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Osman Ratib

Hand Bone Age

A Digital Atlas of Skeletal Maturity



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A Digital Atlas of Skeletal Maturity

With 88 Figures

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Introduction

Bone age assessment is frequently performed in pediatric patients to evaluate growth and to diagnose and manage a multitude of endocrine disorders and pediatric syndromes. For decades, the determination of bone maturity has relied on a visual evaluation of the skeletal development of the hand and wrist, most commonly using the Greulich and Pyle atlas. With the advent of digital imaging, multiple attempts have been made to develop image-processing techniques that automatically extract the key morphological features of ossification in the bones to provide a more effective and objective approach to skeletal maturity assessments. However, the design of computer algorithms capable of automatically rendering bone age has been impeded by the complexity of evaluating the wide variations in bone mineralization tempo, shape and size encompassed in the large number of ossification centers in the hand and wrist. Clearly, developing an accurate digital reference that integrates the quantitative morphological traits associated with the different degrees of skeletal maturation of 21 tubular bones in the hand and 8 carpal bones in the wrist is not an easy task.

In the development of this digital atlas, we circumvented the difficulties associated with the design of software that integrates all morphological parameters through the selection of an alternative approach: the creation of artificial, idealized, sex- and age-specific images of skeletal development. The models were generated through rigorous analyses of the maturation of each ossification center in the hands and wrists of healthy children, and the construction of virtual images that incorporate composites of the average development for each ossification center in each age group. This computer-generated set of images should serve as a practical alternative to the reference books currently available.

Bone Development

Skeletal maturity is a measure of development incorporating the size, shape and degree of mineralization of bone to define its proximity to full maturity. The assessment of skeletal maturity involves a rigorous examination of multiple factors and a fundamental knowledge of the various processes by which bone develops.

Longitudinal growth in the long bones of the extremities occurs through the process of endochondral ossification. In contrast, the width of the bones increases by development of skeletal tissue directly from fibrous membrane. The latter is the mechanism by which ossification of the calvarium, the flat bones of the pelvis, the scapulae, and the body of the mandible occurs. Initial calcification begins near the center of the shaft of long bones in a region called the primary ossification center [1].

Although many flat bones, including the carpal bones, ossify entirely from this primary center, all of the long bones develop secondary centers that appear in the cartilage of the extremities of the bone. Maturation in these centers proceeds in a manner identical to that in the primary centers

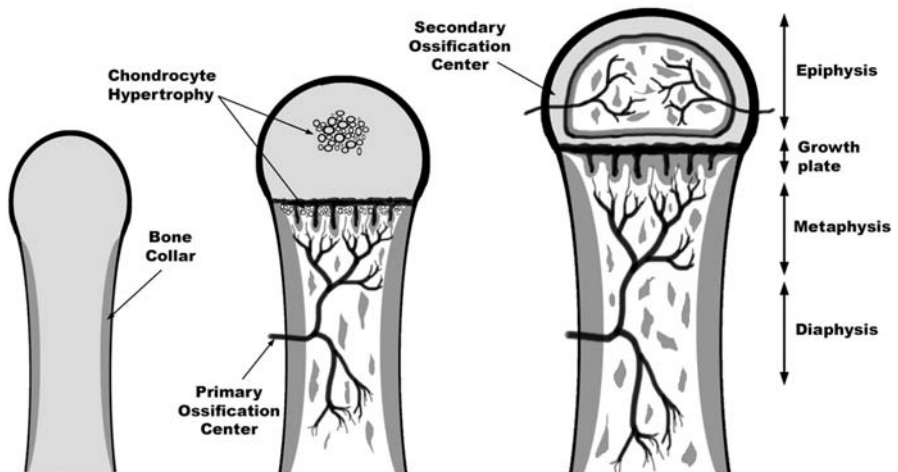


Fig. 1. Schematic representation of endochondral bone formation. Skeletal maturity is mainly assessed by the degree of development and ossification of the secondary ossification centers in the epiphysis

with ossification of cartilage and invasion of osteoclasts and osteoblasts. The bone ossified from the primary center is the diaphysis, while the bone ossified from the secondary center is the epiphysis. As the secondary center is progressively ossified, the cartilage is replaced by bone until only a thin layer of cartilage, the epiphyseal plate, separates the diaphyseal bone from the epiphysis. The part of the diaphysis that abuts on the epiphysis is referred to as the metaphysis and represents the growing end of the bone. As long as the epiphyseal cartilage plate persists, both the diaphysis and epiphysis continue to grow, but, eventually, the osteoblasts cease to multiply and the epiphyseal plate is ossified. At that time, the osseous structures of the diaphysis and epiphysis are fused and growth ceases [1].

In the fetal phase of life, the principle interest in skeletal growth is associated with the diagnosis of prematurity. The end of the embryonic period and the beginning of the fetus is marked by the event of calcification, which begins at 8 or 9 weeks. By the 13th fetal week, most primary centers of the tubular bones are well-developed into diaphyses, and, at birth, all diaphyses are completely ossified, while most of the epiphyses are still cartilaginous. Ossification of the distal femoral epiphysis begins during the last two months of gestation, and this secondary center is present in most full term babies. Similarly, the ossification center for the proximal epiphysis of the humerus usually appears about the 40th week of gestation. On the other hand, the centers for the proximal epiphyses of the femur and tibia may not be present in full term infants, but appear in the first few months of life [2, 3].

After birth, the epiphyses gradually ossify in a largely predictable order, and, at skeletal maturity, fuse with the main body of the bone. Comparing the degree of maturation of the epiphyses to normal age-related standards forms the basis for the assessment of skeletal maturity, the measure of which is commonly called “bone age” or “skeletal age”. It is not clear which factors determine a normal maturational pattern, but it is certain that genetics, environmental factors, and hormones, such as thyroxine, growth hormone, and sex steroids, play important roles. Studies in patients with mutations of the gene for the estrogen receptor or for aromatase enzyme have demonstrated that it is estrogen that is primarily responsible for ultimate epiphyseal fusion, although it seems unlikely that estrogen alone is responsible for all skeletal maturation [4].

Clinical Applications for Skeletal Determinations

A single reading of skeletal age informs the clinician of the relative maturity of a patient at a particular time in his or her life, and, integrated with other clinical findings, separates the normal from the relatively advanced or re-

tarded. Successive skeletal age readings indicate the direction of the child's development and/or show his or her progress under treatment. In normal subjects, bone age should be roughly within 10 per cent of the chronological age. Greater discordance between skeletal age and chronological age occurs in children who are obese or who start puberty early, as their skeletal age is accelerated.

There are two main applications for evaluations of skeletal maturation: the diagnosis of growth disorders and the prediction of final adult height.

Diagnosis of Growth Disorders

Assessments of skeletal age are of great importance for the diagnosis of growth disorders, which may be classified into two broad categories with different etiologies, prognoses and treatments. Primary growth deficiency is due to an intrinsic defect in the skeletal system, such as bone dysplasia, resulting from either a genetic defect or prenatal damage and leading to shortening of the diaphysis without significant delay of epiphyseal maturation. Hence, in this form of growth disorder, the potential normal bone growth (and therefore, body growth) is impaired, while skeletal age is not delayed or is delayed much less than is height.

Secondary growth deficiency is related to factors, generally outside the skeletal system, that impair epiphyseal or osseous maturation. These factors may be nutritional, metabolic, or unknown, as in the syndrome of idiopathic (constitutional) growth delay. In this form of growth retardation, skeletal age and height may be delayed to nearly the same degree, but, with treatment, the potential exists for reaching normal adult height.

The distinction between these categories may be difficult in some instances in which skeletal age is delayed to a lesser degree than height. In general, however, differentiation between primary and secondary categories of growth failure can be determined from clinical findings and skeletal age [5].

Final Height Predictions

The adult height of a child who grows up under favorable environmental circumstances is, to a large extent, dependent on heredity. The final height of the child may, therefore, be postulated from parental heights. Indeed, various methods of final height predictions, which take into account parental height, have been described [6]. A child's adult height can also be predicted from his or her heights at earlier ages, with correlations on the order of 0.8. However, children differ greatly in rate of development; some attain maturity at a relatively early age, while others have a slow tempo and finish

growing relatively late. Hence, knowledge of the degree of development increases the accuracy of final height predictions. The only practical guide to acquire this knowledge is by assessment of skeletal maturity, usually estimated from a hand and wrist radiograph.

Tables for prediction of ultimate height based on the individual's height, skeletal age, sex, age, and growth rate have been published. Using skeletal age for prediction of ultimate height, it is also possible to make a rough calculation as follows: measure the individual's height, plot it on a standard growth curve, and extrapolate the value horizontally to the age on the chart that is equal to the bone age. If the point of extrapolation falls between the 5th and 95th centiles, then a guarded prediction of normal adult stature can be given. The closer the extrapolated value is to the 50th centile, the more accurate it is likely to be [5].

Other bone age and height prediction methods commonly in use are those of Bayley-Pinneau, Roche et al and Tanner-Whitehouse [7–9]. All of these methods use radiographs of the hand and wrist to assess skeletal maturity and were based on population data from normal children followed to adult height. Overall, these methods have 95% confidence intervals of 7 to 9 cm when used to predict the final height of individuals. It is necessary to realize, however, that estimations of final height are most accurate in children who are healthy, and, in the sick, these predictions are less reliable.

Below is the formula for the prediction of adult height estimated by J.M. Tanner et al [9]:

$$\begin{aligned} \text{Predicted Final Height} = & \text{Height Coefficient} \times \text{Present Height (cm)} + \\ & \text{Age Coefficient} \times \text{Chronological Age (years)} + \\ & \text{Bone Age Coefficient} \times \text{Bone Age (years)} + \\ & \text{Constant} \end{aligned}$$

In girls, these investigators incorporated knowledge of whether or not menarche had occurred, which improved their predictions. The tables for the coefficients for prediction of adult height are on pages 93 and 94.

Conventional Techniques for Skeletal Determinations

In the evaluation of physical development in children, variations in maturation rate are poorly described by chronological age. Thus, for many decades, scientists have sought better techniques to assess the degree of development from birth to full maturity. Measures of height, weight, and body mass, although closely related to biological maturation, are not sufficiently accurate due to the wide variations in body size. Similarly, the large varia-

tions in dental development have prevented the use of dental age as an overall measure of maturation, and other clinically established techniques are of limited value. As examples, the age at menarche, although an important biological indicator, relates to only half the population, and determinations of sexual development using the Tanner classification, while an extremely useful clinical tool, is subjective and restricted to the adolescent period. Unfortunately, most available maturational “age” scales have specific uses and tempos that do not necessarily coincide.

Skeletal age, or bone age, the most common measure for biological maturation of the growing human, derives from the examination of successive stages of skeletal development, as viewed in hand-wrist radiographs. This technique, used by pediatricians, orthopedic surgeons, physical anthropologists and all those interested in the study of human growth, is currently the only available indicator of development that spans the entire growth period, from birth to maturity. Essentially, the degree of skeletal maturity depends on two features: growth of the area undergoing ossification, and deposition of calcium in that area. While these two traits may not keep pace with each other, nor are they always present concurrently, they follow a fairly definite pattern and time schedule, from infancy to adulthood. Through radiographs, this process provides a valuable criterion for estimating normal and abnormal growth and maturation.

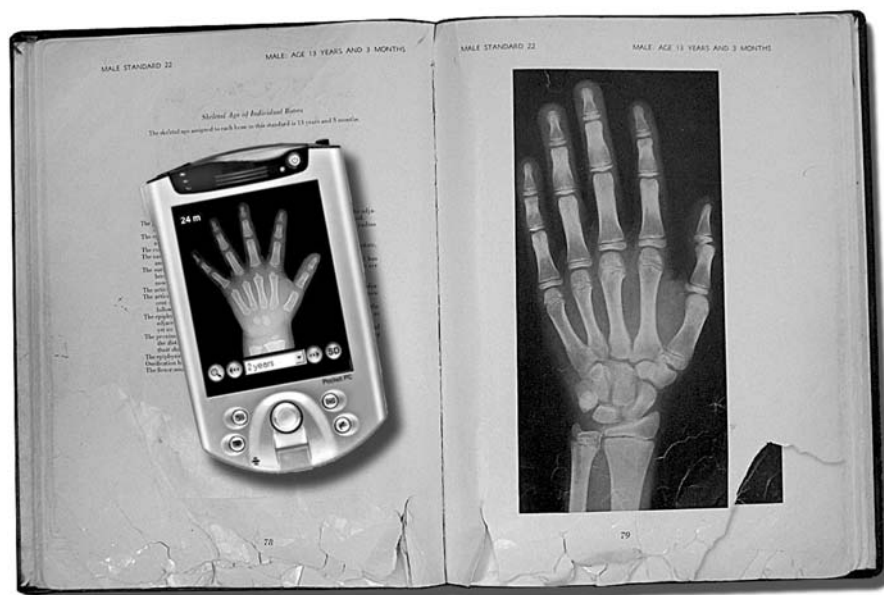


Fig. 2. Comparison of the traditional Greulich and Pyle atlas used for determination of bone maturity from hand radiographs and the electronic alternative, a digital atlas of “idealized” hand radiographs that can be reviewed on standard hand-held PDAs

Greulich and Pyle and Tanner-Whitehouse (TW2) are the most prevalently employed skeletal age techniques today [10, 11]. Despite their differing theoretical approaches, both are based on the recognition of maturity indicators, i.e., changes in the radiographic appearance of the epiphyses of tubular bones from the earliest stages of ossification until fusion with the diaphysis, or changes in flat bones until attainment of adult shape [12].

The standards established by Greulich and Pyle, undoubtedly the most popular method, consist of two series of standard plates obtained from hand-wrist radiographs of white, upper middle-class boys and girls enrolled in the Brush Foundation Growth Study from 1931 to 1942. Represented in the Greulich and Pyle atlas are 'central tendencies', which are modal levels of maturity within chronological age groups. The skeletal age assigned to each standard corresponds to the age of the children on whom the standard was based. When using the Greulich and Pyle method, the radiograph to be assessed is compared with the series of standard plates, and the age given to the standard plate that fits most closely is assigned as the skeletal age of the child. It is often convenient to interpolate between two standards to assign a suitable age to a radiograph. The apparent simplicity and speed with which a skeletal age can be assigned has made this atlas the most commonly used standard of reference for skeletal maturation worldwide.

Underlying the construction of the Greulich and Pyle atlas are the assumptions that, in healthy children, skeletal maturation is uniform, that all bones have an identical skeletal age, and that the appearance and subsequent development of body centers follow a fixed pattern. However, considerable evidence suggests that a wide range of normal variation exists in the pattern of ossification of the different bones of the hand and the wrist and that this variation is genetically determined. In fact, most standards in the atlas include bones that differ considerably in their levels of maturity [10].

Greulich and Pyle did not formally recommend any specific technique for the use of their atlas. Rather, they suggested that atlas users develop their own method depending on their preferences. Pyle et al did, however, suggest the rather cumbersome approach that each ossification center be assigned a bone-specific bone age, and the average of the ages calculated. By and large, when there is a discrepancy between the carpal bones and the distal centers, greater weight should be assigned to the distal centers because they tend to correlate better with growth potential [5].

A number of important caveats concerning bone age must be considered. First, experience in skeletal maturity determinations and a similar analytic approach are essential to enhance inter- and intra-observer reproducibility. Clinical studies and trials involving bone age as an outcome measure greatly benefit from the inclusion of experienced readers who use similar approaches in their assessments. Second, the normal rate of skeletal maturation

tion differs between males and females, and ethnic variability exists. Lastly, these references are not necessarily applicable to children with skeletal dysplasias, endocrine abnormalities or a variety of other causes of growth retardation.

Computer Assisted Techniques for Skeletal Determinations

With the advent of digital imaging, several investigators have attempted to provide an objective computer-assisted measure for bone age determinations and have developed image processing techniques from reference databases of normal children that automatically extract key features of hand radiographs [13–17]. To date, however, attempts to develop automated image analysis techniques capable of extracting quantitative measures of the morphological traits depicting skeletal maturity have been hindered by the inability to account for the great variability in development and ossification of the multiple bones in the hand and wrist. In an attempt to overcome these difficulties, automated techniques are being developed that primarily rely on measures of a few ossification centers, such as those of the epiphyses.

In the design of this digital atlas, the complexities associated with the design of software that integrates all morphological parameters was circumvented through the selection of an alternative approach. We designed artificial, idealized, sex- and age-specific images of skeletal development that incorporated the different degrees of maturation of each ossification center in the hand and wrist. The idealized image was derived from a composite of several hand radiographs from healthy children and adolescents that were identified as the perfect average for each ossification center in each age group.

Our aim was to provide a portable alternative to the reference books currently available, while avoiding the complexity of computer assisted image analysis. The wide adoption of personal digital assistants (PDAs) and pocket computer devices allowed the implementation of a low-cost portable solution that could effectively replace the traditional reference books. Technical challenges included the development of proper compression and image enhancement techniques for interpretation of hand radiographs on a small screen with adequate quality, and the need to store a large number of images on instruments with limited memory capacity.

Indicators of Skeletal Maturity in Children and Adolescents

The purpose of this section is to describe which bones in the hand and wrist are the most suitable indicators of skeletal maturity during the different phases of postnatal development. In the majority of healthy children, there is an established sequence of ossification for the carpal (Figure 3), metacarpal and phalangeal bones, which is remarkably constant and the same for both sexes. Overall, the first ossification center to appear in hand and wrist radiographs is the capitate, and the last is, most often, the sesamoid of the adductor pollicis of the thumb [18].

The first epiphyseal center to appear is that of the distal radius, followed by those of the proximal phalanges, the metacarpals, the middle phalanges, the distal phalanges, and, finally, the ulna. There are, however, two main exceptions to this sequence: the epiphysis of the distal phalanx of the thumb commonly appears at the same time as the epiphyses of the metacarpals, and the epiphysis of the middle phalanx of the fifth finger is frequently the last to ossify.

Since the predictive value of the ossification centers differs and changes during growth, the reviewer should primarily focus on the centers that best characterize skeletal development for the subject's chronological age. To fa-

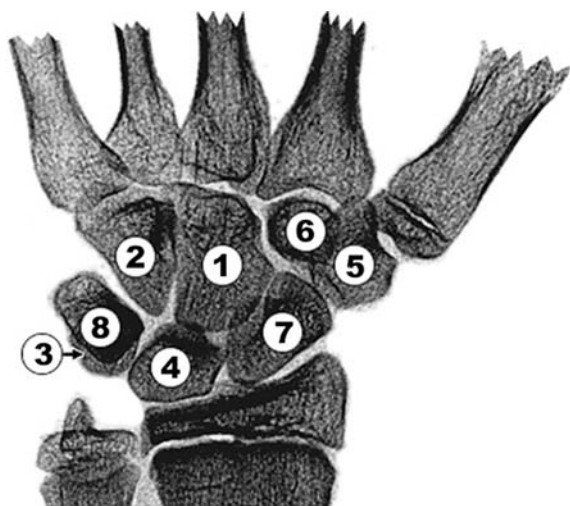


Fig. 3. Depiction of the order of appearance of the individual carpal bones. The usual sequence is: capitate (1), hamate (2), triquetrum (3), lunate (4), trapezium (5), trapezoid (6), navicular or scaphoid (7) and pisiform (8). The distal epiphysis of the radius ossifies before the triquetrum and that of the ulna before the pisiform

Facilitate bone age assessments, we have divided skeletal development into six major categories and highlighted in parentheses the specific ossification centers that are the best predictors of skeletal maturity for each group:

- 1) Infancy (the carpal bones and radial epiphyses);
- 2) Toddlers (the number of epiphyses visible in the long bones of the hand);
- 3) Pre-puberty (the size of the phalangeal epiphyses);
- 4) Early and Mid-puberty (the size of the phalangeal epiphyses);
- 5) Late Puberty (the degree of epiphyseal fusion); and,
- 6) Post-puberty (the degree of epiphyseal fusion of the radius and ulna).

While these divisions are arbitrary, we chose stages that reflect pubertal status, since osseous development conforms better with the degree of sexual development than with the chronologic age. The features that characterize these successive stages of skeletal development are outlined in schematic drawings depicting their appearance as seen in posterior anterior roentgenograms of the hand and wrist.

Infancy

Females: Birth to 10 months of age

Males: Birth to 14 months of age

All carpal bones and all epiphyses in the phalanges, metacarpals, radius and ulna lack ossification in the full-term newborn. The ossification centers of the capitate and hamate become apparent at about 3 months of age and remain the only useful observable features for the next six months. At about 10 months of age for girls, and about 1 year and 3 months of age for boys, a small center of ossification in the distal epiphysis of the radius appears. Due to the lack of ossification centers, assessment of skeletal maturity using hand and wrist radiographs during infancy is difficult. Estimates of bone maturation in the first year of life frequently require evaluation of the number, size and configuration of secondary ossification centers in the upper and lower extremities.



Fig. 4. During Infancy, bone age is primarily based on the presence or absence of ossification of the capitate, the hamate and the distal epiphysis of the radius. The capitate usually appears slightly earlier than the hamate, and has a larger ossification center and rounder shape. The distal radial epiphysis appears later

Toddlers

Females: 10 months to 2 years of age

Males: 14 months to 3 years of age

The ossification centers for the epiphyses of all phalanges and metacarpals become recognizable during this stage, usually in the middle finger first, and the fifth finger last. Bone age determinations are primarily based on the assessment of the number of identifiable epiphyseal ossification centers, which generally appear in an orderly characteristic pattern, as follows:

- 1) Epiphyses of the proximal phalanges;
- 2) Epiphyses of the metacarpals;
- 3) Epiphyses of the middle phalanges; and,
- 4) Epiphyses of the distal phalanges.

Two common exceptions to this rule are:

- 1) The early appearance of the ossification center of the distal phalanx of the thumb, which is usually recognizable at 1 year and 3 months in males, and 1 year and six months in females; and,



Fig. 5. During this stage, bone age is primarily based on the number of recognizable epiphyseal ossification centers in the phalanges and metacarpals

- 2) The late appearance of the ossification center of the middle phalanx of the fifth finger, which is the last phalangeal epiphysis to appear.

The number and degree of maturation of the carpal bones in the wrist are less useful indicators at this stage, as only three or four (capitate, hamate and lunate and, at times, trapezoid) are recognizable.

Pre-puberty

Females: 2 years to 7 years of age

Males: 3 years to 9 years of age

Assessments of skeletal maturity in pre-pubertal children are primarily based on the epiphyseal size of the phalanges as they relate to the adjacent metaphyses. During this stage of development, the ossification centers for the epiphyses increase in width and thickness, and eventually assume a transverse diameter as wide as the metaphyses. More weight is given to the size of the epiphyses in the distal phalanges than to that in the middle phalanges, and even less to that in the proximal phalanges. However, since the development of the distal phalanges appears similar at several different ages, at times the assessment is also based on the degree of maturity for the

Fig. 6. Depiction of the progressive growth of the width of the epiphyses, which, during this stage of development, become as wide as the metaphyses

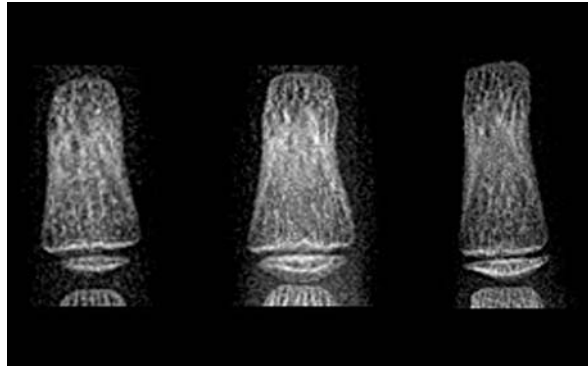


Fig. 7. Assessments of bone age are primarily based on the degree of difference in width between the smaller epiphyses and the larger metaphyses at the distal and middle phalanges

epiphyses of the middle phalanges. On very rare occasions when there continues to be doubt, the development of the proximal phalanx may be included in the assessment.

The epiphysis of the ulna and all carpal bones, with the exception of the pisiform, usually become recognizable before puberty. However, these ossification centers, like those of the metacarpals, are less reliable indicators of bone age at this stage of life.

Early and Mid-puberty

Females: 7 years to 13 years of age

Males: 9 years to 14 years of age

As in pre-pubertal children, assessments of skeletal maturity in early and mid-puberty are also based on the size of the epiphyses in the distal phalanges (first) and the middle phalanges (second). The epiphyses at this stage continue to grow and their widths become greater than the metaphyses.

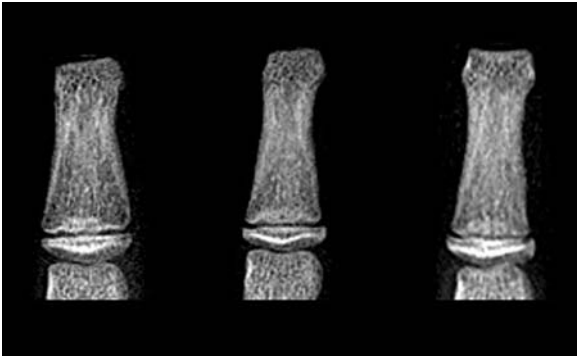


Fig. 8. Depiction of the progressive growth of the epiphyses, which, during this stage of development, become larger than the metaphyses. Special attention is also placed on epiphyseal shape, which, prior to epiphyseal fusion, overlaps the metaphyses, depicting tiny horn-like structures (picture at far-right)



Fig. 9. During this stage of development, like for prepubertal and late-pubertal children, assessments are based primarily on the distal and middle phalanges

ses. Thereafter, the contours of the epiphyses begin to overlap, or cap, the metaphyses. This capping effect is depicted in a two-dimensional radiograph as small bony outgrowths, like tiny horns, on both sides of the shaft.

The pisiform and the sesamoid in the tendon of the abductor pollicis, just medial to the head of the first metacarpal, become recognizable during puberty. However, these centers, as well as those of the other carpals and metacarpals, are less reliable as indicators of bone age at this stage of development.

Late Puberty

Females: 13 years to 15 years of age

Males: 14 years to 16 years of age

Assessments of skeletal maturity in this stage are primarily based on the degree of epiphyseal fusion of the distal phalanges. Fusion of the epiphyses to the metaphyses in the long bones of the hand tends to occur in an orderly characteristic pattern, as follows:

- 1) Fusion of the distal phalanges;
- 2) Fusion of the metacarpals;
- 3) Fusion of the proximal phalanges; and,
- 4) Fusion of the middle phalanges.

Because of their morphologies, the epiphyseal fusion of the metacarpals is poorly depicted by radiographs and greater attention is, therefore, placed on the degree of fusion at the phalanges. Since all carpal bones have now attained their early adult shape, they are of less value for determination of bone age.

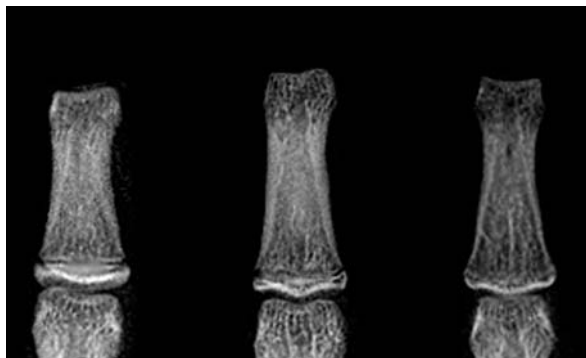


Fig. 10. Depiction, from left to right, of the progressive degrees of fusion of the epiphyses to the metaphyses, which usually begins at the center of the physis

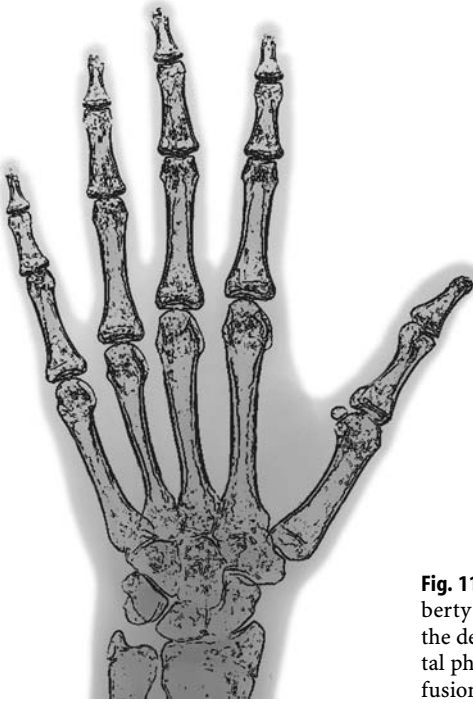


Fig. 11. Assessments in late stages of puberty and sexual maturity are based on the degree of epiphyseal fusion of the distal phalanges (first) and on the degree of fusion of the middle phalanges (second)

Post-puberty

Females: 15 years to 17 years of age

Males: 17 years to 19 years of age

At this stage, all carpals, metacarpals and phalanges are completely developed, their physes are closed, and assessments of skeletal maturity are based on the degree of epiphyseal fusion of the ulna and radius.



Fig. 12. Depiction, from left to right, of the progressive degrees of fusion of the ulna and the radial epiphyses, which usually begins at the center of the physis



Fig. 13. At this stage of development, skeletal maturity is based on epiphyseal fusion of the ulna, which occurs first, and the radius

Digital Bone Age Atlas

Subjects

During the past two decades, multiple studies on normal growth and skeletal development have been conducted at Childrens Hospital Los Angeles. The hand and wrist radiographs obtained for these studies form the basis of the data used to develop the digital bone age atlas. Participants were healthy children and adolescents who were recruited from schools and boys and girls clubs in the Los Angeles area. All studies were approved by the local IRB and all subjects and/or their parents signed informed consent.

The hand and wrist radiographs selected as standards for the digital atlas were obtained from children whose parents and both sets of grandparents were of European descent, who had no diagnosis of chronic illness, and who were not taking any medications regularly. The height and weight of each child was between the 3rd and 97th percentiles and the Tanner stage was within 2 SD for the mean age-adjusted values [19, 20].

A total of 522 left hand and wrist radiographs were evaluated (50% female, 50% male) and were the basis for the reference standards. The standards were grouped by age based on the variability for skeletal age at the different stages of development. The intervals between groupings are roughly equal to one standard deviation for skeletal maturity at that chronological age (Table 4, page 95) and increase from 2 months in infancy to 1 year by 6 years of age. Each of the standards was selected from nine radiographs of children of the same sex and age.

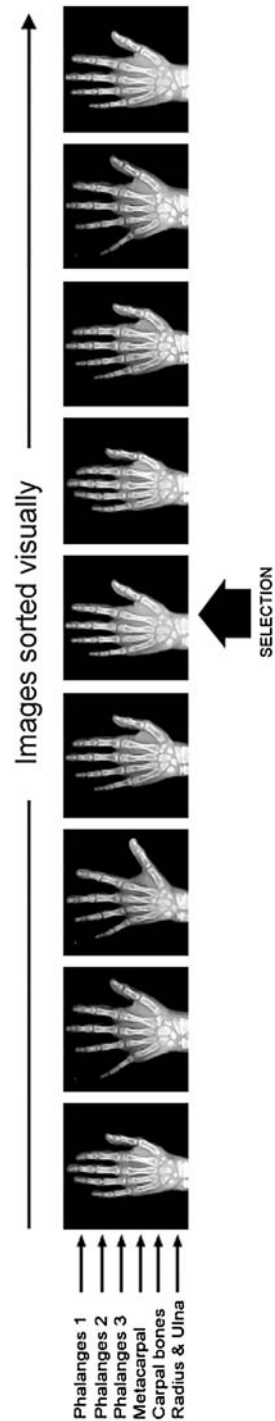
Methods and Techniques

Idealized images were developed from 522 left hand and wrist radiographs of Caucasian boys and girls that were divided into 29 age groups ranging from 8 months to 18 years of age. For each age group, nine images were sorted by two independent radiologists based on the degree of skeletal maturity at different ossification centers. The middle image was then identified as the “average” image; half of the remaining images depicted less skeletal maturity and half depicted more skeletal maturity at the region examined. This process was applied to six different anatomical regions of the

hand and wrist: the proximal, middle and distal phalanges, the metacarpals, the carpals, and, lastly, the distal radius and ulna. Frequently, the selected “middle” images for the six anatomical regions belonged to different children from the same sex and age groups. Computer image combinations allowed the merger of the different average images into one single representative idealized image for that age group.

For each age group, prior to creating a composite idealized image from the different selected key images, three image processing steps and enhancements were applied for standardization. First, the background was replaced by a uniform black setting and the image size was adjusted to fit into square images of 800 × 800 pixels. Second, contrast and intensity were optimized using predefined window and level thresholds. Lastly, the image was processed through a special edge enhancement filter based on an unsharp masking algorithm tailored to provide optimum sharpness of bone structure for hand-held devices.

After proper processing and enhancement, the selected images were combined to generate a single “idealized” image for each age group and for each gender. Several images, ranging from two to six, were combined by carefully replacing segments of bones through translation, rotation and warping operations to match the underlying combination image (Fig. 4). The result was a single image representing a combination of parts of hand radiographs from several images. Prior to



▷ **Fig. 14.** Method of selection of the “average” image from a set of nine normal hand radiographs of a given age group. The images were sorted by skeletal maturity six consecutive times based on six anatomical regions. Each time, the middle image was noted as the “average” image for a given anatomical region for that particular age group. This often resulted in the selection of more than one and up to six different images for a given group. An idealized “average” image was then generated by combination of the selected images. Phalanges 1, 2 and 3 indicate proximal, middle and distal, respectively

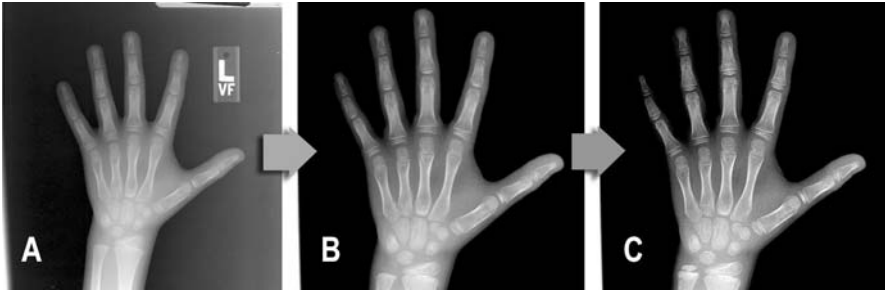


Fig. 15. Processing and enhancement of images. A) Original image; B) Background replaced by a uniform black setting and image size adjusted; C) Optimization of contrast and intensity

using this computer-generated image as a reference, it was reviewed by two experienced pediatric radiologists to evaluate its congruency with other reference images in the digital atlas and its compliance with existing knowledge of progression of bone maturation.

The final set of images was then resized to an image resolution that is compatible with most display resolutions of existing hand-held devices (240 × 240 pixels). Images were also compressed using a JPEG compression algorithm ensuring a reduced size of the image file down to approximately 15 to 20 Kbytes per file. Two versions of each image were generated: one depicting the entire hand and one with an enlargement of specific anatomical segments to enhance reviewer assessment of subtle details and changes in bone structures for each age group. These images provide a “zoomed” version of each image without the need for implementing complex image enlargement functions on the viewing program.

Special software for hand-held PDA devices was developed for easy navigation through the set of images and visual selection of the closest image to a given patient study. A simple user interface consisting of three buttons and a pull-down menu allows the user to easily navigate through the images either chronologically through the age groups or by selecting a specific age from the pull down list (Fig. 5). Once an image has been identified to match the image of a given patient, the user can determine the degree of bone maturity by comparing the chronological age of the patient to the age of the selected image in the atlas. The program includes a formula to calculate the standard deviation by a simple process entailing data entry of the patient’s chronological age.

The basic components of the software were developed in web-compliant HTML format using standard java-scripts for some of the simple functions. This ensures compatibility with most handheld or portable computers that support a web browser capable of displaying standard HTML documents. A special variant of the software was also developed for PALM-operating sys-



Fig. 16. Example of the combination of two hand radiographs from two different individuals of the same age group into a single “idealized” image. The degree of ossification of the carpal bones of the first image were selected as more representative of the “average” skeletal maturation for this age group and were transferred to the second image in replacement of its original carpal bones

tems and for PALM-compatible PDAs. The HTML standard allows the same program to run on a laptop or desktop computer with operating systems such as Windows, Unix, Linux or Macintosh OS. In addition, a separate version of the software was developed that supports a larger image size of 512×512 pixels.

Validation of Standards and Technique

Readings of skeletal maturity using the digital atlas program were validated through comparisons of skeletal maturation determinations using the Greulich and Pyle method by two experienced radiologists. Images from an additional 200 healthy Caucasian children (100 boys, 100 girls) were examined in a double blind reading. Regardless of the radiologist or the method employed to assess skeletal maturity, strong correlations were present between chronological age and bone age, with no statistical difference observed between the digital and Greulich and Pyle atlases.

The digital atlas was tested on a variety of handheld devices, and laptop and desktop computers. Devices displaying color images with at least 8 bits of dynamic range and a screen resolution of at least 320×320 pixels were capable of depicting the hand radiographs with reasonably good quality. The zoom function improved visualization of the centers that best characterize skeletal development for the subject’s chronological age. While a more flexible zoom and panning option could further enhance the depiction of the images, the current diversity of handheld devices on the market precludes the generic implementation of such a function on all existing devices; brand specific versions would be necessary for each operating system.

Table 1. Correlations between chronological age and bone age assessed with the Greulich and Pyle method and the digital atlas in healthy children of European descent of all ages and in adolescents 12 to 15 years old. The digital system provided slightly stronger correlations, although these differences were not statistically significant.

Ages 0 – 18 Y				
	Greulich and Pyle		Digital Atlas	
	Finger	Carpal	Finger	Carpal
Sex (n)				
Boys (100)	.987	.985	.991	.988
Girls (100)	.984	.985	.988	.987

Ages 12–15 Y				
	Greulich and Pyle		Digital Atlas	
	Finger	Carpal	Finger	Carpal
Sex (n)				
Boys (26)	.845	.793	.881	.867
Girls (26)	.822	.780	.853	.842

Software User Manual

The first page of the digital atlas displays two distinctive icons for selection of male or female images.

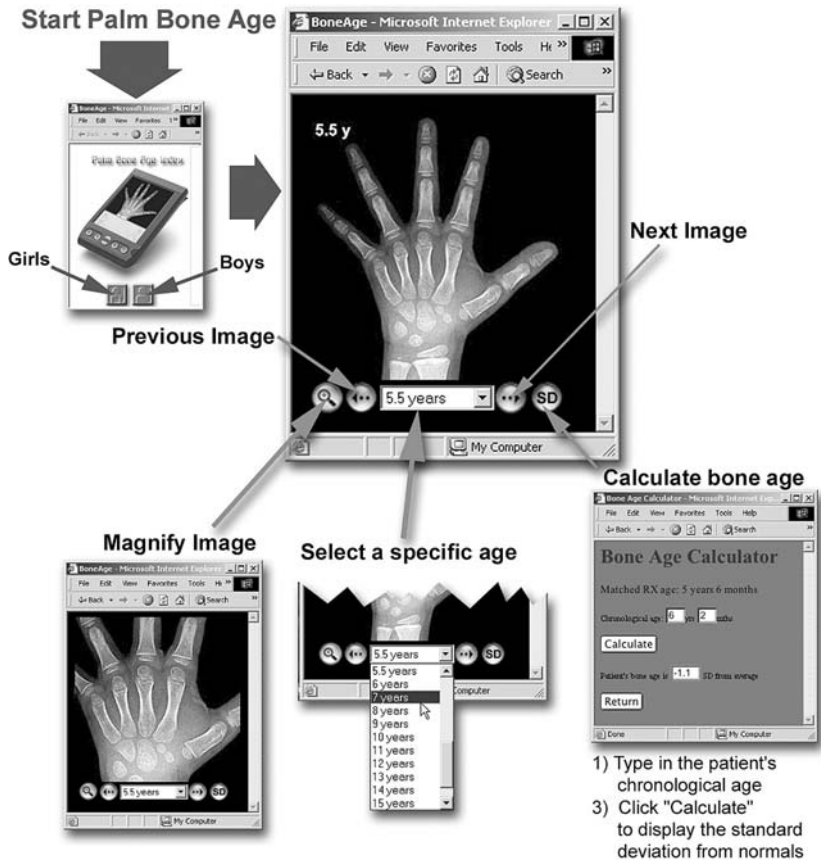


Fig. 17. Schematic diagram depicting the main features of the software and the simplified user interface that facilitates navigation between chronological hand radiographs to select a matching image corresponding to the patient image being assessed. The software also provides a simple way to obtain the estimated standard deviation from normal

The most practical way of using the software to estimate bone maturity from a hand radiograph is as follows:

- 1) First, locate the closest matching image to the hand and wrist radiograph to be interpreted. The reviewer should primarily focus on the centers that best characterize skeletal development for the subject's chronological age. As stated previously, during infancy and in toddlers, the presence or absence of certain carpal or epiphyseal ossification centers will provide the most useful clues. Throughout childhood, the size of the epiphyses in relation to the metaphyses in the distal and middle phalanges will be the most helpful markers of skeletal maturity. In younger teenagers, the degree of epiphyseal fusion in the phalanges, and in older teenagers, the degree of epiphyseal fusion in the radius and ulna, are the strongest indicators of skeletal maturity. If the radiograph being evaluated does not exactly correspond to a specific age standard, but falls between two adjacent references, the bone age should also be interpreted as an intermediate between the two standards. Occasionally, there may also be a disparity between the skeletal maturation of the phalanges and carpal bones. In such cases, two different estimated ages can be reported.
- 2) Once the matching image is identified, press the "SD" button on the lower right corner of the screen.
- 3) A calculation page will then appear indicating the bone age of the image selected at the top of the screen. Enter the chronological age of the subject being evaluated and press "Calculate". The program will provide the offset of the bone age and chronological age and calculate the standard deviation from the normal population. If needed, the process may be repeated for separate assessments of the phalangeal and carpal bones.

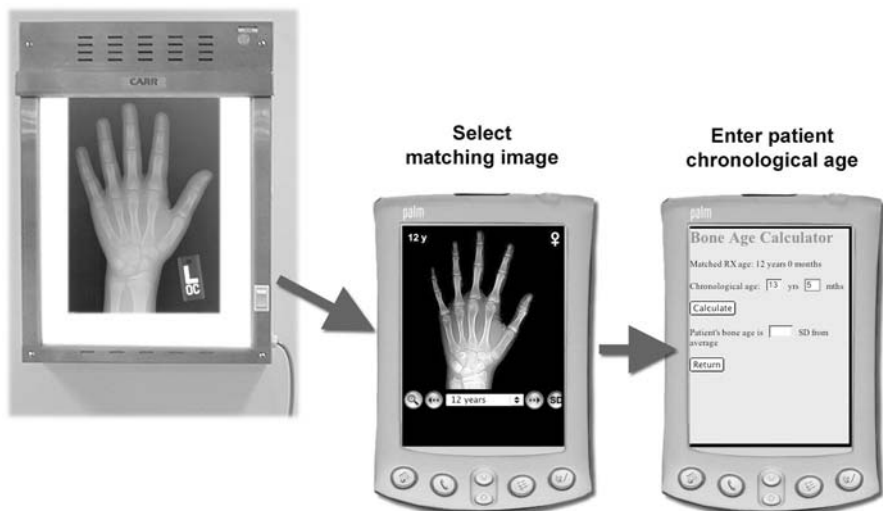


Fig. 18. Illustration of the two-step process needed for bone age assessment using the digital atlas

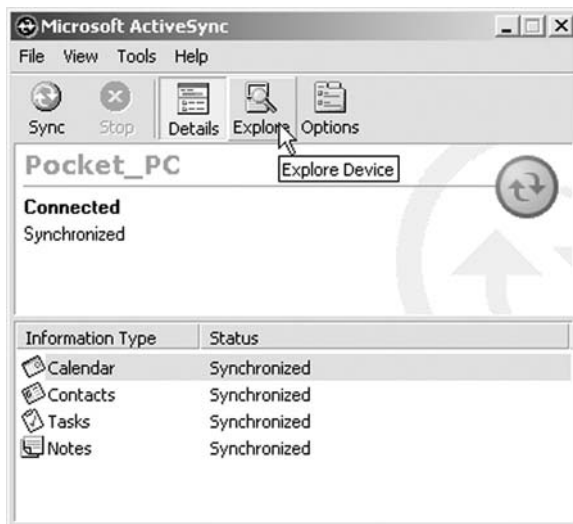
Software Installation

Installing the digital bone age atlas on a PC

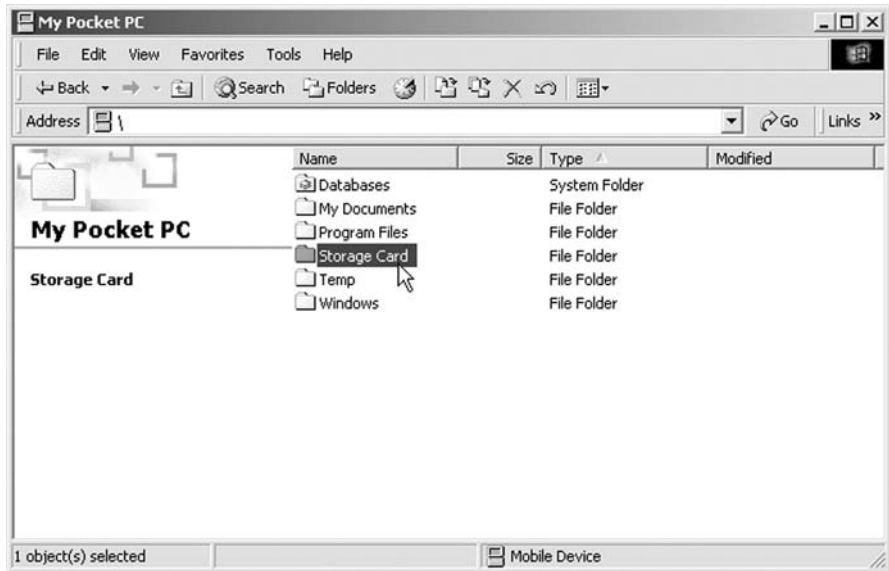
A version of the digital atlas compatible with Macintosh- or Windows-based personal computers is provided in the companion CD of this book. The atlas is composed of HTML pages that only need a web browser to display and navigate through the images of different ages. The PC version is located in a separate folder called “Computer Version” on the CD. The main home page, called “Bone Age”, can be directly accessed from the CD or by copying the contents of the folder onto the hard disk and then opening the main home page. Depending on the speed of the computer’s CD ROM drive, the performance of navigating rapidly between different ages may be significantly faster if the files are copied onto the hard disk.

Installing the digital bone age atlas on a Pocket PC

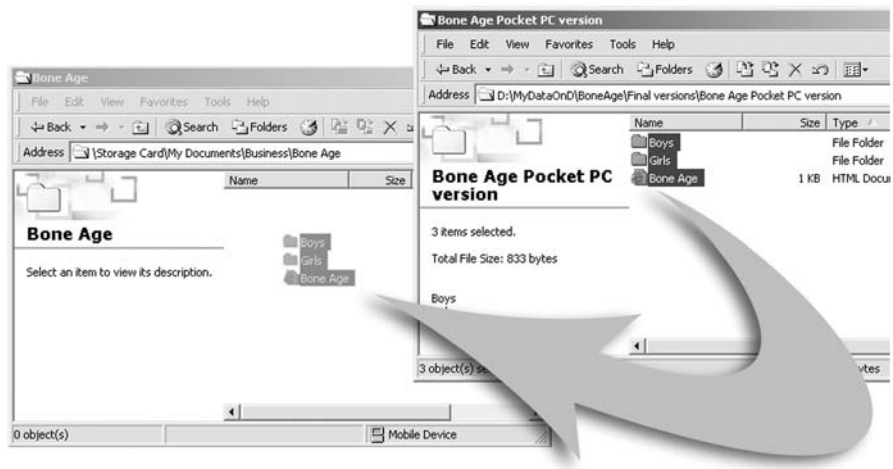
The Pocket PC version of the digital atlas is also in an HTML format that is compatible with Internet Explorer browser version designed for Pocket PC devices. The difference with the PC version is that the images are resized to 240×240 pixels to fit in most current Pocket PC display resolutions. The files for the Pocket PC version are located on the CD in a separate folder called “Pocket PC version”. Once the CD is inserted in the computer, open the folder and connect the Pocket PC or Handheld device to the computer, which should automatically launch the synchronization program. Once the synchronization of your calendar, contacts etc., is completed, select the “Explore” icon to access the files on your Pocket PC memory.



Choose the directory on the Pocket PC that contains the digital atlas files. These files may be stored in the main memory or on a separate memory card inserted in the Pocket PC.

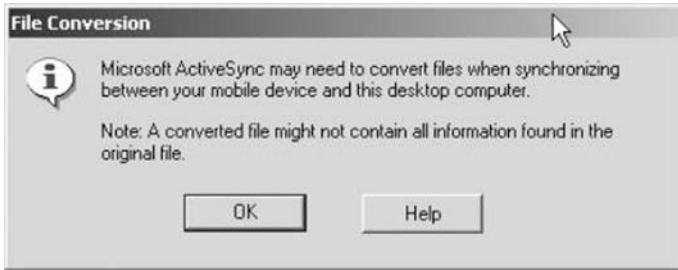


It is recommended that a new folder be created called "Bone Age" where all files can be transferred. Once the destination folder has been selected, return to the window that was opened on the CD containing the Pocket PC version.

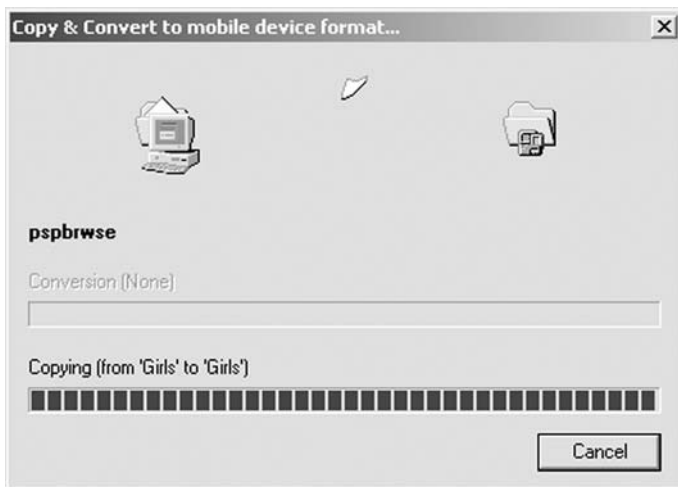


Thereafter, “drag-and-drop” the three items called Bone Age, Girls, and Boys from the CD folder to the Pocket PC folder.

Before starting the file transfer, a warning will appear on the computer:



Click OK to continue. The program will then start transferring the files from the CD to the Pocket PC. This can take several minutes.



When the transfers are completed, disconnect the Pocket PC and open the file called Bone Age. There are two methods to open the Bone Age file: indirectly through the Explorer browser, or directly through retrieving it from the folder where it was downloaded by double clicking on it. The home page of the program that offers you the choice between Boys and Girls through two distinctive icons will appear.



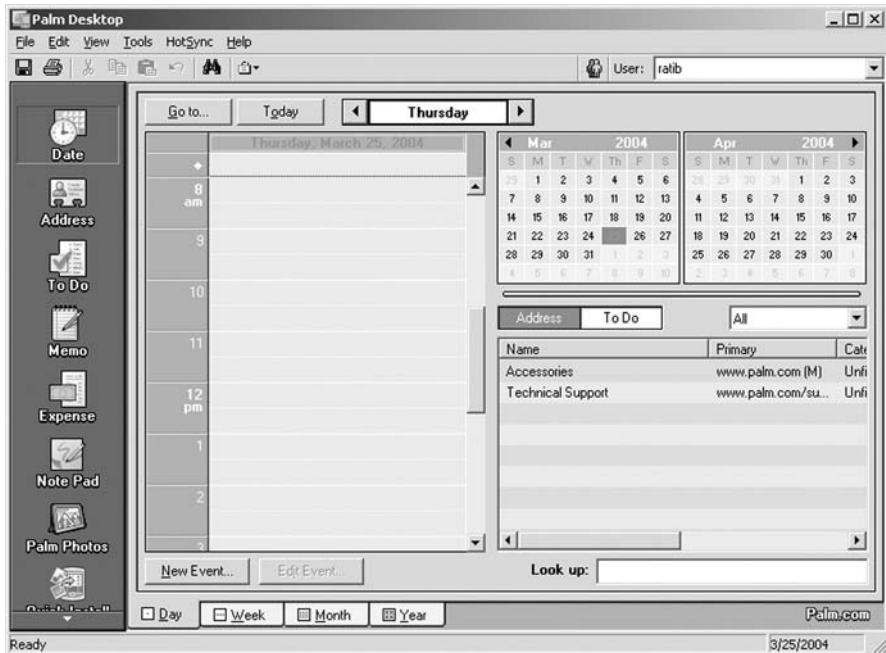
Installing the digital bone age atlas on a Palm PDA

Connect the PDA to your computer.

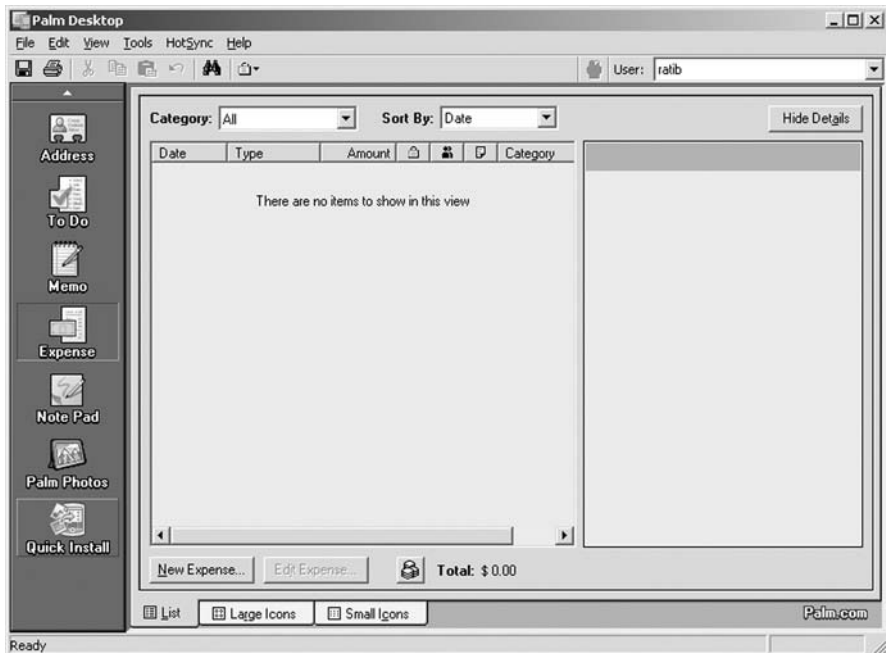
Make sure the Palm PDA can be synchronized to the computer using the Hotsync program.

Step 1. Copy the BoneAge.prc file from the CD ROM to the computer hard drive.

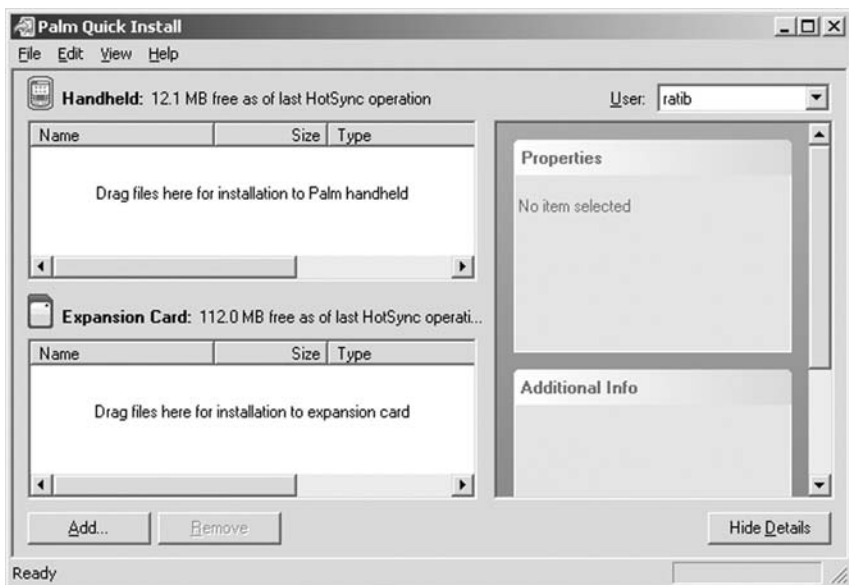
Step 2. Open the Palm PDA desktop program. If Windows is being used, click Start → Programs → Palm Desktop → Palm Desktop.



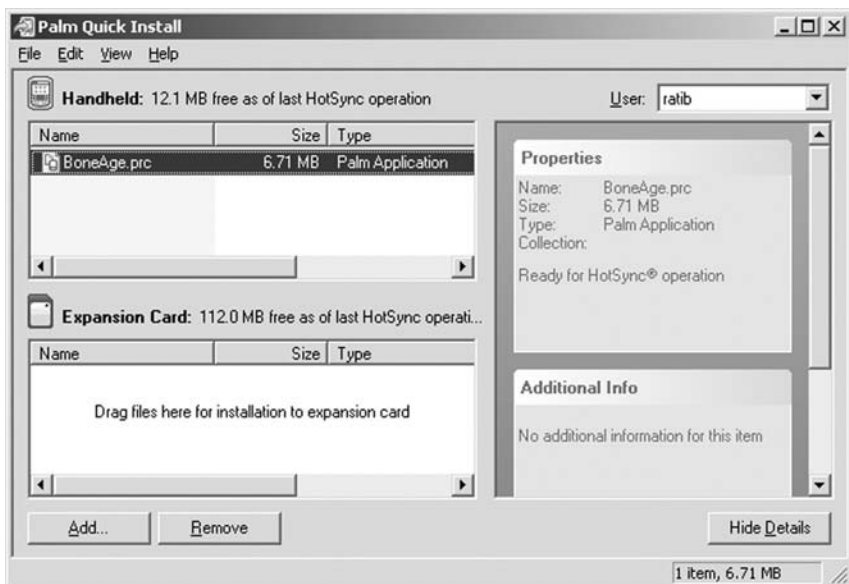
Step 3. On the left hand quick panel, choose **Quick Install**.



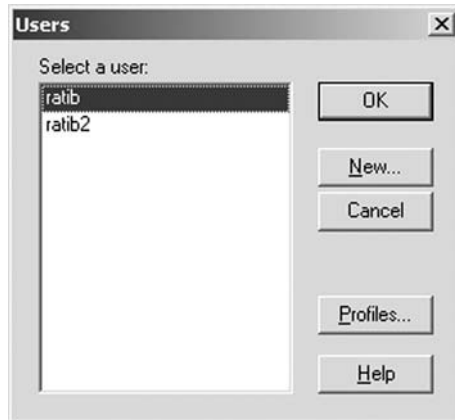
Step 4. Verify that the correct handheld device name is selected in the top right hand drop down box.



Step 5. Drag the BoneAge.prc file from the hard drive into the top left window panel, entitled **Handheld**, with the notation “Drag files here for installation to Palm handheld”.



Step 6. Click the hot sync button on the hot sync cradle. Choose the handheld name to hot sync to.



Once the hot sync is finished, the application can now be found in the Palm PDA titled "Bone Age".



Reference Images

Caucasian Boys and Girls

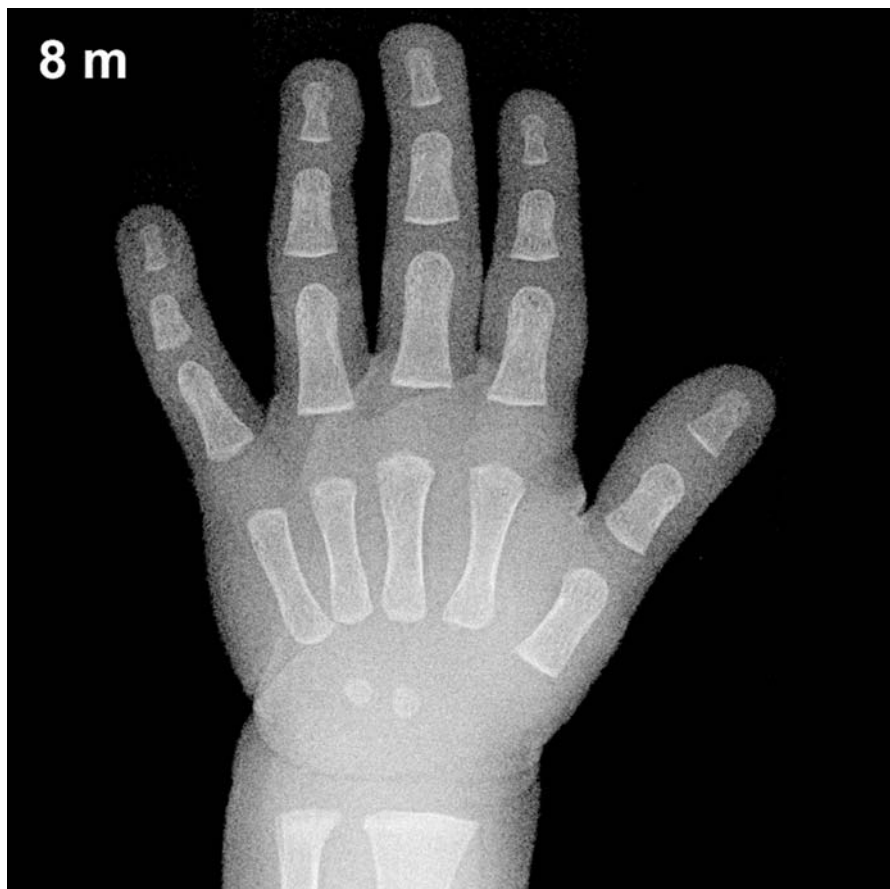


Fig. A1. 8-month-old boy

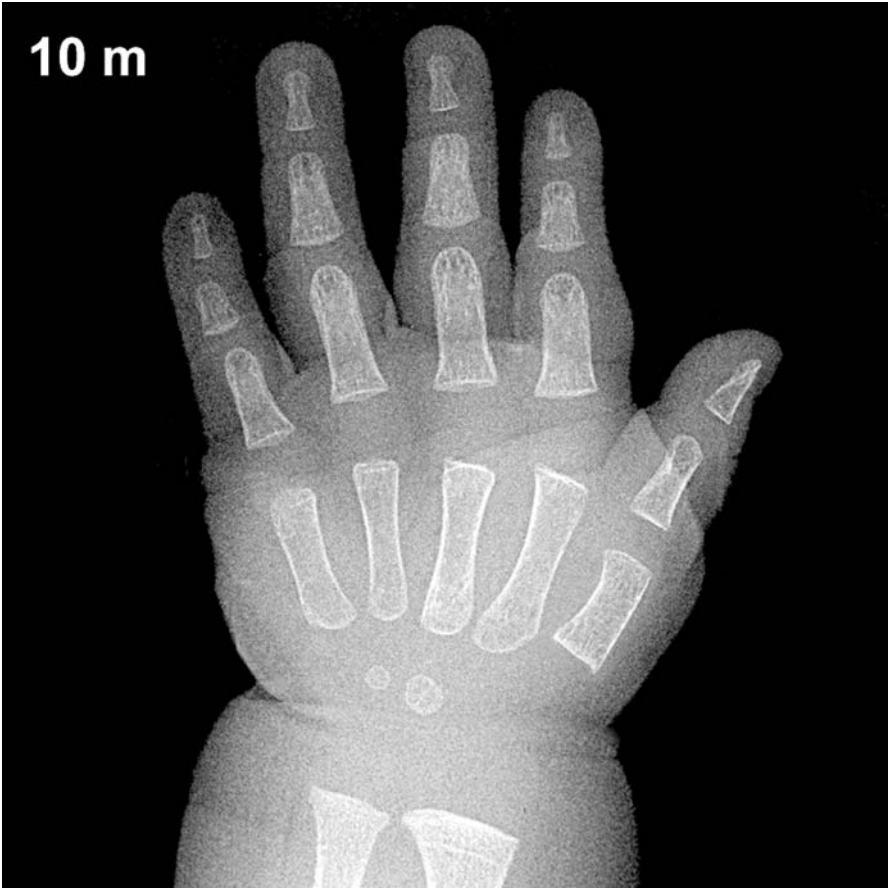


Fig. A2. 10-month-old boy

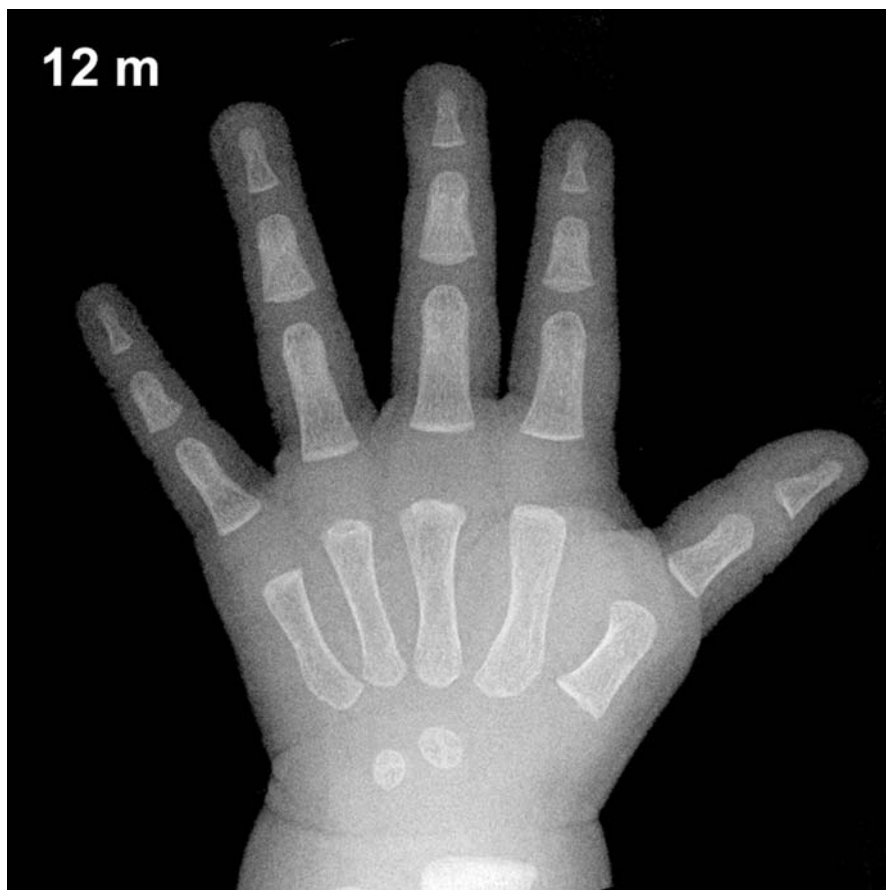


Fig. A3. 12-month-old boy

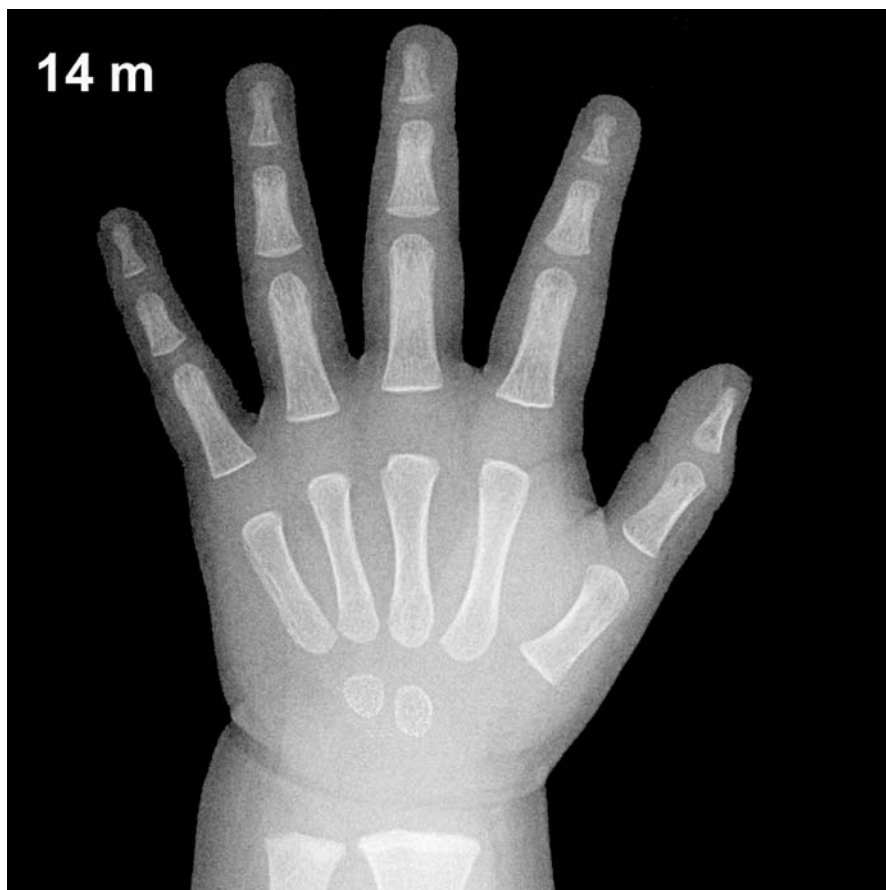


Fig. A4. 14-month-old boy



Fig. A5. 16-month-old boy



Fig. A6. 18-month-old boy

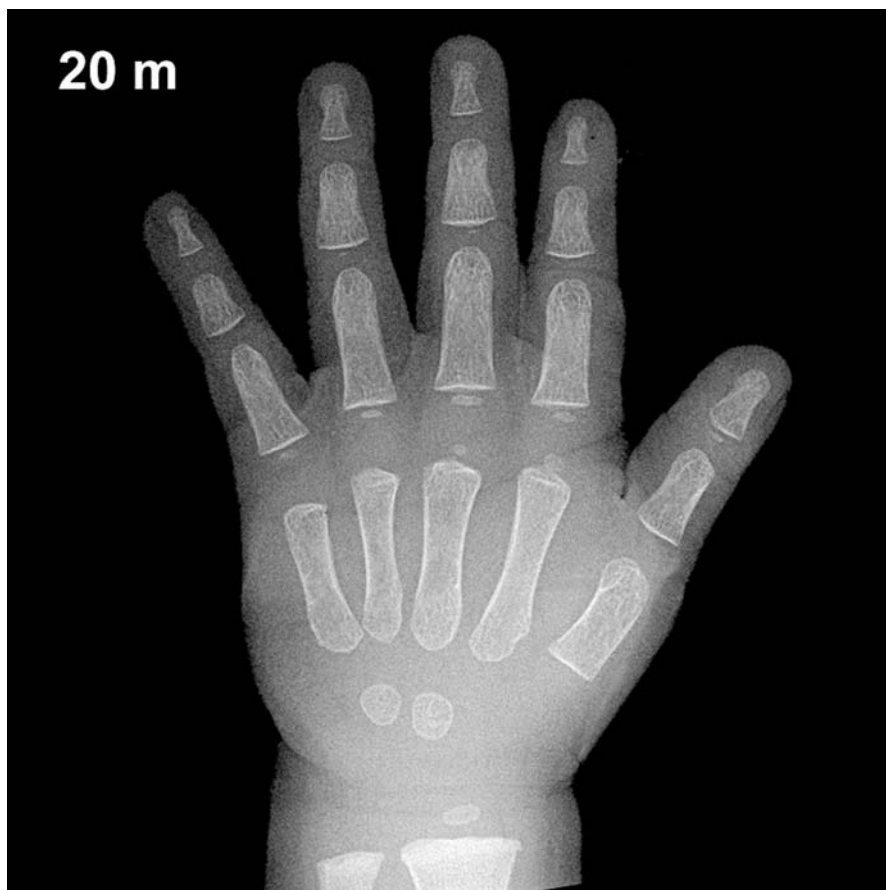


Fig. A7. 20-month-old boy

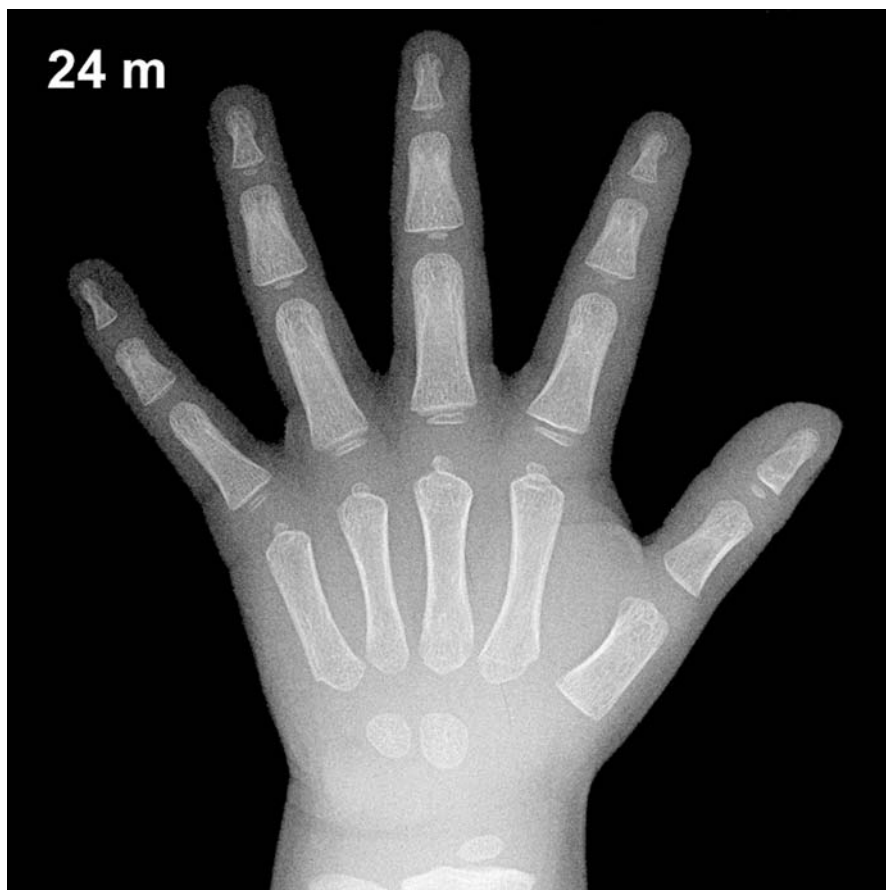


Fig. A8. 2-year-old boy

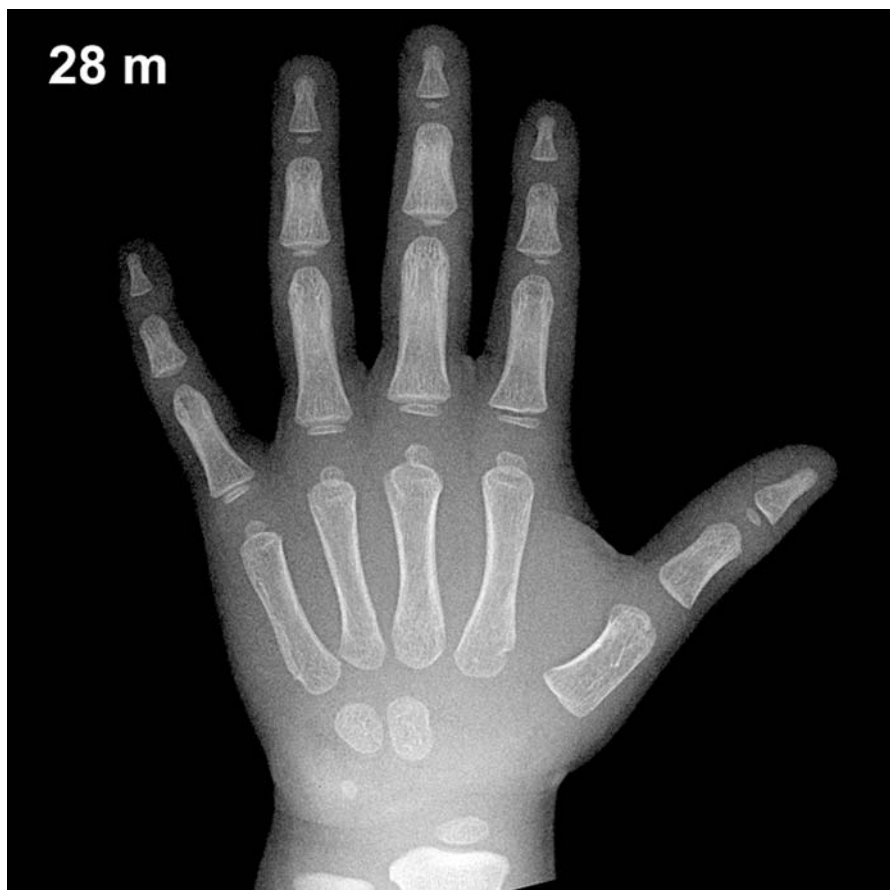


Fig. A9. 28-month-old boy

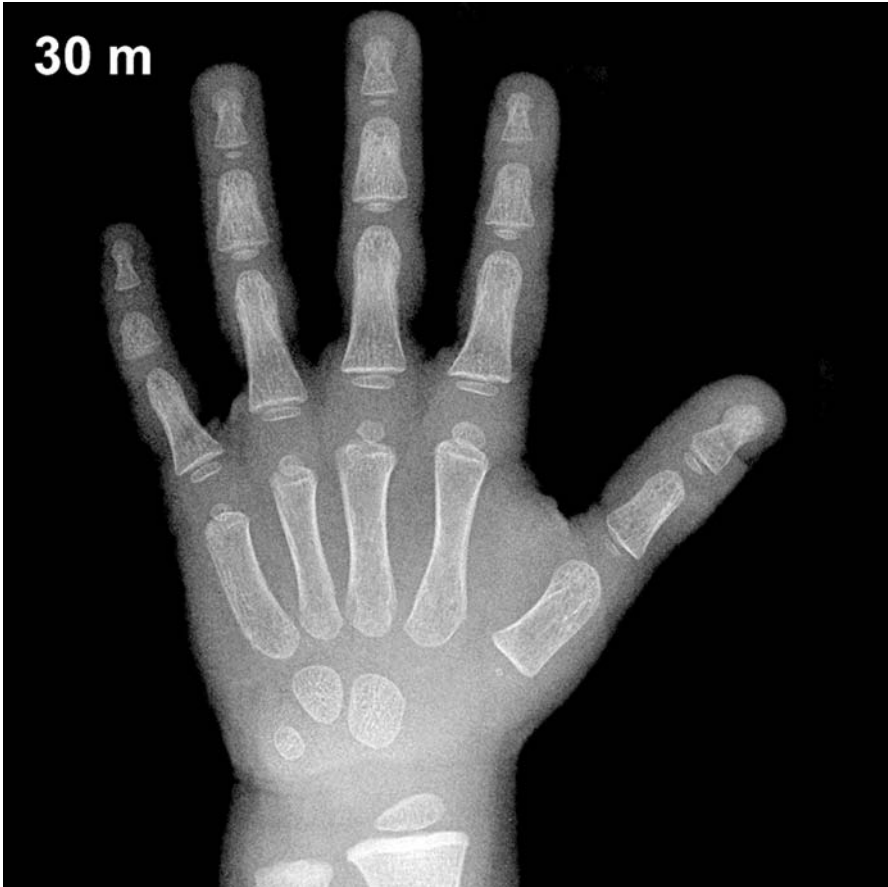


Fig. A10. 2.5-year-old boy



Fig. A11. 3-year-old boy



Fig. A12. 3.5-year-old boy



Fig. A13. 4-year-old boy



Fig. A14. 4.5-year-old boy

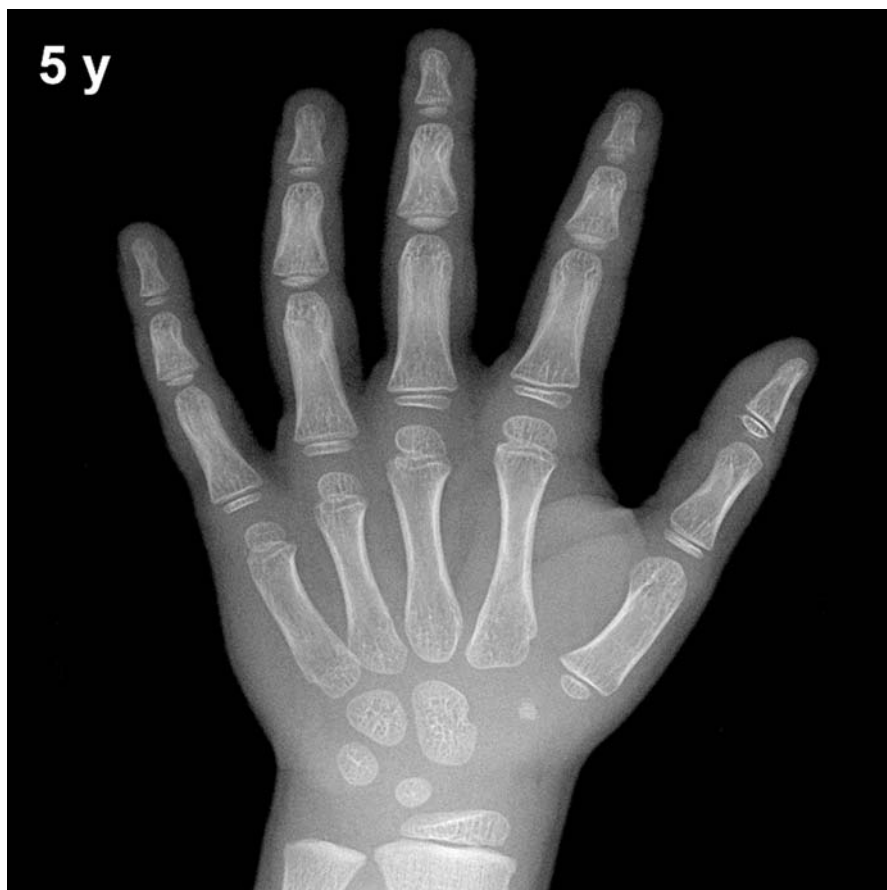


Fig. A15. 5-year-old boy



Fig. A16. 5.5-year-old boy

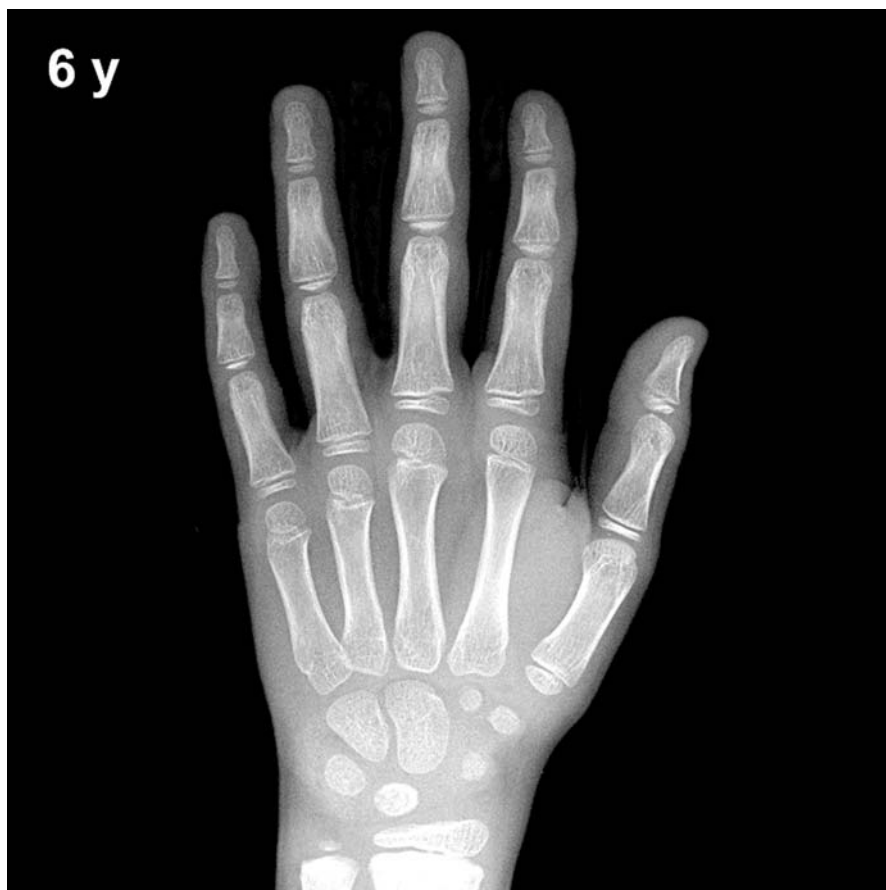


Fig. A17. 6-year-old boy



Fig. A18. 7-year-old boy

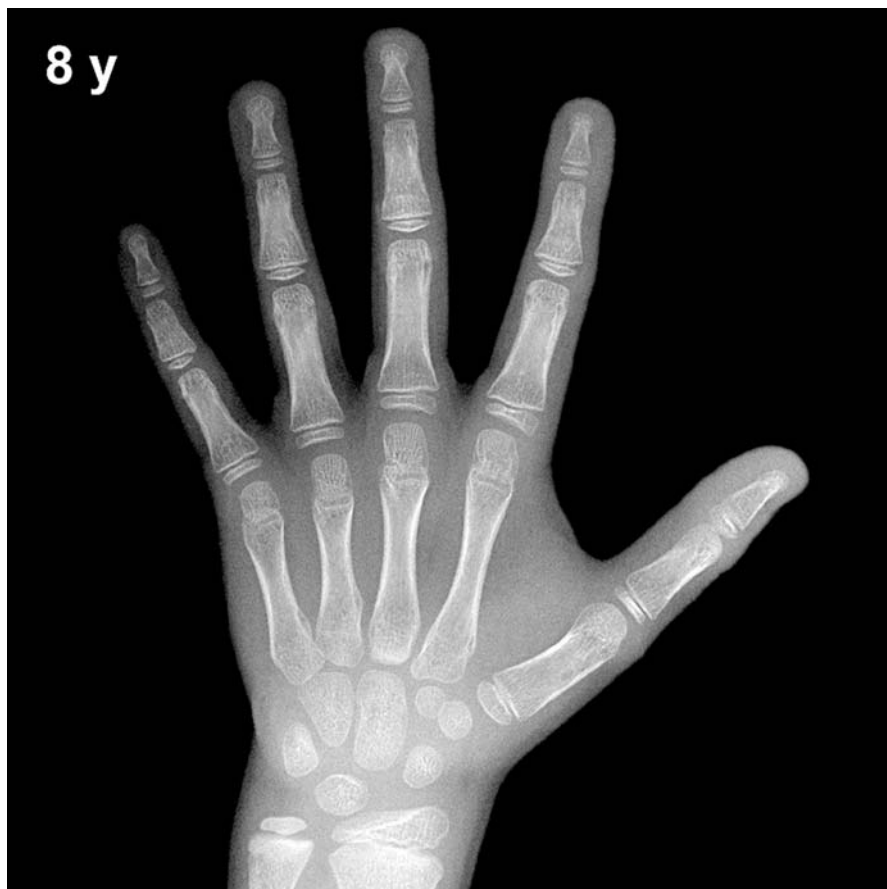


Fig. A19. 8-year-old boy

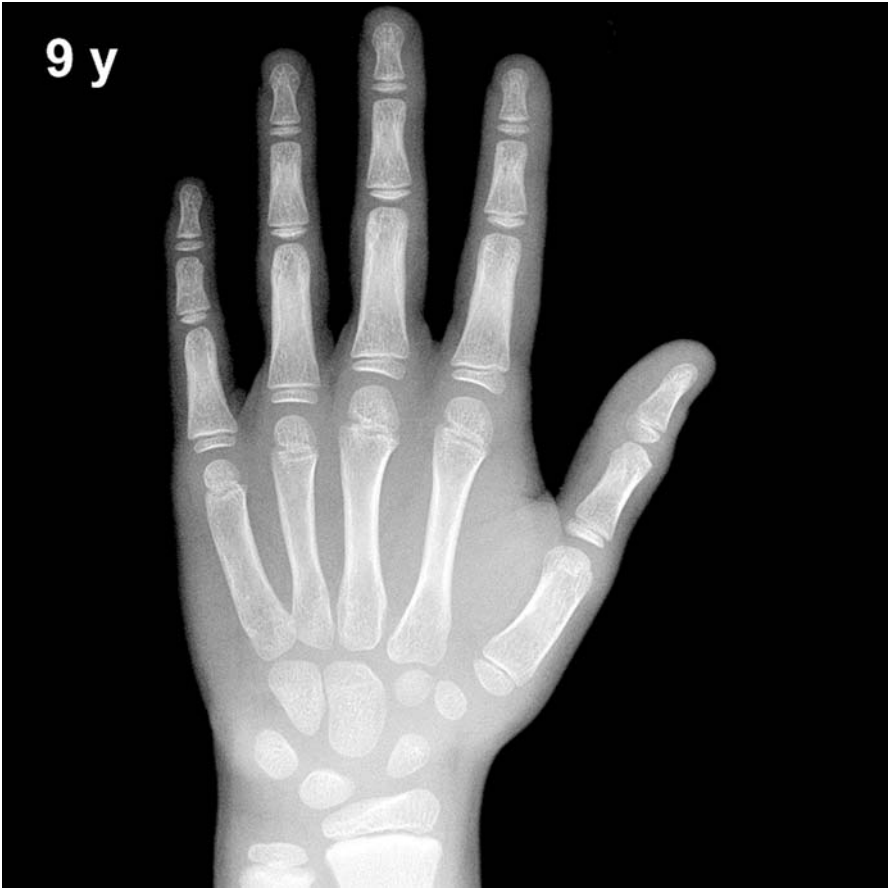


Fig. A20. 9-year-old boy

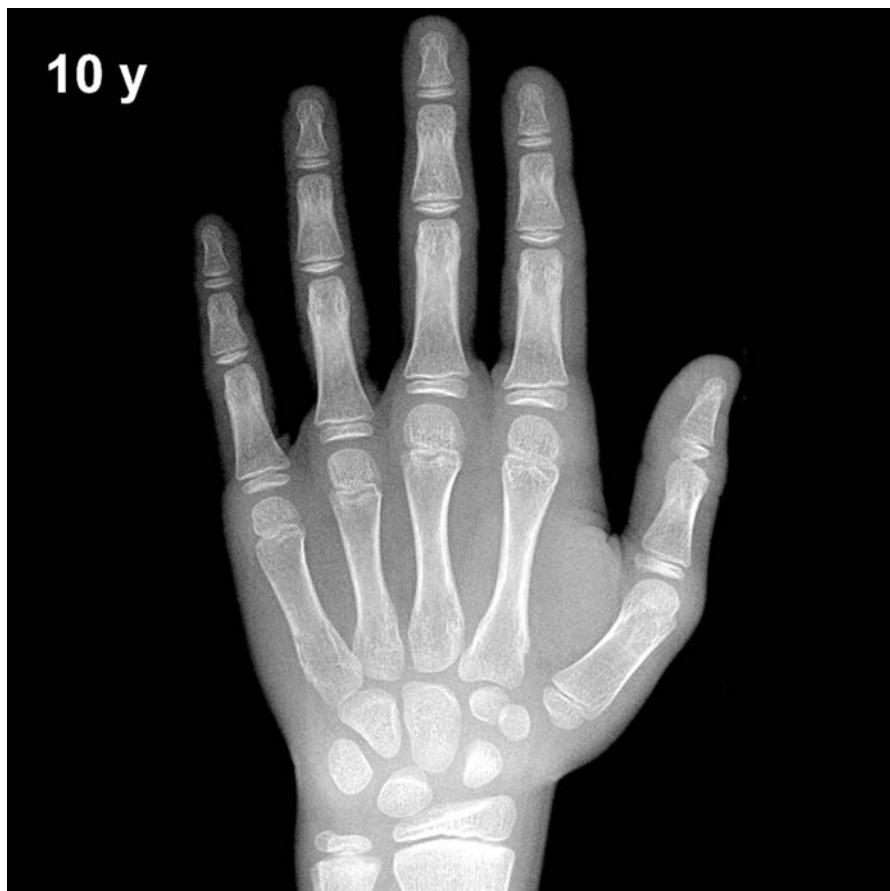


Fig. A21. 10-year-old boy

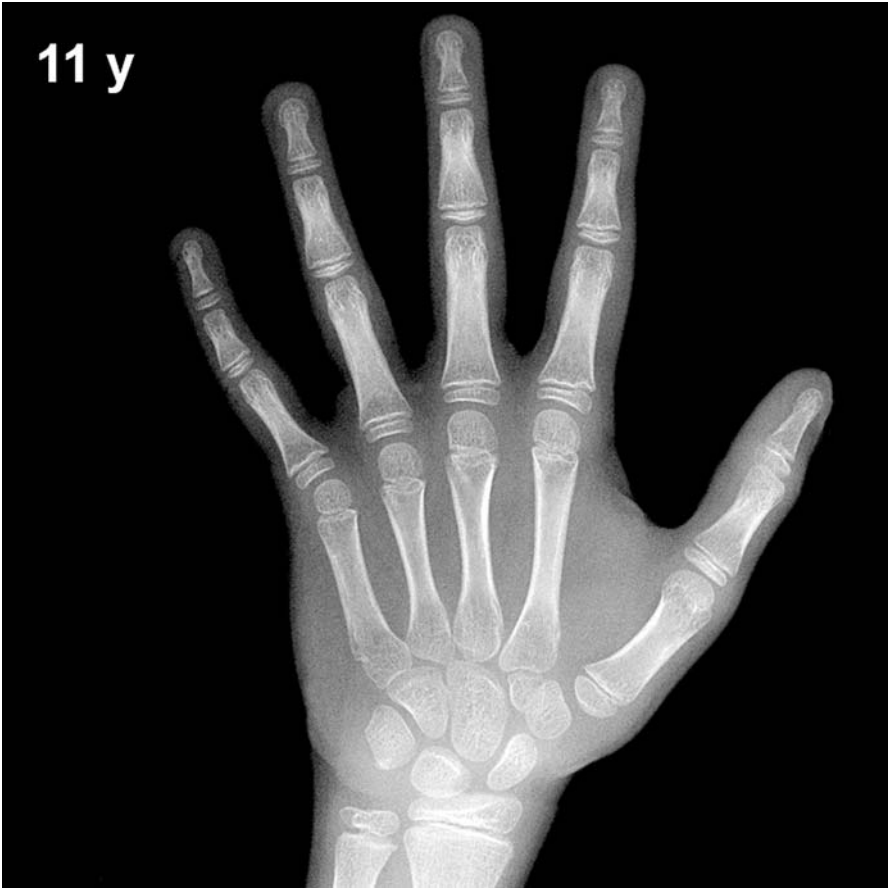


Fig. A22. 11-year-old boy

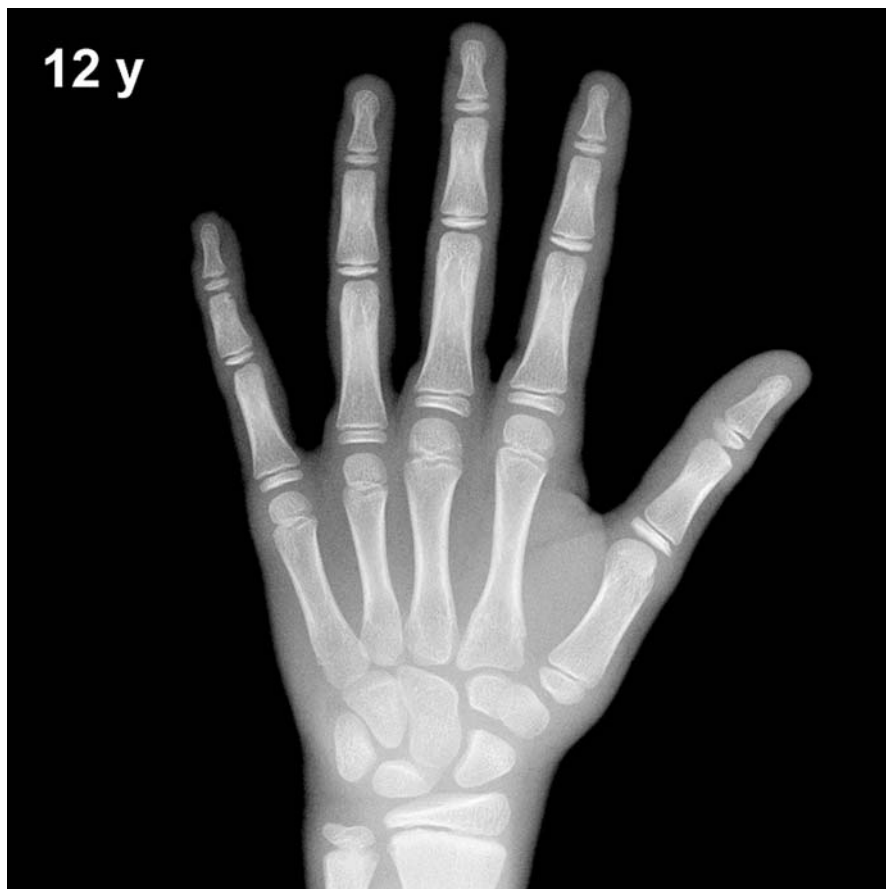


Fig. A23. 12-year-old boy



Fig. A24. 13-year-old boy



Fig. A25. 14-year-old boy



Fig. A26. 15-year-old boy

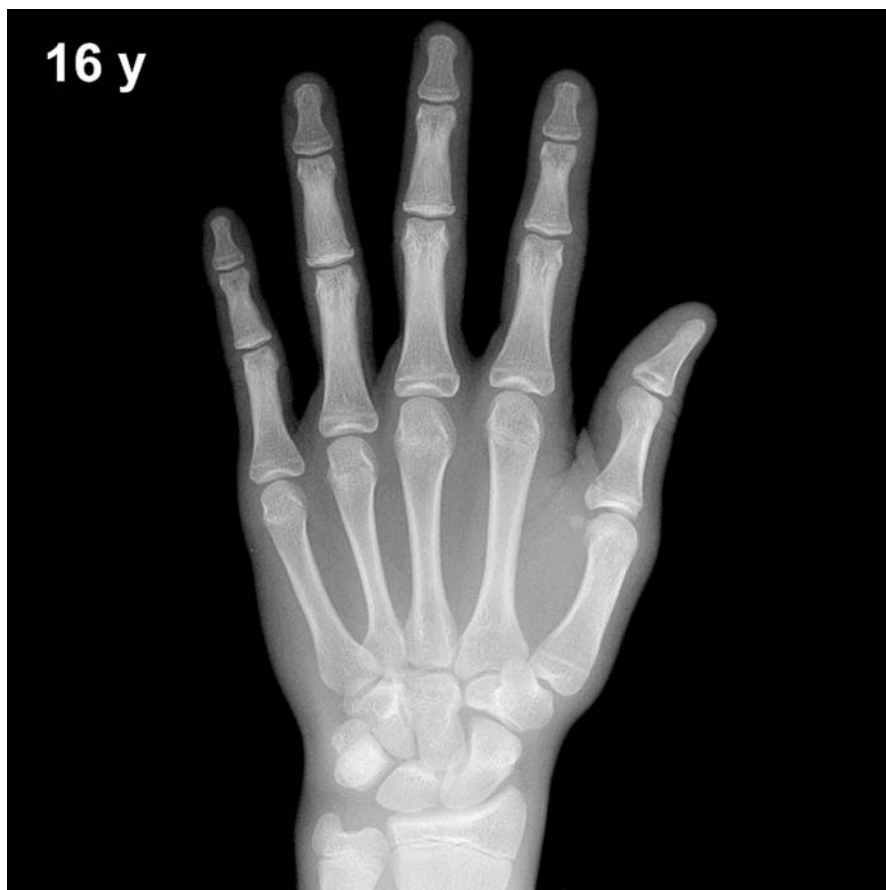


Fig. A27. 16-year-old boy



Fig. A28. 17-year-old boy



Fig. A29. 18-year-old boy

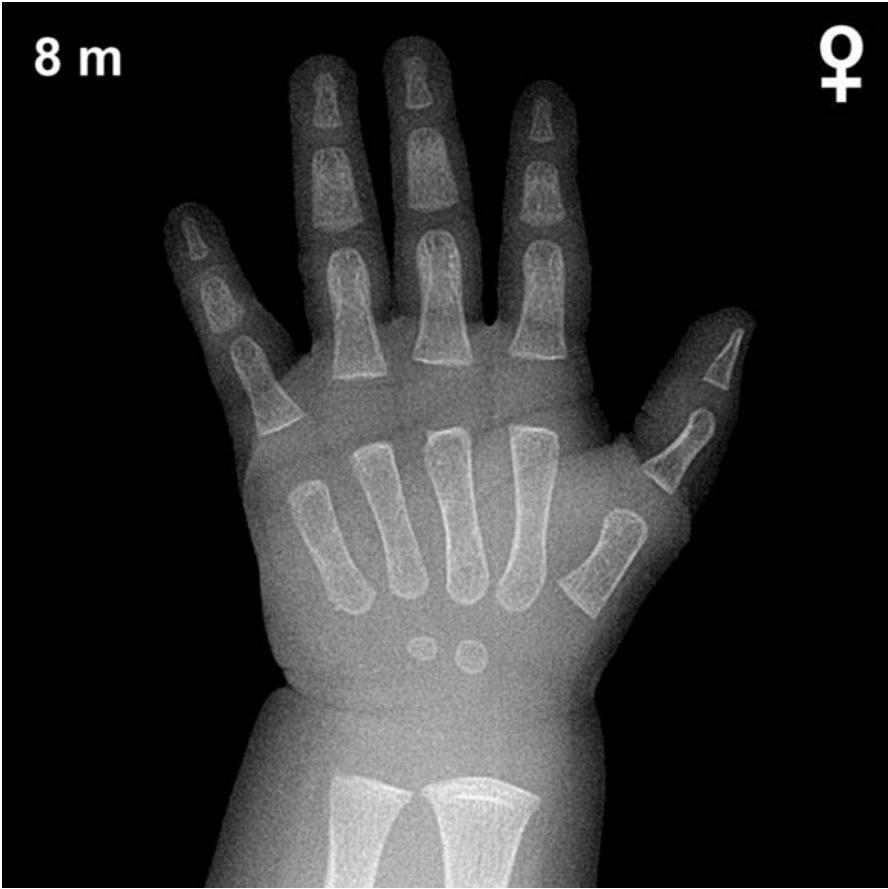


Fig. A30. 8-month-old girl

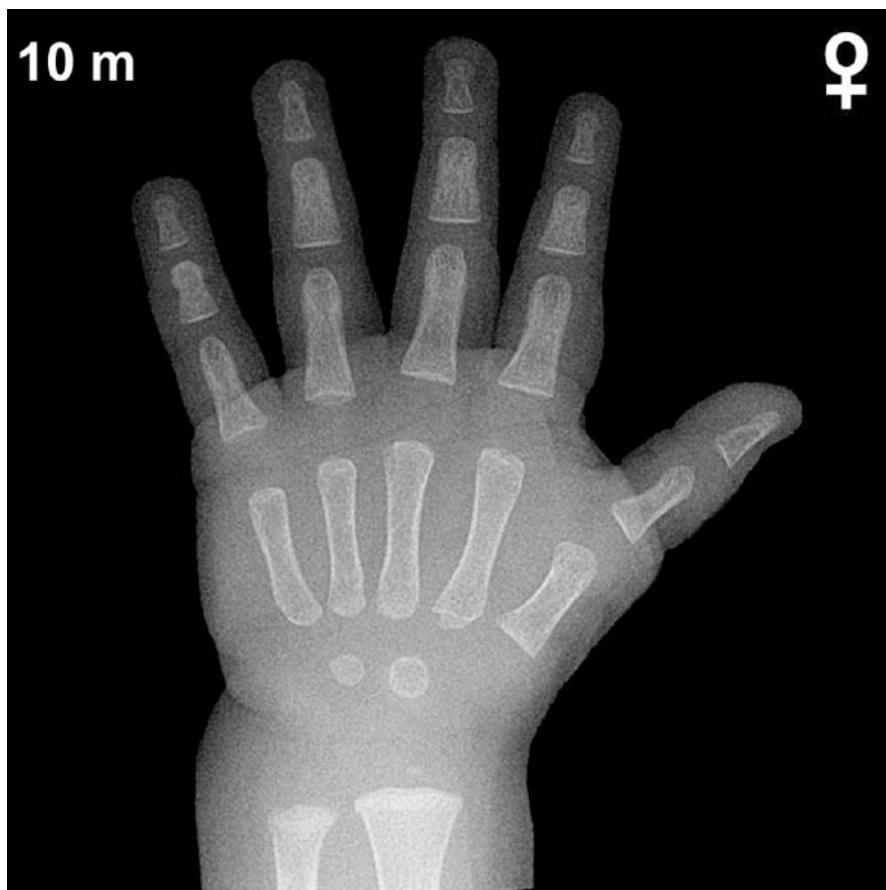


Fig. A31. 10-month-old girl

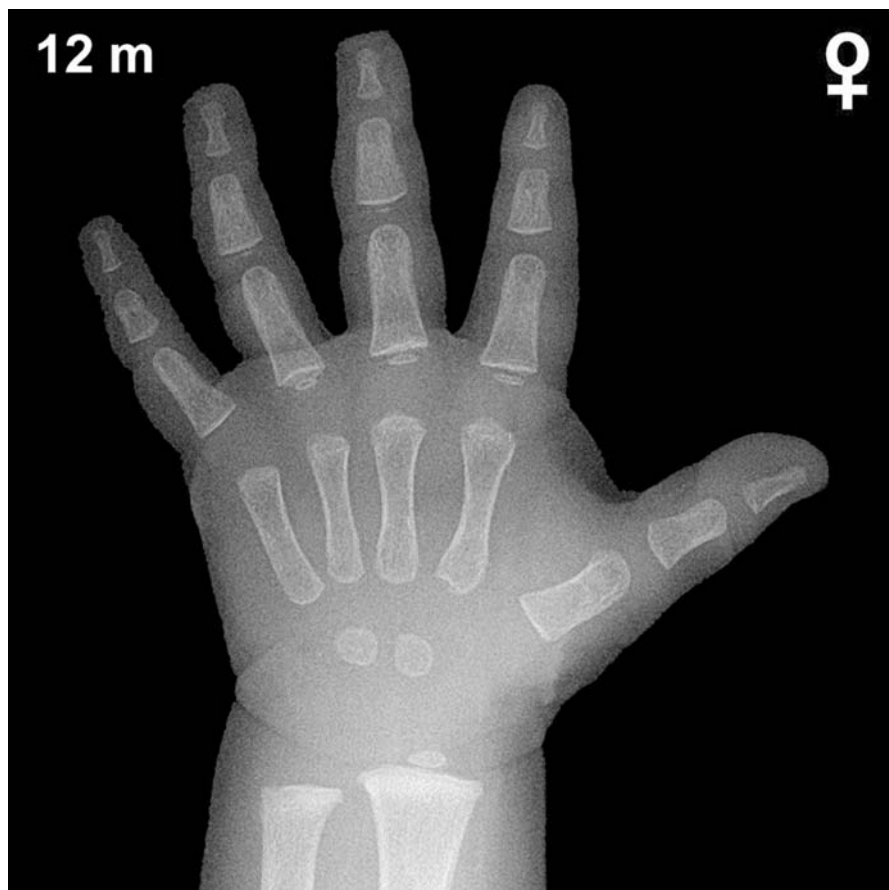


Fig. A32. 12-month-old girl

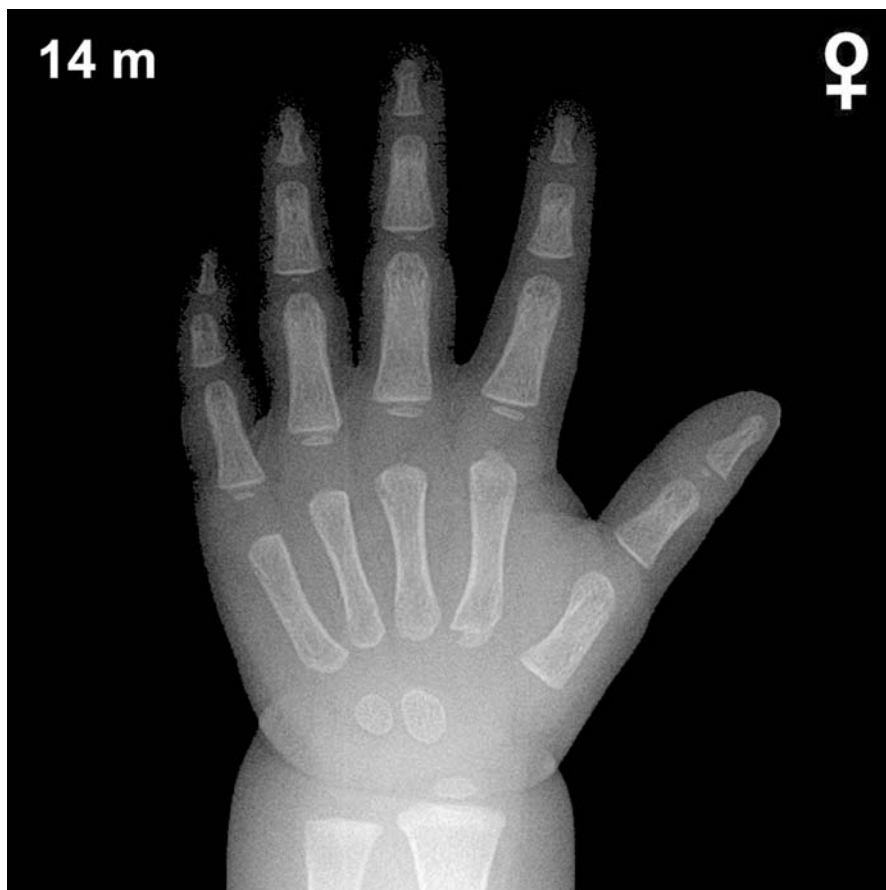


Fig. A33. 14-month-old girl

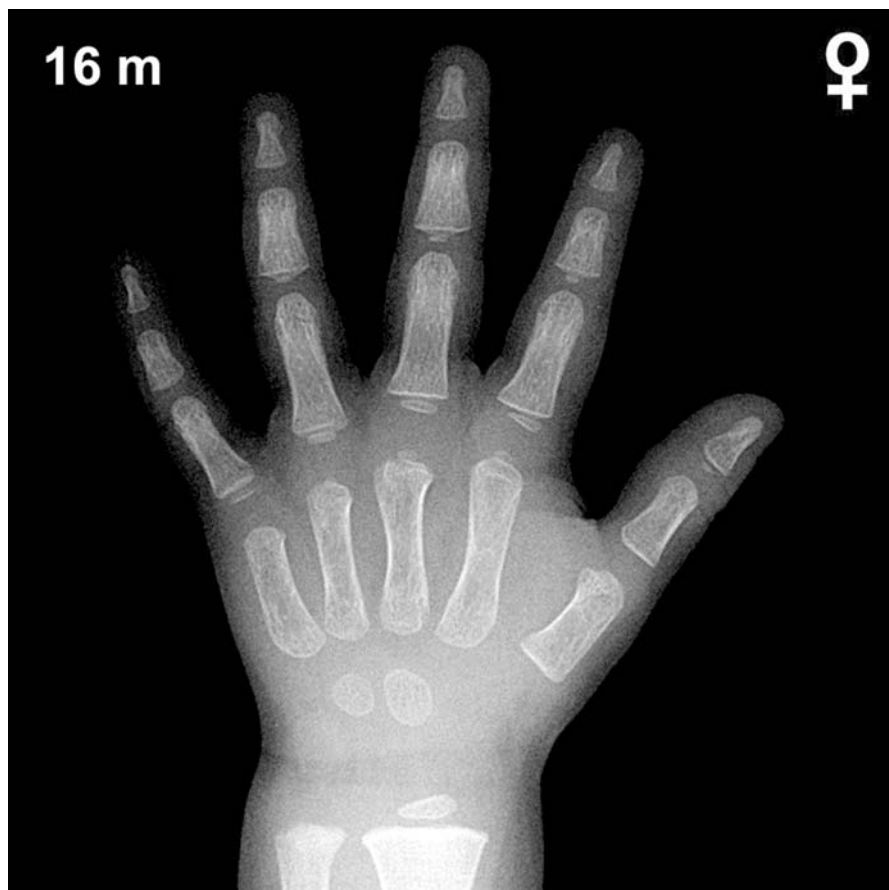


Fig. A34. 16-month-old girl

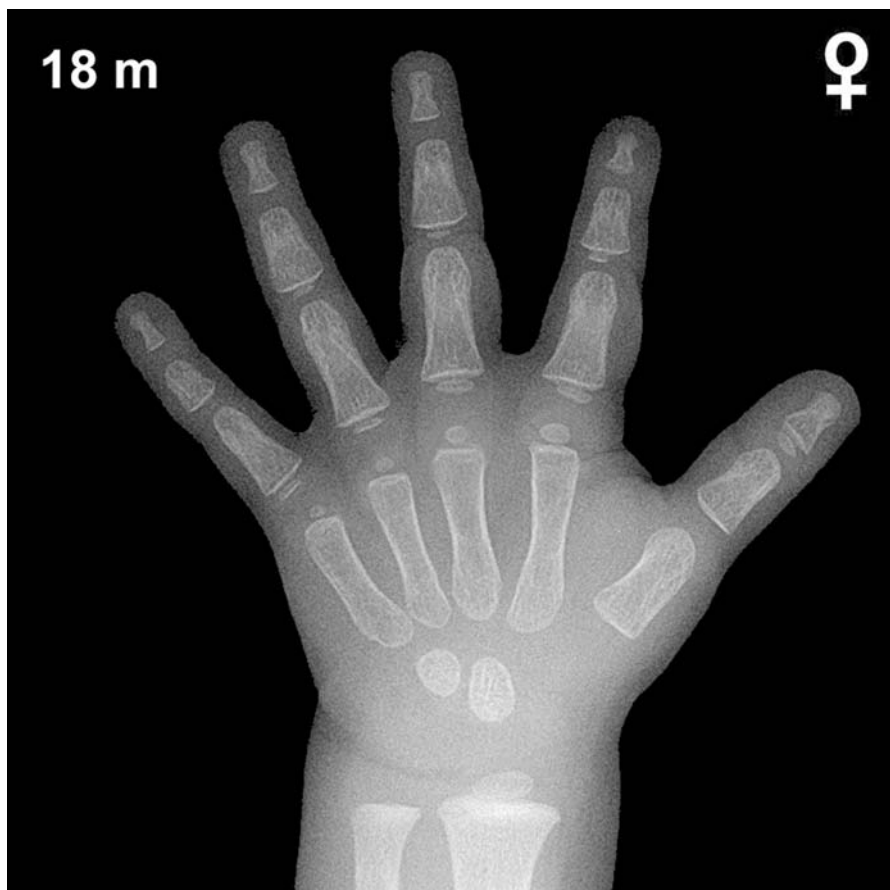


Fig. A35. 18-month-old girl

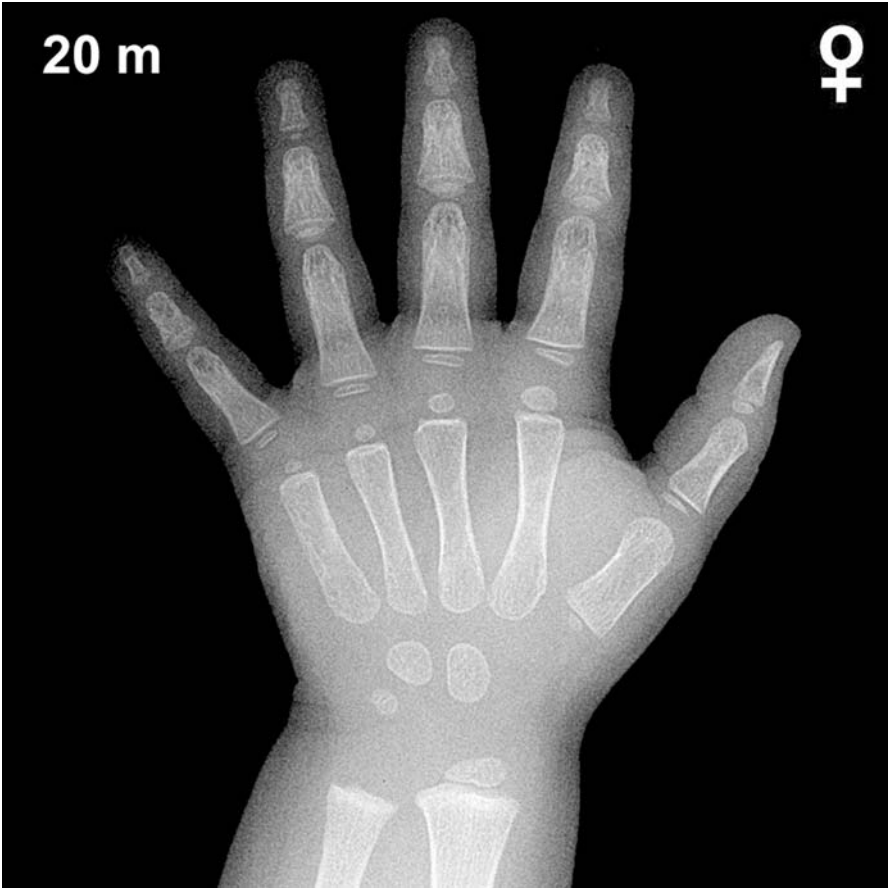


Fig. A36. 20-month-old girl

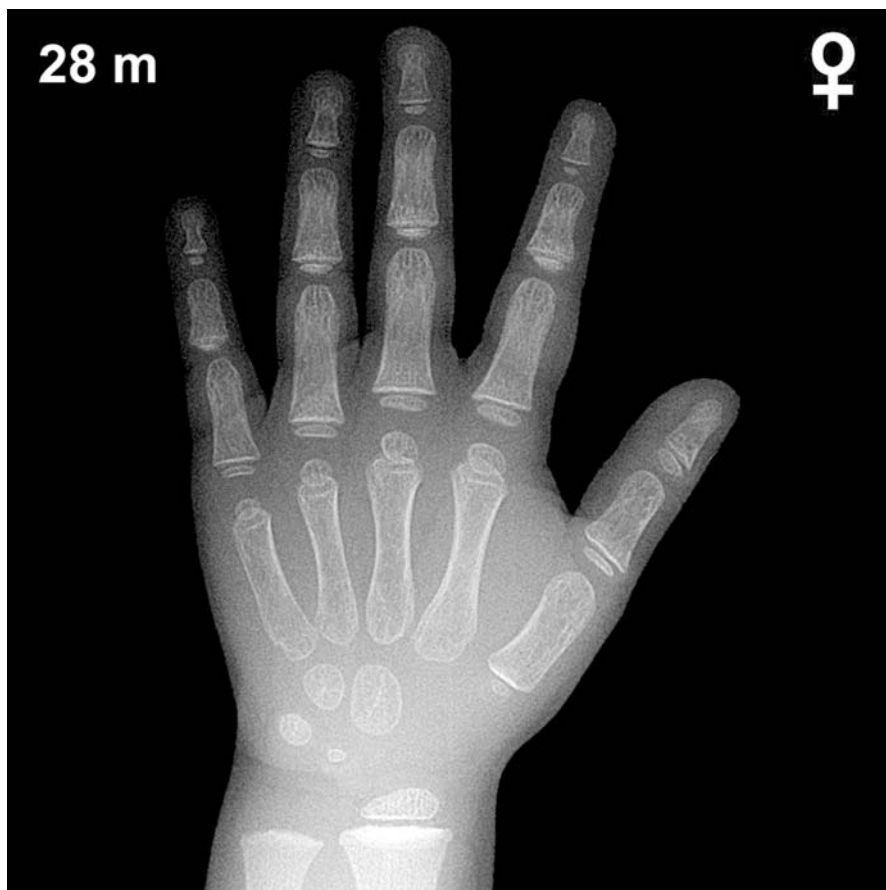


Fig. A37. 24-month-old girl

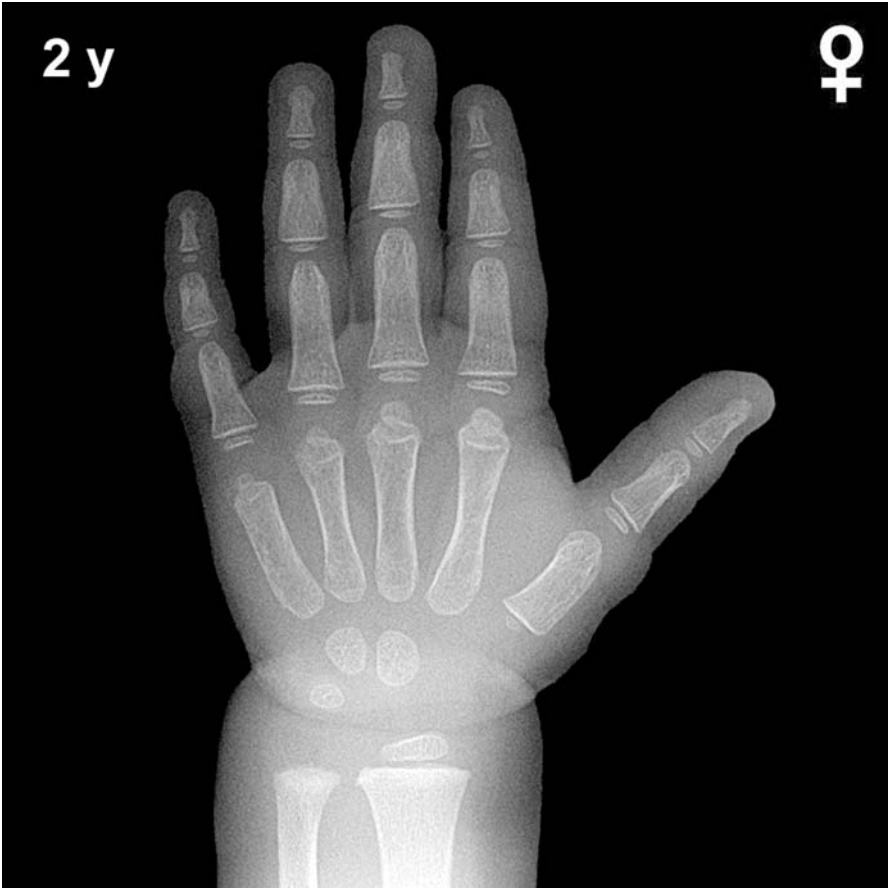


Fig. A38. 28-month-old girl

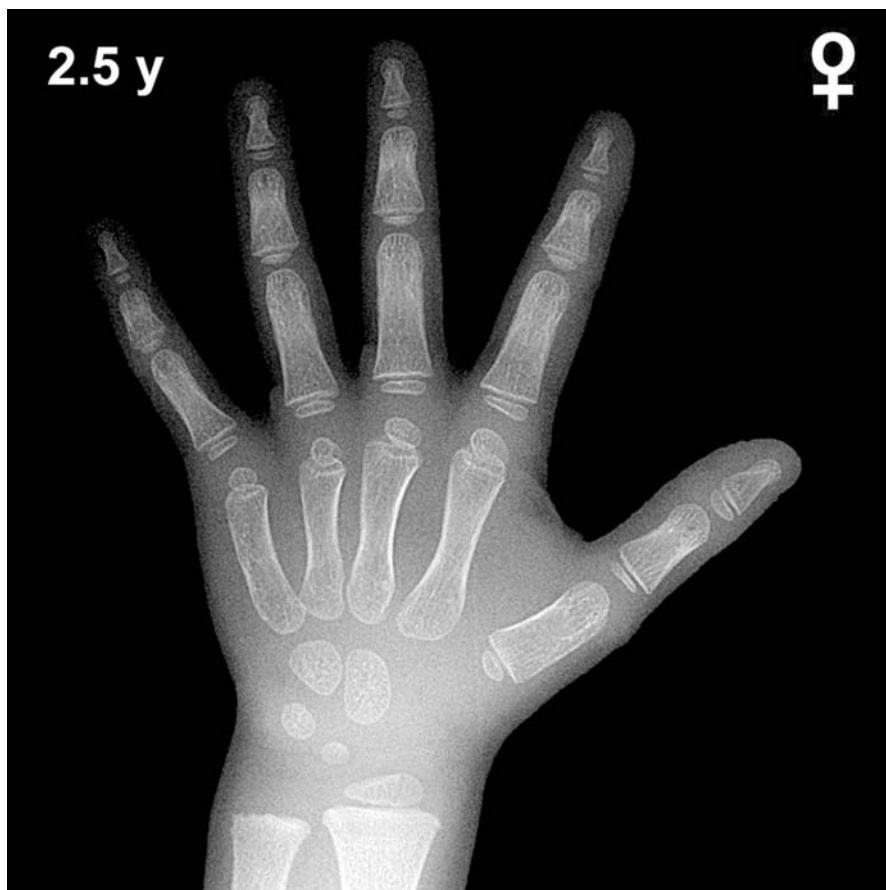


Fig. A39. 2.5-year-old girl

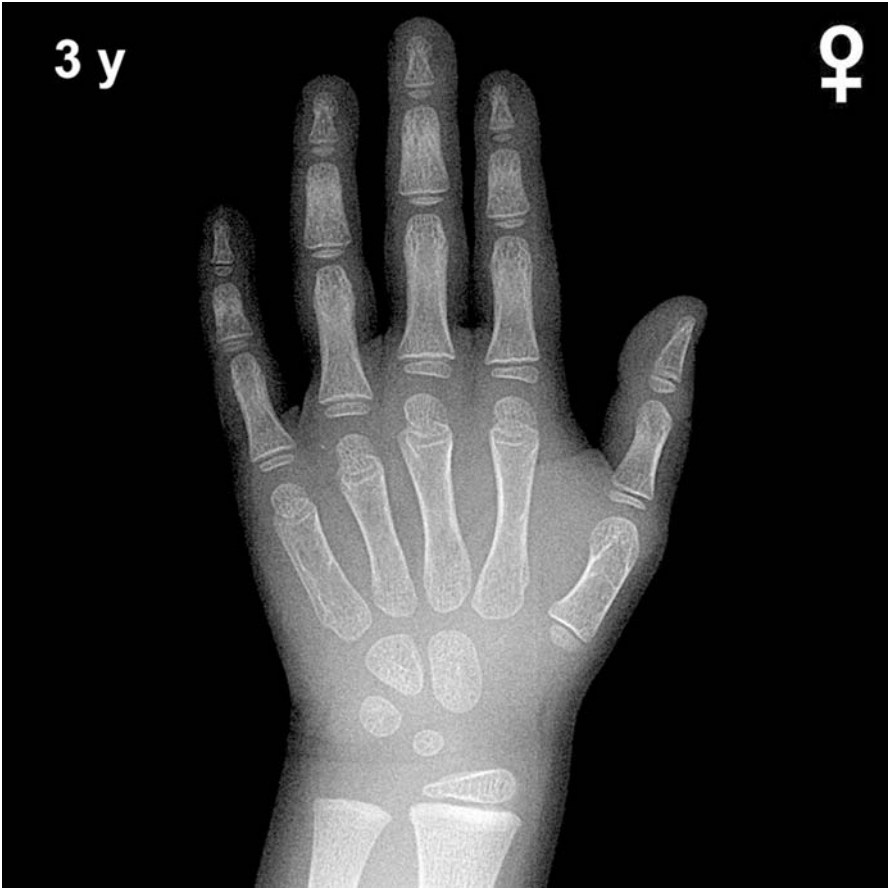


Fig. A40. 3-year-old girl

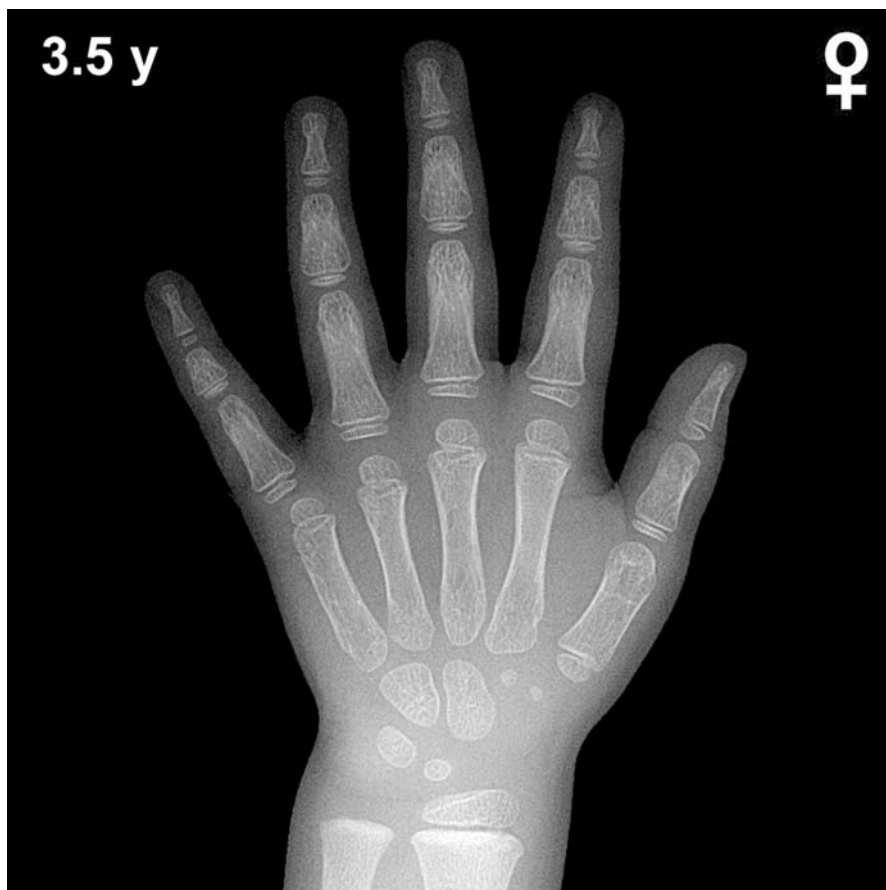


Fig. A41. 3.5-year-old girl



Fig. A42. 4-year-old girl



Fig. A43. 4.5-year-old girl

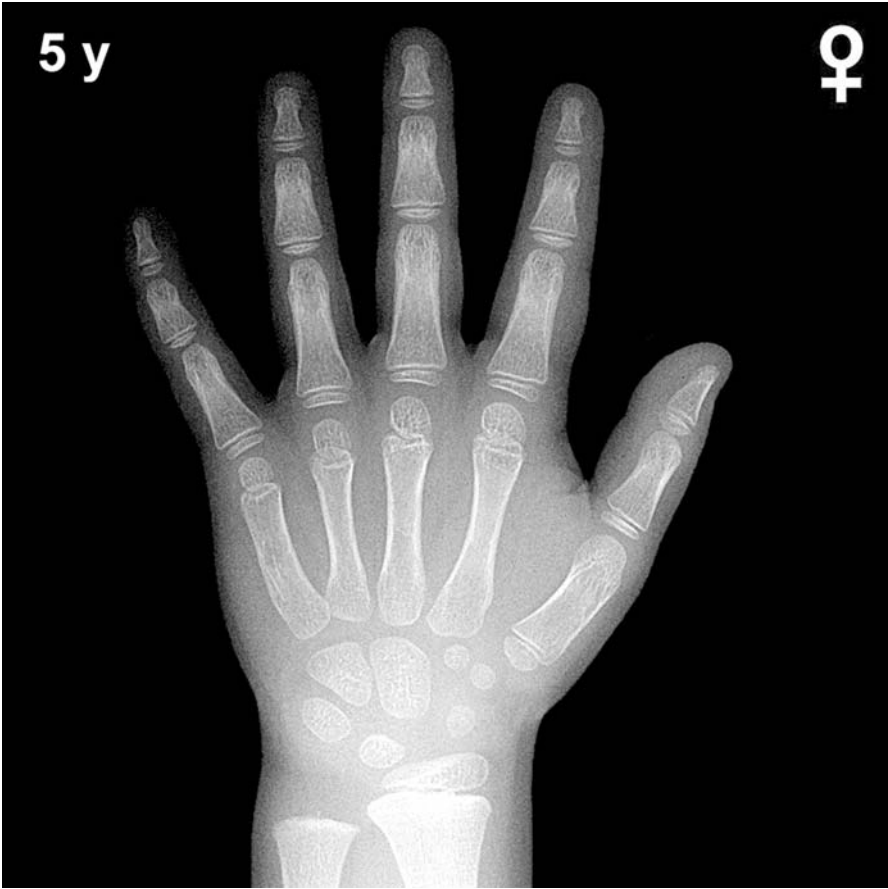


Fig. A44. 5-year-old girl



Fig. A45. 5.5-year-old girl

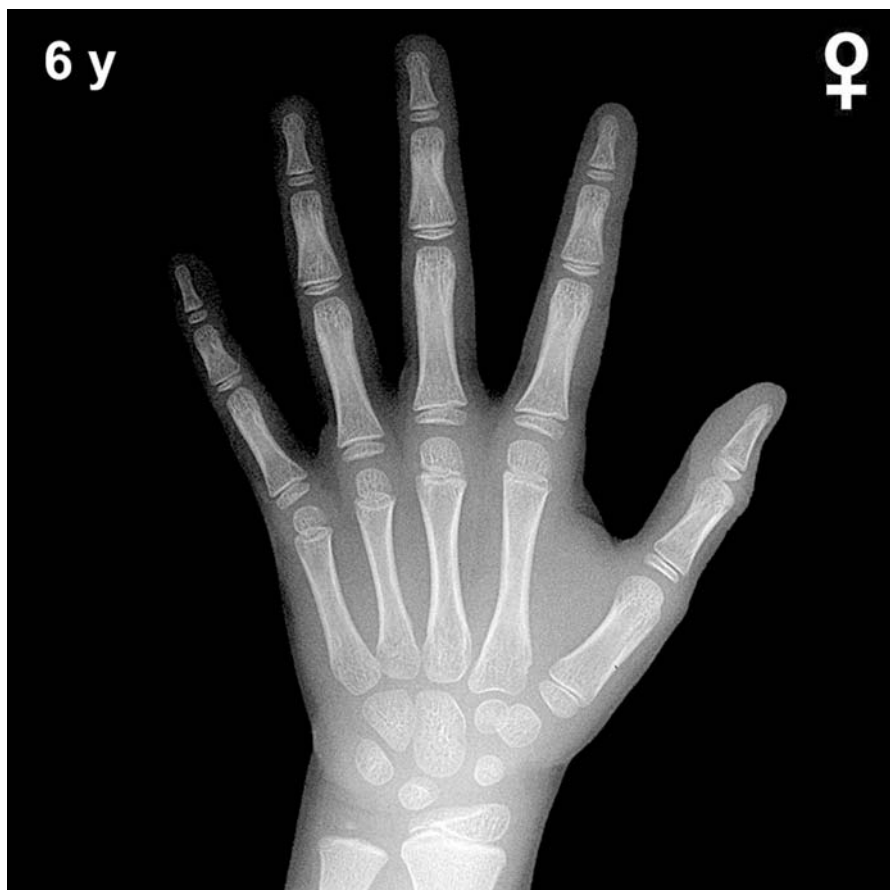


Fig. A46. 6-year-old girl

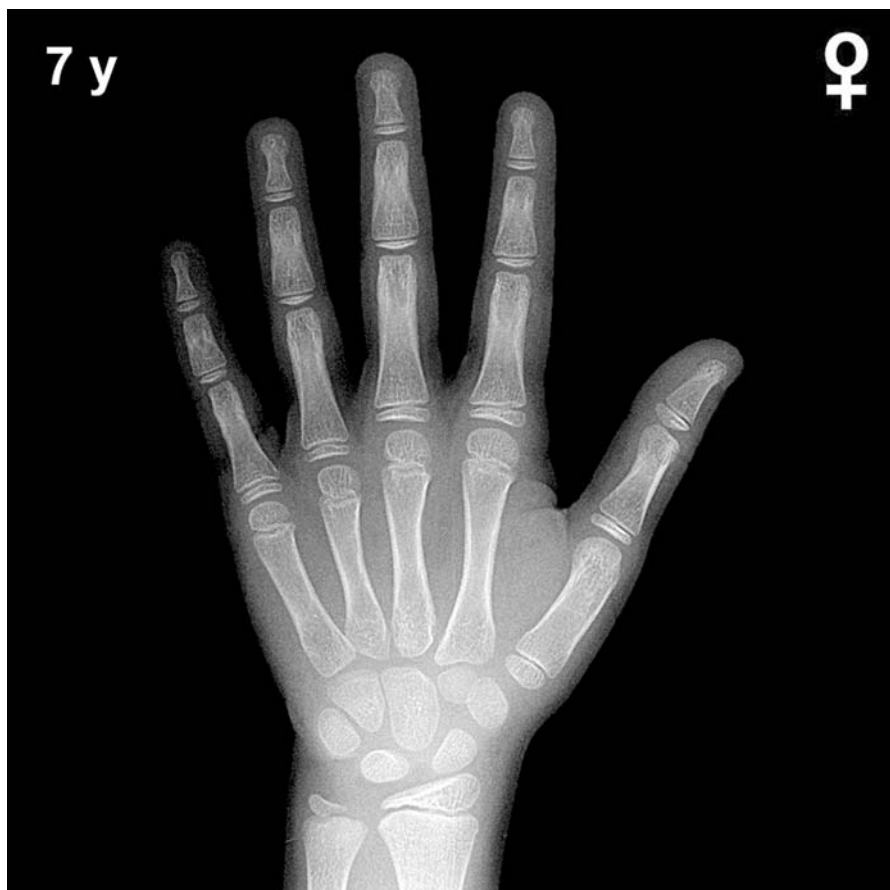


Fig. A47. 7-year-old girl

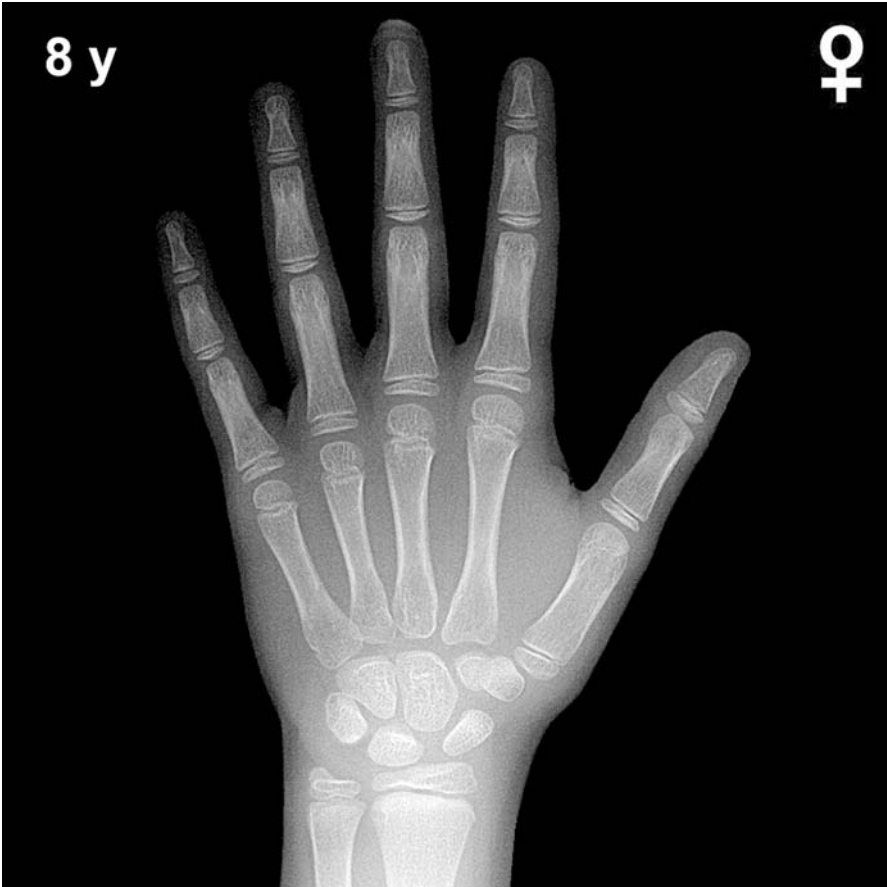


Fig. A48. 8-year-old girl

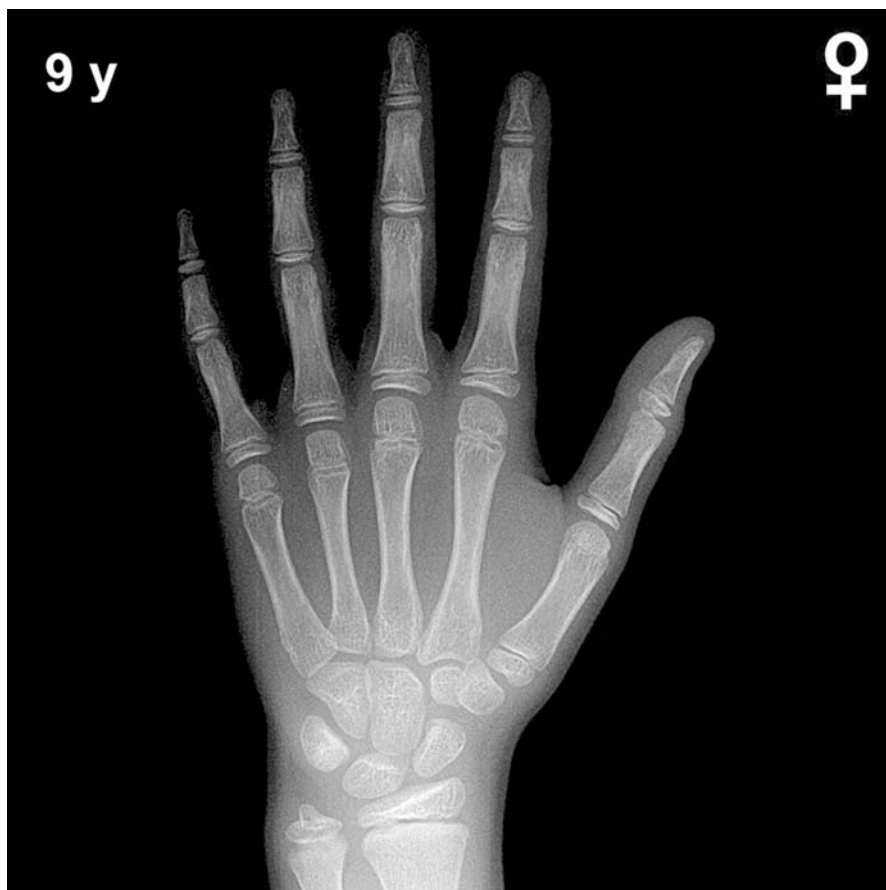


Fig. A49. 9-year-old girl



Fig. A50. 10-year-old girl

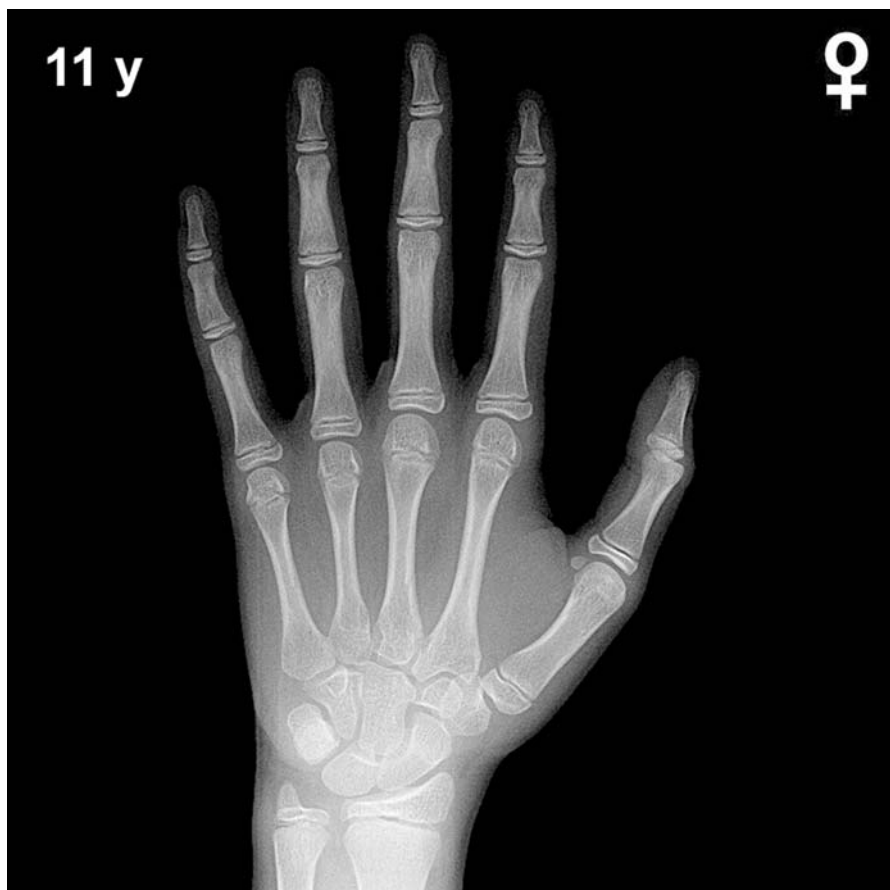


Fig. A51. 11-year-old girl

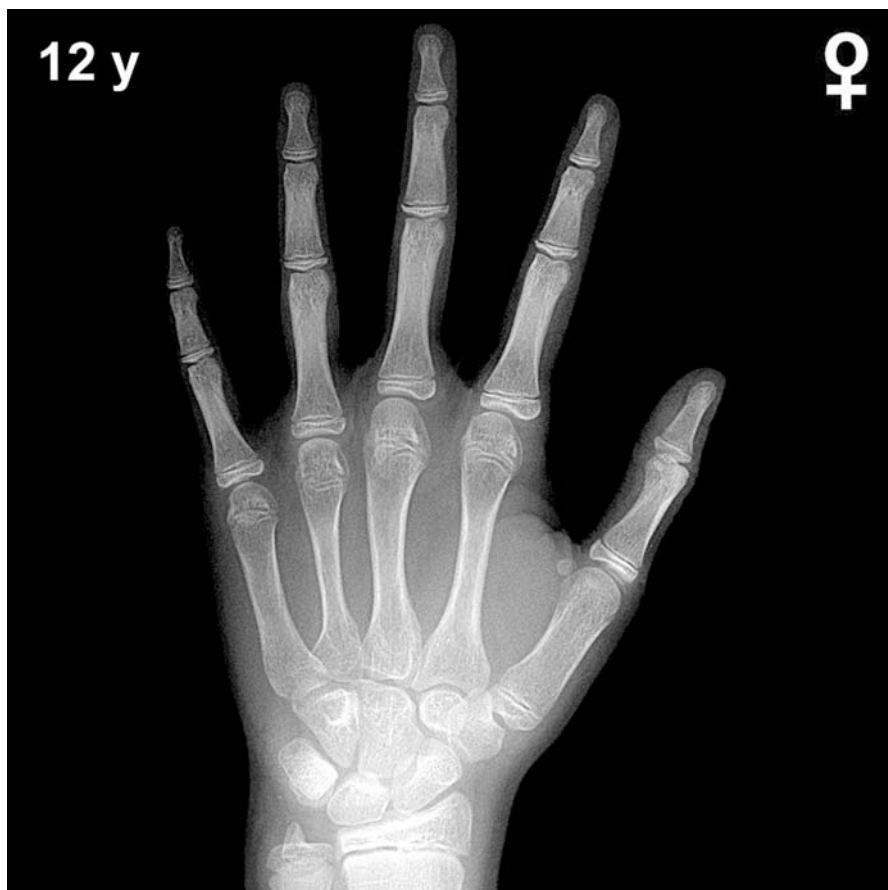


Fig. A52. 12-year-old girl



Fig. A53. 13-year-old girl



Fig. A54. 14-year-old girl



Fig. A55. 15-year-old girl



Fig. A56. 16-year-old girl



Fig. A57. 17-year-old girl



Fig. A58. 18-year-old girl

Tables

Table 2. Coefficients for Prediction of Adult Height for Boys*

Age (years)	Coefficient for Height	Coefficient for Age	Coefficient for Bone Age	Constant
4-7	1.20	-7.3	0	82
8.0	1.22	-7.2	-0.4	82
8.5	1.23	-7.0	-0.7	82
9.0	1.22	-6.8	-0.8	82
9.5	1.21	-6.5	-0.8	82
10.0	1.20	-6.2	-1.0	83
10.5	1.19	-5.9	-1.2	84
11.0	1.16	-5.5	-1.6	89
11.5	1.13	-5.1	-2.0	94
12.0	1.08	-4.2	-2.6	98
12.5	1.03	-3.4	-3.2	108
13.0	0.98	-2.6	-3.8	108
13.5	0.94	-1.9	-4.4	113
14.0	0.90	-1.4	-4.5	114
14.5	0.87	-1.0	-4.6	114
15.0	0.84	-0.8	-3.8	104
15.5	0.82	-0.6	-3.1	94
16.0	0.88	-0.4	-2.4	71
16.5	0.94	-0.3	-1.8	48
17.0	0.96	-0.2	-1.2	34
17.5	0.98	-0.1	-0.7	19

* Adapted from reference 9

Example

A boy is referred because his parents are worried about his short stature. He is 13.5 years old and 145 cm in height, corresponding to the 3rd percentile. His bone age is determined to be 12 years. From Table 2 we can obtain his predicted final height: $(0.94 \times 145) + (-1.9 \times 13.5) + (-4.4 \times 12) + 113 = 136.3 - 25.65 - 52.8 + 113 = 170.85$ cm.

Table 3. Coefficients for Prediction of Adult Height for Girls*

Age (years)	Coefficient for Height	Coefficient for Age	Coefficient for Bone Age	Constant
<i>Premenarche</i>				
4-5	0.95	-6.5	0	93
6.0	0.95	-6.0	-0.4	93
6.5	0.95	-5.5	-0.8	93
7.0	0.94	-5.1	-1.0	94
7.5	0.93	-4.7	-1.1	94
8.0	0.92	-4.4	-1.5	95
8.5	0.92	-4.0	-1.9	96
9.0	0.92	-3.8	-2.3	99
9.5	0.91	-3.6	-2.7	102
10.0	0.89	-3.2	-3.2	106
10.5	0.87	-2.7	-3.6	109
11.0	0.83	-2.6	-3.6	114
11.5	0.82	-2.5	-3.6	115
12.0	0.83	-2.4	-3.4	111
12.5	0.83	-2.3	-3.3	108
13.0	0.85	-2.0	-3.1	98
13.5	0.87	-1.8	-3.0	90
14.0	0.91	-1.6	-2.8	79
14.5	0.99	-1.4	-2.5	67
<i>Postmenarche</i>				
11.0	0.87	-2.3	-3.3	100
11.5	0.89	-1.9	-3.3	91
12.0	0.91	-1.4	-3.2	82
12.5	0.93	-1.0	-2.7	67
13.0	0.95	-0.9	-2.2	55
13.5	0.96	-0.9	-1.8	48
14.0	0.96	-0.8	-1.4	40
14.5	0.97	-0.8	-1.3	37
15.0	0.98	-0.6	-1.1	30
15.5	0.99	-0.4	-0.7	20

* Adapted from reference 9

Example

A girl is referred because she is worried she will be too tall when she grows up. She is 11 years old and 158 cm in height, about the 97th percentile. Her bone age is determined to be 12, and she is premenarche. From Table 3 we can obtain her predicted final height: $(0.83 \times 158) + (-2.2 \times 11) + (-3.6 \times 12) + 114 = 131.14 - 24.2 - 43.2 + 114 = 177.74$ cm.

Table 4. Tanner Stages of Sexual Development*

Females		Male	
Stage	Mean age (yrs ± SD)	Stage	Mean age (yrs ± SD)
Breast 2	11.2 ± 1.1	Genital 2	11.4 ± 1.1
Pubic hair 2	11.7 ± 1.2	Pubic hair 2	12.0 ± 1.0
Breast 3	12.2 ± 1.1	Genital 3	12.9 ± 1.0
Pubic hair 3	12.4 ± 1.1	Pubic hair 3	13.9 ± 1.0
Breast 4	13.1 ± 1.2	Genital 4	13.8 ± 1.0
Pubic hair 4	13.0 ± 1.1	Pubic hair 4	14.4 ± 1.1
Breast 5	15.3 ± 1.7	Genital 5	14.9 ± 1.1
Pubic hair 5	14.4 ± 1.1	Pubic hair 5	15.2 ± 1.1
Menarche	13.5 ± 1.0	-	-

* Adapted from references 19, 20

Table 5. Variability in Bone Age

Age in Months	Boys SD	Girls SD
12	2.1	2.7
18	2.7	3.4
24	4	4
30	5.4	4.8
36	6	5.6
42	6.6	5.5
48	7	7.2
54	7.8	8
60	8.4	8.6
66	9.1	8.9
72	9.3	9
84	10.1	8.3
96	10.8	8.8
108	11	9.3
120	11.4	10.8
132	10.5	12.3
144	10.4	14
156	11.1	14.6
168	12	12.6
180	14	11.2
192	15	15
204	15.4	15.4

The standard deviation calculation for each age category in the digital bone age atlas was based on the equation for the linear regression that best fit the variability of multiple samples at different ages.

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