeutung aus multidisziplinärer und institutionsübergreifender Perspektive. Available at: https://primsa.eu (Accessed: 14.09.2019)

42. Weidner CI, Lin Q, Koch CM, Eisele L, Beier F, Ziegler P, Bauerschlag DO, Jockel KH, Erbel R, Muhleisen TW, Zenke M, Brummendorf TH, Wagner W (2014) Aging of blood can be tracked by DNA methylation changes at just three CpG sites. Genome Biol 15:R24

43. Wittschieber D, Ottow C, Vieth V, Kuppers M, Schulz R, Hassu J, Bajanowski T, Puschel K, Ramsthaler F, Pfeiffer H, Schmidt S, Schmeling A (2015) Projection radiography of the clavicle: still recommendable for forensic age diagnostics in living individuals? Int J Legal Med 129:187-193

44. Wittschieber D, Ottow C, Schulz R, Puschel K, Bajanowski T, Ramsthaler F, Pfeiffer H, Vieth V, Schmidt S, Schmeling A (2016) Forensic age diagnostics using projection radiography of the clavicle: a prospective multi-center validation study. Int J Legal Med 130:213-219

45. Zbiec-Piekarska R, Spolnicka M, Kupiec T, Makowska Z, Spas A, Parys-Proszek A, Kucharczyk K, Ploski R, Branicki W (2015) Examination of DNA methylation status of the ELOVL2 marker may be useful for human age prediction in forensic science. Forensic Sci Int Genet 14:161-167

46. Zhang A, Sayre JW, Vachon L, Liu BJ, Huang HK (2009) Racial differences in growth patterns of children assessed on the basis of bone age. Radiology 250:228-235

7 List of Figures

8 List of Tables

9 Appendices

9.1 Letter of invitation for healthy volunteers (German)

Sehr geehrte Eltern,

Mein Name ist Ruth Dirksen, ich bin Assistenzärztin an der Uniklinik Homburg. Ich arbeite zusammen mit Prof. Rohrer in der pädiatrische endokrinologische Ambulanz und wir führen zurzeit eine Studie mit dem Bundesministerium für Forschung durch. Zusammen mit dem Fraunhofer Institut in St. Ingbert haben wir ein neues Ultraschallgerät zum Knochenalterbestimmung entwickelt.

Das Gerät wurde als Teil eines größeres Projekt gegen Menschenhandels entwickelt. Das Gerät soll durch Bestimmung der Wahrscheinlichkeit der Volljährigkeit einer Person mittels nichtinvasiver Ultraschallmesstechnik zur Aufdeckung und Bekämpfung illegalen Menschenhandels mit Minderjährigen beitragen.

Wir suchen daher weibliche Probandinnen zwischen 15 und 21 Jahren um das Gerät zu kalibrieren. Die Messungen dauern maximal 3 Minuten pro Person.

Wir bieten die folgenden Messtermine an:

1. 11.06.18 – 14-17 Uhr Uniklinikum Homburg, Kinderklinik Geb. 9, allgemeinpädiatrische Ambulanz, EG.
2. 15.6.18 15 – 20 Uhr Langer Nacht der Wissenschaft, Uniklinikum Homburg, Kinderklinik Geb. 9, allgemeinpädiatrische Ambulanz, EG (leider nicht in Programm zu finden!).
3. 26.6.18 9-11 Uhr Uniklinikum Homburg, Kinderklinik Geb. 9, allgemeinpädiatrische Ambulanz, EG.

Weitere Termine bei Anfrage.
Anbei erhalten Sie die Aufklärung des Projektes und die Einverständniserklärung. Wir bitten Sie um sie auszufüllen und zum Termin mitzubringen.

Bei weiteren Fragen stehe ich gerne zu Verfügung. Vielen Dank für Ihre Unterstützung!

mit freundlichen Grüßen,

Ruth Dirksen
Assistenzärztin UKS Homburg
06841-16-28231
Ruth.Dirksen@uks.eu

9.2 Study information sheet for parents of participants with an x-ray (German)

Patienten-Aufklärung zur Teilnahme an einer Studie zur Bestimmung des Knochenalters mittels Ultraschall

Elterninformation

Ziel dieser Studie ist die Evaluierung eines Ultraschallgeräts, das ohne Anwendung ionisierender Strahlen in wenigen Minuten eine Knochenalterbestimmung absolvieren kann. Hierbei misst das Gerät die Geschwindigkeit einer Ultraschallwelle durch unterschiedliche Verknöcherung von Handgelenksknochen oder Wachstumsfugen zwischen Handgelenk und Unterarm. Mit zunehmender Verknöcherung nimmt die Schallgeschwindigkeit zu. Somit kann sich die Ultraschallwelle je nach Verknöcherungsgrad unterschiedlich schnell durch das Handgelenk ausbreiten. Durch Messung der Zeit nach Aussendung einer Ultraschallwelle bis zum Empfang auf der gegenüberliegenden Seite kann bei bekanntem Abstand auf die mittlere Schallgeschwindigkeit der Welle in der Verknöcherung geschlossen werden. Da die Verknöcherung für das jeweilige Alter der Person signifikant ist, lässt sich das Alter der Person eingrenzen.

Die Studie erfolgt ausschließlich mit Patientinnen.

Es wird ein Röntgenbild der linken Hand gemacht. Die Evaluation des Ultraschall-Messgerätes stellt eine nicht-invasive, kurzzeitige Messung dar, die die Patientinnen nicht belastet.

Ablauf der Studie

1. Aufklärung und Einverständnis einholen
2. Bestimmung von Größe und Gewicht
3. Röntgenbild der linken Hand
4. Knochenalterbestimmung nach Greulich und Pyle sowie nach Tanner und Whitehouse anhand einer Röntgenaufnahme der linken Hand in Bezug auf das chronologische Alter
5. Messung der Verknöcherung der Wachstumsfuge zwischen Handgelenk und Unterarm mittels Ultraschall in Bezug auf das chronologische Alter

Die Studienteilnahme ist absolut freiwillig und kann jederzeit ohne Angabe von Gründen abgebrochen werden. Alle Studienteilnehmer bzw. deren Eltern können Ihre Einwilligung jederzeit und ohne Nennung von Gründen widerrufen.

9.3 Study information sheet for underage participants without an x-ray (German)

Patienten-Aufklärung zur Teilnahme an einer Studie zur Bestimmung des Knochenalters mittels Ultraschall

Information für Kinder

Wenn man bestimmen möchte, wie alt die Knochen eines Menschen bereits sind, wird normalerweise ein Röntgenbild der linken Hand gemacht. Darauf kann ein Arzt erkennen wie weit die Entwicklung der Knochen in der Hand ist. Bei Kindern erkennt man Wachstumsfugen in den Knochen. Das sind Bereiche die aus Knorpel bestehen und sich im Laufe der Zeit in Knochen umwandeln. Bei Erwachsenen sind Wachstumsfugen verschwunden. So kann anhand des Röntgenbildes bestimmt werden, ob dies eine Hand von einem Erwachsenen oder von einem Kind ist.

In der Studie, an der du teilnehmen wirst, geht es darum ein neues Gerät zur Knochenalterbestimmung zu entwickeln. Dies wird ein Ultraschallgerät sein, mit dessen Hilfe man schnell ohne Röntgenstrahlung ein Bild von den Wachstumsfugen in deiner Hand machen kann. Je nach Größe und Aussehen dieser Wachstumsfugen kann man dann ungefähr sagen, wie alt deine Knochen sind.

Die Studie wird nur mit Kindern und jungen Erwachsenen durchgeführt. Es wird ein Röntgenbild deiner linken Hand gemacht.

Das Ausprobieren des neuen Gerätes an deiner Hand ist dann eine kurze Messung, die dich nicht belastet und nicht weh tut.

Wie läuft das alles ab?

1. Du bekommst von uns erzählt wie das Gerät funktioniert und wie der Ablauf der Untersuchung ist

2. Wir schauen wie groß und wie schwer Du bist.

3. Messung der Wachstumsfuge deiner Hand mit dem neuen Ultraschallgerät, um auch damit das Alter deiner Knochen zu bestimmen.

Die Teilnahme an der Studie kann jederzeit ohne Nennung von Gründen abgerochen werden. Du oder deine Eltern können jederzeit ihre Einwilligung widerrufen.

9.4 Parental consent form for underage participant (German)

Einwilligungserklärung

Name der Studie: Bestimmung des Knochenalters mittels Ultraschall

Inhalt, Vorgehensweise, Risiken und Ziel des obengenannten Forschungsprojektes sowie die Befugnis zur Einsichtnahme in die erhobenen Daten hat mir/uns Dr. ..... ausreichend erklärt.

Ich/Wir hatte(n) Gelegenheit Fragen zu stellen und habe(n) hierauf Antwort erhalten.

Ich/Wir hatte(n) ausreichend Zeit, mich/uns für oder gegen die Teilnahme meines/unseres Kindes am Projekt zu entscheiden.

Eine Kopie der Elterninformation und Einwilligungserklärung habe(n) ich/wir erhalten.

Ich/Wir willigen in die Teilnahme unseres Kindes an diesem Forschungsprojekt ein.

.....	.....
Name des Kindes	Unterschrift des Vaters (oder des gesetzlichen Vormundes)
.....	.....
Ort, Datum	Unterschrift der Mutter (oder des gesetzlichen Vormundes
.....	.....
Ort, Datum	Unterschrift der Probandinnen

Information und Einwilligungserklärung zum Datenschutz

Bei wissenschaftlichen Studien werden persönliche Daten und medizinische Befunde über Ihr Kind erhoben. Die Speicherung, Auswertung und Weitergabe dieser studienbezogenen Daten erfolgt nach gesetzlichen Bestimmungen und setzt vor Teilnahme an der Studie folgende freiwillige Einwilligung voraus:

Ich/Wir erkläre(n) mich/uns damit einverstanden, dass im Rahmen dieser Studie erhobene Daten/Krankheitsdaten meines/unseres Kindes auf Fragebögen und elektronischen Datenträgern aufgezeichnet und ohne Namensnennung verarbeitet werden.

Außerdem erkläre(n) ich/wir mich/uns damit einverstanden, dass eine autorisierte und zur Verschwiegenheit verpflichtete Person (z.B.: des Auftraggebers, der Universität) in die erhobenen personenbezogenen Daten meines/unseres Kindes Einsicht nimmt, soweit dies für die Überprüfung des Projektes notwendig ist. Für diese Maßnahme entbinde(n) ich/wir den Arzt von der ärztlichen Schweigepflicht.

9.5 Consent form for mature participant (German)

Einwilligungserklärung

Name der Studie: Bestimmung des Knochenalters mittels Ultraschall

Inhalt, Vorgehensweise, Risiken und Ziel des obengenannten Forschungsprojektes sowie die Befugnis zur Einsichtnahme in die erhobenen Daten habe ich ausreichend erklärt bekommen.

Ich/Wir hatte(n) Gelegenheit per Email und am Untersuchungstag Fragen zu stellen und habe(n) hierauf Antwort erhalten.

Ich/Wir hatte(n) ausreichend Zeit, mich/uns für oder gegen die Teilnahme meines/unseres Kindes am Projekt zu entscheiden.

Eine Kopie der Elterninformation und Einwilligungserklärung habe(n) ich/wir erhalten.

Ich/Wir willigen in die Teilnahme unseres Kindes an diesem Forschungsprojekt ein.

.....	.....	.....
Name der Probandinnen	Unterschrift der Probandinnen	Ort, Datum

Information und Einwilligungserklärung zum Datenschutz

Bei wissenschaftlichen Studien werden persönliche Daten und medizinische Befunde über Ihr Kind erhoben. Die Speicherung, Auswertung und Weitergabe dieser studienbezogenen Daten erfolgt nach gesetzlichen Bestimmungen und setzt vor Teilnahme an der Studie folgende freiwillige Einwilligung voraus:

Ich/Wir erkläre(n) mich/uns damit einverstanden, dass im Rahmen dieser Studie erhobene Daten/Krankheitsdaten meines/unseres Kindes auf Fragebögen und elektronischen Datenträgern aufgezeichnet und ohne Namensnennung verarbeitet werden.

Außerdem erkläre(n) ich/wir mich/uns damit einverstanden, dass eine autorisierte und zur Verschwiegenheit verpflichtete Person (z.B.: des Auftraggebers, der Universität) in die erhobenen personenbezogenen Daten meines/unseres Kindes Einsicht nimmt, soweit dies für die Überprüfung des Projektes notwendig ist. Für diese Maßnahme entbinde(n) ich/wir den Arzt von der ärztlichen Schweigepflicht.

9.6 Questionnaire A

Fragebogen zur Knochenalter Untersuchung

Liebe Studienteilnehmerin,

Sie haben sich entschlossen bei der Studie zur Bestimmung des Knochenalters mittels Ultraschall teilzunehmen. Damit wir unsere Teilnehmerin besser kennenlernen und einige wichtige Informationen erhalten, bitten wir Sie, uns vorab diese Angaben zu machen.

Vielen Dank für Ihre Mitarbeit.

Name, Vorname: _____

Geburtsdatum: _____

Entwicklung

Haben Sie eine chronische Krankheit?

__ Ja __ Nein

Wenn ja, welche und seit wann?

_____

Nehmen Sie zurzeit Medikamente ein?

__ Ja __ Nein

Name des Medikamentes	Dosierung	seit wann (Datum)
_____	_____	_____
_____	_____	_____

Pubertät:

Wann fing bei Ihnen die Pubertätsentwicklung an? Alter: _____ Jahre

Alter bei der 1.Blutung (Menarche) Alter: _____ Jahre

_____ _____

9.7 Questionnaire B

Fragebogen zur Knochenalter Untersuchung

Liebe Studienteilnehmerin,

Sie haben sich entschlossen bei der Studie zur Bestimmung des Knochenalters mittels Ultraschall teilzunehmen. Damit wir unsere Teilnehmerin besser kennenlernen und einige wichtige Informationen erhalten, bitten wir Sie, uns vorab diese Angaben zu machen.

Vielen Dank für Ihre Mitarbeit.

Name, Vorname: _____

Geburtsdatum: _____

Ethnizität der Eltern und Großeltern

Eltern:_____

Großeltern:_____

Haben Sie eine chronische Krankheit?

__ Ja __ Nein

Wenn ja, welche und seit wann?

_____

Nehmen Sie zurzeit Medikamente ein?

__ Ja __ Nein

Name des Medikamentes	Dosierung	seit wann (Datum)
_____	_____	_____
_____	_____	_____

Pubertät:

Wann fing bei Ihnen die Pubertätsentwicklung an? Alter: _____ Jahre

Alter bei der 1.Blutung (Menarche) Alter: _____ Jahre

_____ _____

10 Publications and Acknowledgements

10.1 Publications

Article published in Applied Sciences, 25.03.2022:

Brausch L, Dirksen R, Risser C, Schwab M, Stolz C, Tretbar S, Rohrer T, Hewener H (2022) Classification of Distal Growth Plate Ossification States of the Radius Bone Using a Dedicated Ultrasound Device and Machine Learning Techniques for Bone Age Assessments. Applied Sciences 12:3361. https://doi.org/10.3390/app12073361

Poster Presentation and oral presentation with nomination for the STEPS-AWARD at “JA-PED 2019”:

Dirksen R, Hewener H, Risser C, Brausch L, Tretbar S, Zemlin M, Rohrer T (2019). Development of a new ultrasound device for determining maturity based on bone age assessment. In Gemeinsame Jahrestagung der Arbeitsgemeinschaft für Pädiatrische Diabetologie (AGPD) e. V. und der Deutschen Gesellschaft für Kinderendokrinologie und -diabetologie (DGKED) e. V. (Saarbrücken, Germany)

10.2 Acknowledgements

Throughout the writing of this dissertation, I have received a great deal of support, assistance and encouragement.

First and foremost, I would like to thank my lead consultant and mentor, Professor Dr. med. Tilman Rohrer, for his inspiration and vigour in fighting for this project. Thank you for your dedication to your work and your team. Thank you for providing me with this opportunity, for believing in me and supporting me through every step in this journey, within this project as well as every day in the clinic.

Secondly, a special thanks to my study mentor, Dr. Anna Marie Jung, for her friendship and intuitive guidance, and to Tina Leßmeister-Bastian for her constant encouragement and support.

I would like to thank the Bundesministerium für Bildung und Forschung (BMBF) for their financial support, as well as the PRIMSA team and Hope for Freedom for their initiative in starting this brilliant international project and letting me be a part of it.

I would also like to thank Dr. Holger Hewener, Christoph Risser, Steffen Tretbar and Lukas Brausch from the Fraunhofer Institution for their hard work in developing this innovative ultrasound device and their constant support, especially their patience in explaining the complicated science behind the device and programming. I stand in awe of your intelligence and abilities!

Thank you to all my colleagues and friends at the Saarland Medical Centre in Homburg; the whole of the paediatric endocrinology team, Professor Dr. Stefan Wagenpfeil in Statistics, the Heads of Departments (Physiotherapy, Medicine, Nursing) and their secretaries. As well as the local school headteachers and their secretaries who helped with the coordination of the healthy volunteers.

A big thank you to all of the participants and their families, our patients from the clinic, as well as the medical, nursing, midwifery and physiotherapy students, and school children who participated as healthy volunteers. Thank you for your time, support and enthusiasm.

Finally, I would like to thank God for his provision during this journey, and my family, my husband Markus, and my parents, Stuart and Julie, for their constant encouragement, understanding and inspiration.

11 Curriculum Vitae

The curriculum vitae has been removed for data protection purposes.

Kolloquiumsvermerk:

Tag der Promotion:	7. November 2022
Dekan:	Univ.-Prof. Dr. med. Michael D. Menger
Berichterstatter:	Prof. Dr. med. Tilman R. Rohrer
	Prof. Dr. med. Arno Bücker