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AUXOLOGICAL TOOLS FOR FOLLOWING GROWTH IN EXTREME SHORT STATURE AND FOR EVALUATING GROWTH PROMOTING INTERVENTIONS

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Auxological tools for following growth in extreme short stature and for evaluating growth promoting interventions

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Ich schreite kaum, doch wähn' ich mich schon weit.

Parsifal

ABSTRACT

Growth charts are inevitable tools for following children in clinical practice and also when evaluating growth promoting therapy. Growth is a concern especially for families to children of extreme short stature such as in skeletal dysplasias but evaluations of growth pattern with changes in height position is complicated when height develops far below normal population range. Height gain from growth hormone therapy is variable for short stature conditions without aberrant growth hormone secretion such as in Turner syndrome. This makes it difficult to communicate realistic adult height estimates to concerned families.

The first part of this PhD project used semi-longitudinal data from 4,375 measuring occasions to construct growth and body proportion references for achondroplasia and to describe these in relation to normal population references. Typical for achondroplasia, tempo in head size was increased attaining final size earlier than normal. Height was at the same time compromised with major loss in height position during the first years of life, due to limited growth capacity of the legs. At adult ages, leg length was half of that in normal population and arm span almost 35 percent lower than normal contributing to severely reduced area of personal access. Pronounced body disproportions distort the BMI-value in achondroplasia, which is why specific BMI charts were constructed.

Clinical achondroplasia charts were developed to support surveillance of these children and, as short stature matrix, possibly also for other children with severe short stature for which syndrome-specific charts are missing. The usability of these achondroplasia charts were tested by illustrating growth pattern of selected skeletal dysplasias.

Obtained achondroplasia references for height, sitting height, leg length and arm span might contribute to a better understanding of the effect of FGFR3 signalling on growth and will also be inevitable tools for evaluation of novel treatments.

In the second part, variability in response to growth hormone therapy was studied by dividing a sample of 455 girls with Turner syndrome, reported in the Swedish National Register for growth hormone treatment of children and adolescents, into good and poor response based on the distribution of total height gain from treatment. As age at treatment initiation was distributed over almost entire growth period, the sample was further grouped into those with treatment start during normally prepubertal and pubertal ages. Differences of clinical relevance were higher mid-parental height, higher GH dose at 12 months of treatment and improved body proportions in the younger good response group; and younger age and shorter height position at treatment initiation and higher GH dose in the older good response group. These findings could possibly be influenced by subgroups identified in graphic presentations. Initial height gain from treatment did not necessarily translate into better total height gain neither in younger or older poor groups. In contrast to previous claims, early initiation of growth hormone treatment per se did often not result in better total height gain.

LIST OF SCIENTIFIC PAPERS INCLUDED IN THE THESIS

I. **Andrea Merker**, Luitgard Neumeyer, Niels Thomas Hertel, Giedre Grigelioniene, Outi Mäkitie, Klaus Mohnike, Lars Hagenäs
Growth in achondroplasia: Development of height, weight, head circumference, and body mass index in a European cohort.
American Journal of Medical Genetics - Part A 2018 (176): 1723-1734
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II. **Andrea Merker**, Luitgard Neumeyer, Niels Thomas Hertel, Giedre Grigelioniene, Klaus Mohnike, Lars Hagenäs
Development of body proportions in achondroplasia: Sitting height, leg length, arm span, and foot length
American Journal of Medical Genetics - Part A 2018 (176): 1819-1829
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III. Luitgard Neumeyer, **Andrea Merker**, Lars Hagenäs
Clinical charts for surveillance of growth and body proportion development in achondroplasia
Manuscript

IV. **Andrea Merker**, Luitgard Neumeyer, Mariana del Pino, Virginia Fano, Giedre Grigelioniene, Karen Heath, Purificación Ros-Perez, Ana Coral Barreda-Bonis, Isabel González Casado, Enrique Galán, Niels Thomas Hertel, Outi Mäkitie, Robert C. Olney, Lars Hagenäs
Using Achondroplasia growth chart as matrix for following children with skeletal dysplasia and extreme short stature
Manuscript

V. **Andrea Merker**, Jovanna Dahlgren, Svante Norgren, Lars Hagenäs
Good and poor response to growth hormone treatment – an auxological evaluation of a cohort with Turner syndrome
Manuscript

RELATED PUBLICATIONS

Christoph Beger, **Andrea Merker**, Rebekka Mumm, Ruth Gausche
Growth prediction of small for gestational age infants within the first weeks after birth
Anthropologischer Anzeiger 2018 (74): 377-382
doi: 10.1127/anthranz/2018/0820

Michael Hermanussen M, Josefin Ipsen, Rebekka Mumm, Christian Assmann, Julia Quitmann, Aleksandra Gomula, Andreas Lehmann, Isabelle Jasch, Vincent Tassenaar, Barry Bogin, Takashi Satake, Christiane Scheffler, Javier Núñez, Elena Godina, Rüdiger Hardeland, Jesper Boldsen, Mortada El-Shabrawi, Mona Elhusseini, Carmen Gabriela Barbu, Ralucca Pop, Jani Söderhäll, **Andrea Merker**, James Swanson, Detlef Groth
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Paola Durán, **Andrea Merker**, Germán Briceño, Eugenia Colón, Dionne Line, Verónica Abad, Kenny del Toro, Silvia Chahín, Audrey Mary Matallana, Adriana Lema, Mauricio Llano, Jaime Céspedes, Lars Hagenäs
Colombian reference growth curves for height, weight, body mass index and head circumference.
Acta Paediatrica 2016 (105):e116-25.
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CONTENTS

LIST OF ABBREVIATIONS

AMDM	AcroMesomelic Dysplasia type Marotaux, a severe short stature skeletal dysplasia caused by homozygous or compound heterozygous mutations in *NPR2* gene, which encodes natriuretic peptide receptor B (NPR-B)
APHV	Age at Peak Height Velocity, period with maximum rate of growth during pubertal development
Auxology	Science of somatic growth and development
Centile/Percentile	A certain position in a growth chart expressed as percentage of the observations below this position; e.g. 3 percent of all observations can be found below the 3rd centile.
COMP	Cartilage Oligomeric Matrix Protein, an extracellular protein important for structural assembly of extracellular matrix
CV	Coefficient of variation, measure of dispersion or variability, equals to S-parameter in LMS method
edf-values	effective degrees of freedom values to specify the degree of smoothness of the LMS curves; e.g. a higher edf value will result in a less smooth curve
FGFR3	Fibroblast Growth Factor Receptor 3, heterozygous activating mutations in the FGFR3 gene cause achondroplasia and hypochondroplasia
GAMLSS	Generalised Additive Models for Location, Scale and Shape are univariable distributional regression models where all parameters of an assumed distribution for the response can be modelled as additive functions of the explanatory variable
GH Rx	Growth Hormone treatment
KIGS	Pfizer International Growth Database, postmarketing register for growth hormone treatment
LMS method	Lambda-Median-Sigma method for constructing normalised growth reference by modelling Box-Cox power (L), median (M) and coefficient of variation (S)
MPH	Mid-Parental Height, average height of parents calculated by average of parents' height SDS or parents height in cm with ±6.5 cm adjustment for sex of the child (i.e. +6.5 cm for boys and -6.5 cm for girls)

ISS	Idiopathic Short Stature, children with height below -2 SD without clinical features of a syndrome, endocrine or disorders or other noticeable cause for short stature
NPR2	Natriuretic Peptide Receptor 2 gene, which encodes natriuretic peptide receptor B (NPR-B). Biallelic loss of NPR2 function results in AMDM
PSACH	PSeudoACHondroplasia, a short limb and short trunk skeletal dysplasia caused by heterozygous mutations in the gene encoding COMP
SD	Standard Deviation, measure of variance
SD bandwidth	the "size of SD" in data of non-normal distribution as distance between one SD line to the next SD line; e.g. the area between +1 and +2 SD
SDS/ z-score	Standard Deviation Score, a position in the growth chart, i.e. relative to a given reference, calculated as SDS = (Measurement-Mean)/SD at a given age for a variable that follows a normal distribution (e.g. height). In variables that contain skewness (e.g. weight), SDS can be calculated from LMS values as SDS = $((\text{Measurement}/M)^L-1)/LS$
SILL	SubIschial Leg Length, measured as difference between height and sitting height
SITAR	SuperImposition by Translation And Rotation, a shape invariant model that adjusts individual height curves for their size, tempo and velocity and results in a mean curve and a value of these three parameters
SH/H	Sitting Height/ Height ratio; i.e. relative sitting height, as measure of body proportion
SLC26A2	SoLute Carrier 26A2 a gene coding for a sulphate transporter important for production of proteoglycans
SHOX	Short Stature HomeoboX gene, heterozygous defects in *SHOX* or deletion of its downstream regulatory domain result in Leri-Weill dyschondrosteosis, a skeletal dysplasia with mild phenotype, and homozygous defects of *SHOX* cause the more severe Langer mesomelic dysplasia
TS	Turner syndrome, chromosomal condition with one missing or structurally altered X chromosome in females

1 INTRODUCTION

The wide variation of short stature conditions ranging from mild to severe phenotypes teach us how many factors are involved in normal growth and what role single genes can have. Severe short stature, especially of familial trait, often has a monogenic background but in the normal population, only a small variation in height may be explained by the hundreds of genes so far found to be associated with height.[1] Genome-wide association studies from hundreds of thousands of individuals identified 780 variants together explaining 27 percent of variation in adult height.[2] Of special interest is that somatotropic axis, i.e. various components of GH, IGF-I, insulin, signalling has no particular role in this assembly. However, population studies in Peru found a special variant of fibrillin 1 (FBN1) that may contribute to a short height in Peruvians, about 2.2 cm deduction in those with one copy and 4 cm in those with 2 copies[3]. Pathogenic variants in *FBN1* may, on the other hand, result in extreme tall stature, Marfan syndrome, or extreme short stature, acromicric dysplasia.

1.1 GROWTH IN HEIGHT AND BODY PROPORTIONS

In addition to height also development of body segments, such as sitting height and leg length, is of interest when analysing growth regulation. Trends in height in a population over time, i.e. secular trends, are partly dependent on leg growth,[4,5] which generally is considered to be sensitive to environmental conditions.[4] Sitting height, as proxy for growth of the spine, is furthermore stimulated by pubertal sex hormones. Trunk and legs develop therefore at different tempi, as can be evaluated as percentage of final size and as yearly increments in Figure 1. It is clear that the majority of growth in legs occurs postnatally and predominately during prepubertal ages. Legs stop growing more abruptly while the pubertal spurt in sitting height, being more intensive, fades away slowly.[6]

Body proportion, such as sitting height as percentage of height ("relative sitting height"), therefore changes with age. Sitting height/ height ratio decreases fast, from 68 percent at one year to 51 percent in male and 53 percent in female adults.[7] Body disproportions are, however, also a typical feature of skeletal dysplasias and can therefore teach us what mechanisms might be involved in the regulation of leg versus spine growth.

It is worthwhile noting that head circumference, as proxy for brain size,[8,9] follows a distinct growth pattern. Most of the final size is attained already by birth and head circumference grows rapidly approaching adult size during the first three years of life.

Children from diverse ethnic and genetic backgrounds grow generally similar up to five years of age,[10,11] suggesting that differences in height are established first from childhood ages. Genetic differences can also be found in body proportions; longer legs are more common in black Americans despite lower sitting and standing height than in white Americans.[12] Differences in growth might, however, not necessarily be limited to genetic differences, as studies on Maya children have shown. Those living in Guatemala were on average 11 cm shorter and 12 kg lighter than their relatives growing up in the USA.[13]
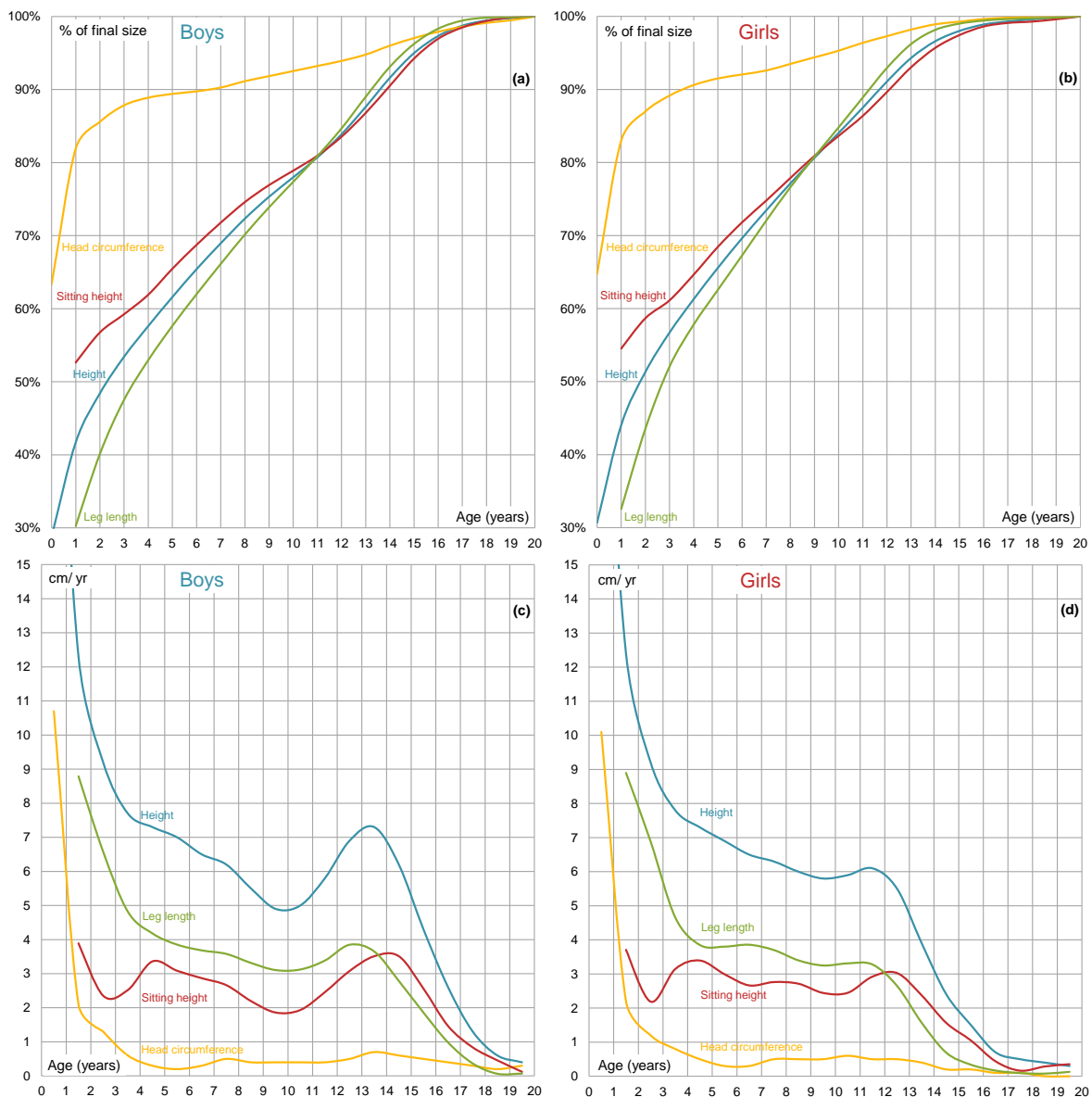
Figure 1 Development of height, head circumference, sitting height and leg length based on references from 4th Dutch nation-wide survey[7,14]: (a-b) as percentage of final size and (c-d) as yearly increments, i.e. differences between mean values of full chronologic ages. Note that birth values for height and head circumference represent values at 2 weeks of age.

Individuals may vary in height or size but also in the speed for reaching final size; i.e. in tempo of growth.[15] Differences in tempo might increase with age becoming more apparent during adolescent ages when the growth curve slope is steeper.[15] Figure 2 illustrates height and height velocity between early, average and late maturational tempo. It is worthwhile mentioning that tempo is not associated to differences in final height. There is no or little evidence that timing of pubertal spurt or of attaining final height is related to final height[15]. Tempo in growth is primarily inherited,[15] which can be demonstrated using age at menarche as proxy for developmental age and tempo. Timing of menarche is strongly influenced by genetic factors[16] and mother-daughter and sister-sister correlations are close to 0.5.[17]

Figure 2 Height (cm) and height velocity (cm/year) development in an example of early, average and late maturational tempo. Illustration adapted from Hauspie and Roelants.[15]

1.2   TARGET HEIGHT AND PREDICTORS OF ADULT HEIGHT

Parental height can be used as a proxy of inherited growth size and tempo and gives an indication for a child's adult height, or its target. Target height can be ca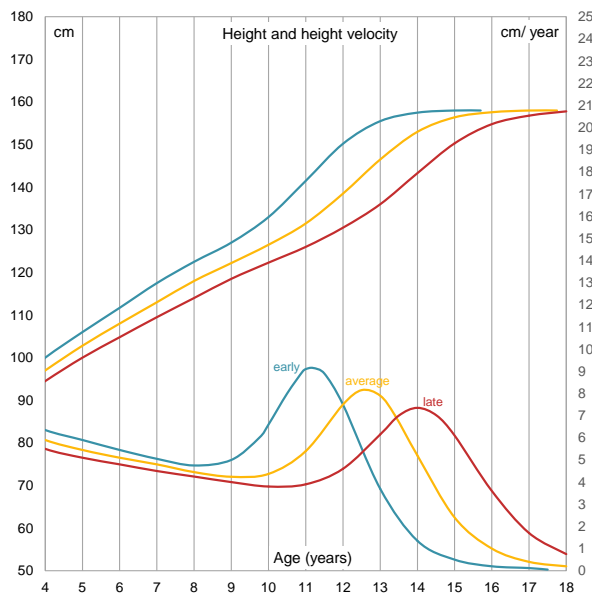lculated as average or mid-parental height (MPH) with ±6.5 cm adjustment for sex of the child (i.e. +6.5 cm for boys/ -6.5 cm for girls) or as average of both parents height expressed in standard deviation score (SDS). Using SDS scale might be more robust.[18] Taking into account a predicted confidence interval of 95% would result in a target height range ±10 cm for boys and ±9 cm for girls.[19] Note that MPH might also have to be adjusted for assortative mating and the correlation between parental height,[19] while others found no such effect.[20]

The child's current height position is another important predictor of its adult height; alone or in combination with MPH.[19,21] The correlation coefficient is only 0.3 at birth but increases to above 0.7 at two years of age.[22] Similar observations from the *First Zürich Longitudinal Growth Study*[23] are summarized in Figure 3. Note that there is a dip during pubertal ages coinciding with age at peak height velocity.[23] Relating bone age, as a measure of maturity, to adult height is, before pubertal ages, less informative than chronologic age.[21,23]

The prepubertal height position can therefore give an indication of expected adult height. For girls with Turner syndrome, for which pubertal growth most often is compromised by ovarian failure, adult height is often estimated by projection of height position on syndrome-specific growth chart irrespective of age for this prediction.[24] Alternative methods are based on the relationship between current height and adult height in historical, untreated (with growth hormone) cohorts of girls with TS[24,25] or various indexes or methods including bone age.[24]
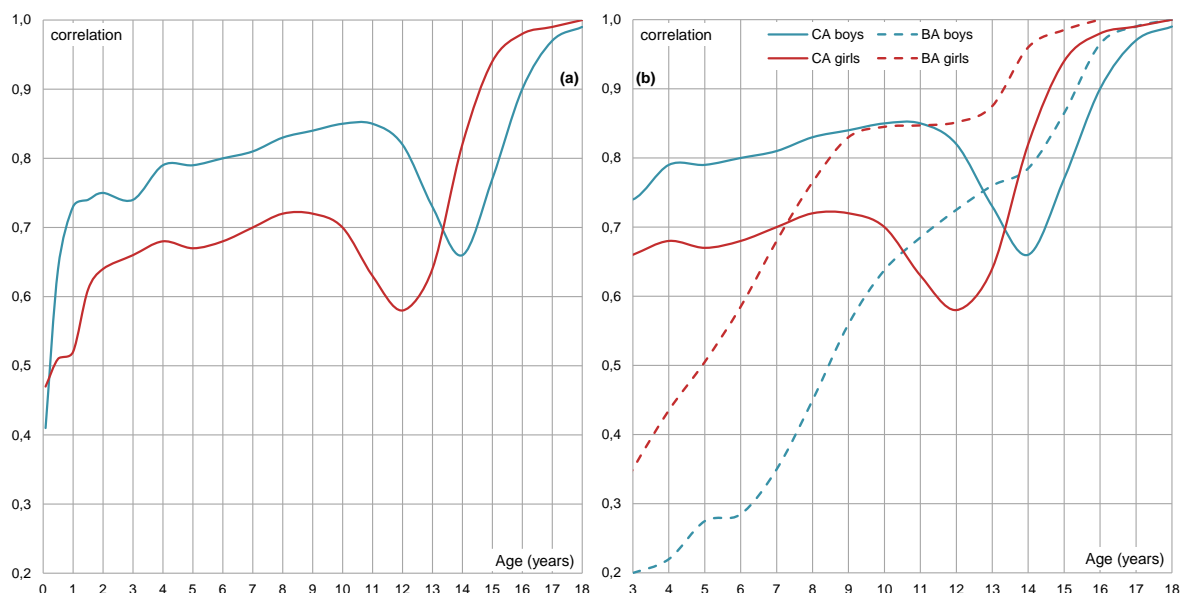
Figure 3 Child-adult height correlations based on individual data from the *First Zürich Longitudinal Growth Study*: (a) for chronological age and (b) comparing chronological age (CA) and bone age (BA) in boys (blue) and girls (red). Illustration adapted from Molinari et al.[23]

1.3   GROWTH CHARTS

A growth reference is a summary of the statistical distribution of an anthropometric measure and is for clinical purposes generally presented as a growth chart.[8] As such, growth curves are essential tools for clinical practice and their layout should therefore facilitate usability for following an individual. Growth references are also used for screening of short stature conditions[26] or disease[27] or to follow growth in a population for instance for evaluating secular trends in height[28,29] or in overweight and obesity.[30–32]

1.3.1   Longitudinal versus cross-sectional references

Growth references are useful for comparing differences among populations. Conclusions should, however, be drawn with caution since studies usually are based on different methodologies and vary in terms of focus group (e.g. dedicated social group, regional focus), exclusion criteria (e.g. breast-feeding, parental origin), prospective/ retrospective design, sample size and other factors.

Most growth references today are based on cross-sectional surveys with each child contributing one measurement. This setup requires a representative sample across all ages and a higher sample size to capture growth in periods of increased velocity changes.[33] Resulting references give, however, only a static picture of the variation.[15] Variation in tempo and pubertal growth can only be obtained from longitudinal studies, [8,15,34,35] but these are time consuming and sensitive to drop-outs. A mix of both, i.e. semi-longitudinal, is therefore sometimes used, for instance in the WHO reference where growth during infancy is based on longitudinal cohorts[36] and growth from school ages on historic health surveys.[37]

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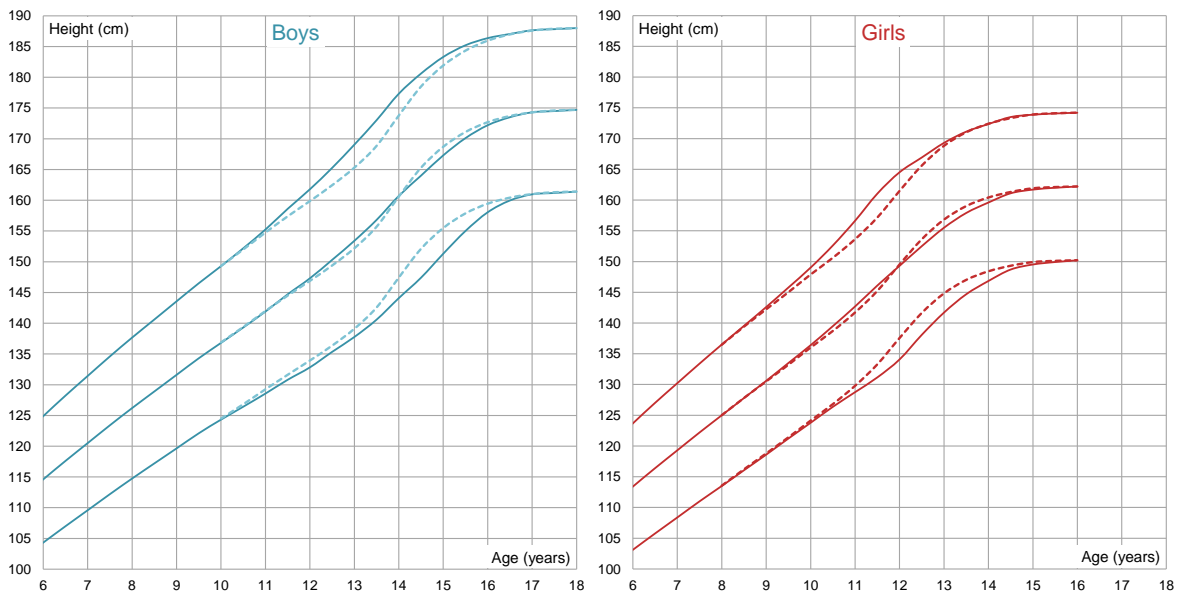
Figure 4 Mean ±2 SD in British height references[34,35], conditional (longitudinal, dashed) and unconditional for tempo (cross-sectional, line): height slopes appear steeper and curve range narrower if adjusted for different tempi.

The most important difference between longitudinal and cross-sectional references is their appearance during pubertal ages. The curves appear steeper with less variability if based on longitudinal data (Figure 4) since individual data series can be centered around average age at peak height velocity (APHV) hereby adjusting for differences in tempo. "Chronological age is thus replaced with age corrected for tempo."[15] References from cross-sectional surveys, on the other hand, are based on a mix of early, average and late maturing children,[15] as seen in Figure 5, where variations in tempo and pubertal growth spurt are smoothed out.[15,34,35] Tanner et al. referred to this phenomenon as "phase difference effect" and distinguished between growth standards "unconditional for tempo" and "tempo-conditioned".[34]
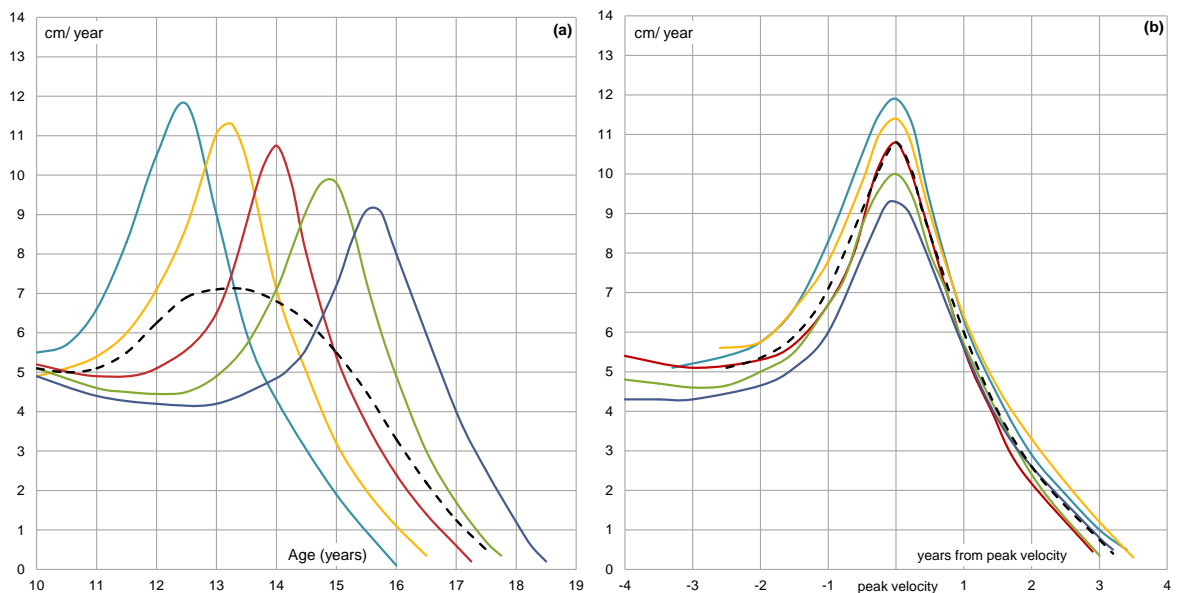
Figure 5 Differences in individual and mean height velocity during pubertal ages: (a) mean height based on cross-sectional data and (b) mean height after centering individual data series around average age at peak height velocity. Illustration are adapted from Tanner et al.[35]

1.3.2 Measuring the child

Accurate measurements require standardized measuring techniques and calibrated instruments. The child per se is often the main source of error since the result depends on how "elastic" the child is, which is influenced by his/her mood. Skeletal dysplasia specific handicap might also hamper the measurements. Cooperation with the child is therefore of central importance to obtain reproducible results. Additionally, time of the day for the measurement can play a role, especially for height and sitting height, because of the tendency to shrink during the course of the day due to compression of vertebral discs.

Length of the supine body is generally measured up to two years of age and height of standing position thereafter, both following the protocol of Hall et al.[38] In skeletal dysplasia it is not unusual to measure height in supine position even after two years of age since some conditions confer muscular hypotonia, ligamentous laxity and/or immature motor development or other difficulties to stand due to severity of disease. Length and height measurements might further be influenced by deformities such as thoraco-lumbar kyphosis, flexion contractures, bowed tibias, genu varum, marked lordosis or scoliosis.

1.3.3 Growth curve modelling

Modelling the height curve is more complex than might be imagined. This includes modelling of individual data series but also modelling of a group of individual data series (longitudinal data) or data points (cross-sectional data). Growth is limited by an individual's potential and growth tempo determines the shape of his/her curve that may, however, be followed at two separate time points.[39] Statistical analysis is further complicated by an individual's measurements being related.[39]

Simple modelling forms such as polynomials can result in a poor fit at both ends of the age range if the age range is wide.[8] This can be avoided by fractional polynomials, which are based on an equation with selected age powers instead of successive integer age powers. Fractional polynomials are, however, ineffective when modelling events such as pubertal spurt or BMI infancy peak. As an alternative, parametric models for height are available for certain growth periods, such as Jenss-Bayley (four parameters) for infancy-childhood and Preece-Baines I (five parameters) for puberty/ adolescence, or for the whole growth process from birth to adult height, such as BTT (Bock-duToit-Thissen, 8 parameters), Shohoji-Sasaki/ Count-Gompertz (6 parameters), JPA-2 (Jolicoeur-Pontier-Abidi, 8 parameters)[40] or ICP (Infancy-Child-Puberty, 9 parameters)[6]. These growth models might, however, not necessarily be good in catching unusual growth patterns[6] nor be suitable for describing how variability changes with age.[8]

Other popular methods are based on spline and kernel smoothing. These techniques use local moving averages based on weighting functions and bandwidth,[8] that guide the smoothness of the curve that is otherwise estimated only from the primary data.[39] Such a nonparametric approach is more sensitive to biologic variation in the data. Individual velocity curves can be estimated and analysed irrespective of how other series in the sample develop.[6] Common

features are then combined in a model or shape function.[6] The SITAR-model (SuperImposition by Translation And Rotation), for instance, estimates a fitted curve from individual curves that are matched by differences in size, tempo and velocity.[41] More specifically, individual curves are shifted up/down (adjustment for size), left-right (adjustment for tempo) with the age scale being shrunk or stretched (adjusted for velocity).[41] The three parameters – size, tempo and velocity – can then be estimated, which may be powerful for comparing groups; e.g. in oxandrolone versus placebo treatment in girls with Turner syndrome.[42]

Some growth references are constructed from the distribution of empirical data, which can, however, be biased in small samples and can also result in (extreme) centiles that touch or cross each other at extreme levels.[8,33] Alternative approaches approximate the distribution of the data assuming that it follows a certain distribution. "Centiles are estimated by fitting the data to the (assumed) distribution, transforming to the normal scale to estimate the centiles, and then back-transforming to the original scale (of the measurement)."[33] A normal distribution with two parameters (mean and SD) is suitable when variability is low, i.e. coefficient of variation is less than 5 percent,[8] and is generally used for modelling height or head circumference for age. Centiles for weight and BMI are, however, better estimated by three-parameter distribution models, i.e. including Box-Cox power as an extra parameter for skewness.[33] For review, see Borghi et al. [36] that summarizes 30 methods for constructing growth curves based on a comprehensive review of Wright and Royston, 1997. An innovative and resource saving method is to construct "synthetic" growth charts.[43,44] Its latest version estimates most common factors or characteristics of a growth reference based on principle component analysis (PCA) of almost 200 growth studies.[44] The first five components describe 98.7/ 98.4 percent of the male/ female variation in height, which thus can be used to construct synthetic curves for a selected population from a small sample.[44]
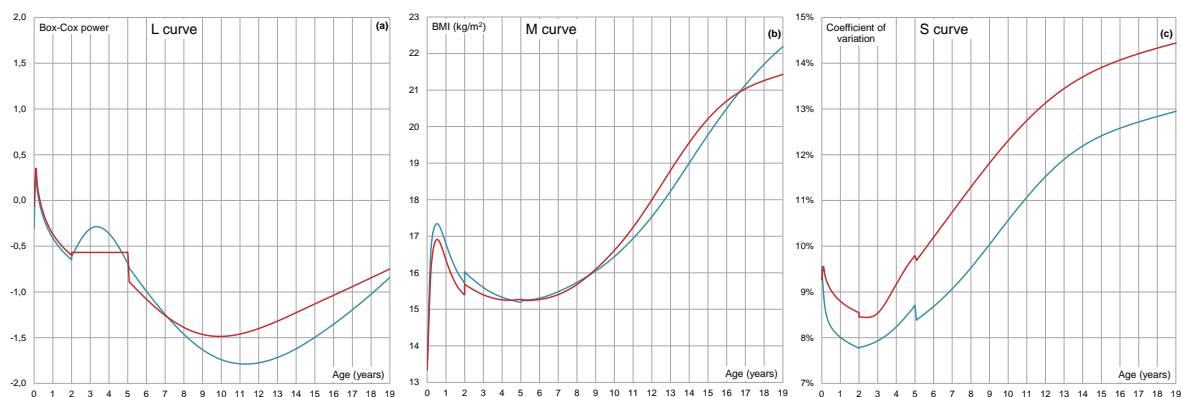
Figure 6 L, M and S curve for BMI for age and sex in the WHO reference[37,45]

Most growth references are today based on the LMS method, which summarises the distribution by three parameters: the Box-Cox power (L), the median (M) and the coefficient of variation (S). In its first version, these three parameters are estimated for pre-defined age groups and are then smoothed across ages.[46] The choice of age groups can, however, influence the estimated reference curves[33] and the current version uses therefore age as a

continuous variable and natural cubic splines for smoothing each of the three parameters.[47] In short, model fitting includes finding the "right" shape of the LMS curves (Figure 6), which can be controlled by smoothers in form of effective degrees of freedom (edf) where choosing higher edf values gives a curve closer to the empirical data and lower edf values smoother curves. Some subjectivity remains therefore in the choice of smoothing parameter.[33]

To apply this method, the LMSChartmaker Pro program can be used, which was for instance done for construction of references for normal population in Argentina[48] or for skinfold thickness in normal German children.[49] The LMS method is also implemented in Rigby & Stasinopoulos framework on generalised additive model for location, scale and shape (GAMLSS)[50,51] and its R package GAMLSS. Here, models can also be compared based on model criteria, such as several forms of generalised Akaike Information Criterion (AIC). The model with the lowest model criterion value represents best fit.[52] In other words, the goal is to find the edf value that minimises the model criterion. Model validation is performed based on the distribution of the residuals, either against fitted values or x-variable, or by normal QQ-plots.[52,53] This might sound straight-forward, yet it should be noted that curve fitting remains a subjective exercise or "black art",[47] since there is always a trade-off between empirical fit and smooth appearance.[47,54]

1.3.4 Layout of growth charts

Growth charts differ in terms of background populations but also to a great extent in their layouts; i.e. their format, scope/ spacing and general appearance. Some charts are presented in portrait, others in landscape format. Some focus on one variable per page while others combine several variables usually for age. In many countries traditional centile curves are used covering 5th to 95th or 3rd to 97th centile, while others use SD lines ±2, ±2.5 or ±3 SD. Note that both scales express the distribution of a given variable; a centile represents the percentage chance of lying below a given line while SD scale is centered on zero[8]. For variables that follow a normal distribution, -1, -2 and -3 SD correspond to respectively 15.9, 2.3 and 0.14 centile. Both centile and SD scale can thus be used to express a position in the growth chart.

Centiles might intuitively be easier to interpret since the position on the growth chart represents a rank between 0 and 100. Yet, centiles are not useful for following how a position changes with age[53] nor for calculating descriptive statistics.[33] This is because the same centile interval corresponds to different intervals of the measurement.[33] A change of 10 centile points between the 60th and 50th centile, for instance, cannot be compared with a decrease between 11th and 1st centile.[53] Also substantial changes in height will result in very small centile changes at the extremes of a distribution.[33] The z-score or SD score (SDS), on the other hand, is normalized and can therefore be compared across ages and sexes. These can be used beyond centile ranges[53] and extreme height positions can thus be expressed in a "meaningful" way (Table 1).

Table 1 Centiles versus z-score/ SDS with examples of corresponding height position based on the WHO height reference[37,45]

Centile	z-score/ SDS	Example
50th	±0	normal average
15.87	-1	"we are not so tall in our family"
2.275	-2	delayed puberty
0.135	-3	Turner and Down syndrome
0.0032	-4	GH-deficiency
0.00003002	-5	"must be a syndrome"
0.0000002148	-6	achondroplasia
0.0000000002746	-7	adult pseudoachondroplasia

It is apparent that the linear development of height is limited to childhood ages. Capturing an entire growth period by linear axes gives equal spacing to the measure and thus neglects differences in growth velocity. In other words, the same focus on the age axis is given for growth during the first year of life as for the sixth year. Similarly, on the BMI axis the same focus is given for BMI between 29 and 30 kg/m^2 as for between 15 and 16 kg/m^2. From a biologic perspective this spacing might not always be reasonable.
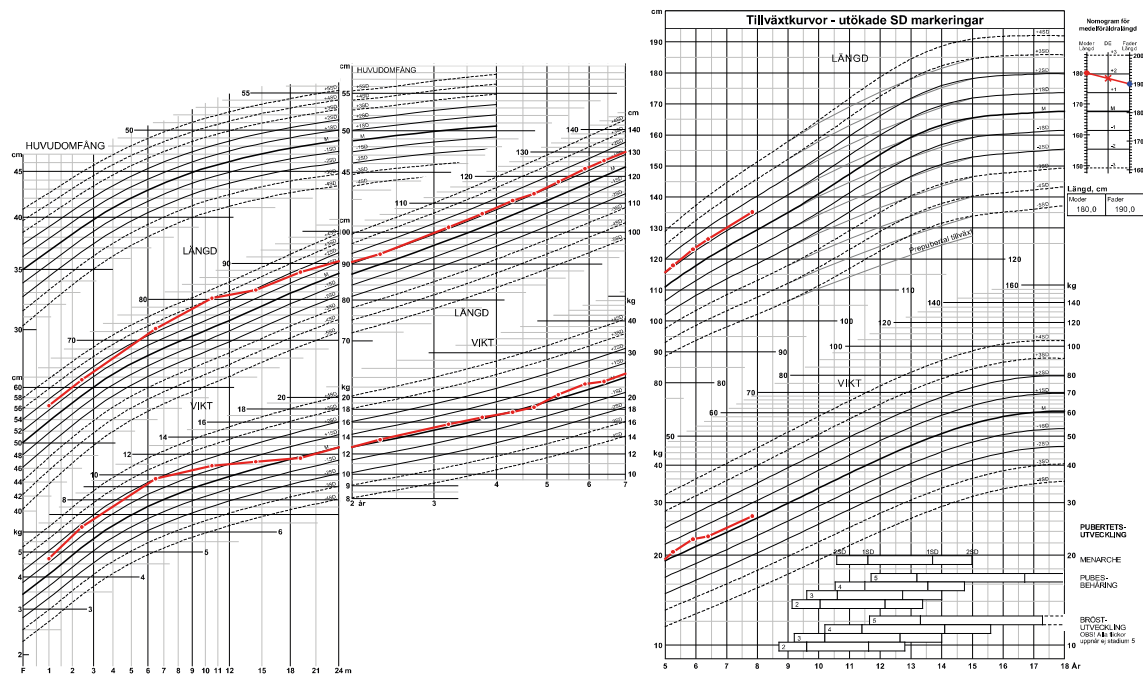
Figure 7 The Swedish growth chart for ages 0 to 24 months, 2 to 7 years and 5-18 years using extended (down to -5) SD lines here showing a clinical example of weight seemingly driving length during the first year of life in a girl.

To minimise the problem of different growth velocities for age, many growth charts are available for separate age periods, allowing for less compression of the chart area. Following a child's growth pattern over time might then be more difficult and require several charts. But height and weight charts are preferable combined on the same page since both measures should be evaluated in comparison to each other. Details on length/ height development is for instance of value in situations with extensive weight gain or loss. The Swedish growth chart, Figure 7, is therefore constructed on logarithmic scales to better capture height and weight development during the first years of life when growth velocity is highest.[55] This approach increases sensitivity both in plotting and reading.

Another feature typical of the Swedish growth charts is prepubertal SD lines that are a projection of growth during childhood into pubertal ages. Similar lines are also constructed from a prepubertal cohort, up to 14 years in boys and 13 years in girls, in the latest Danish chart,[56] thus representing growth of late maturers.

1.4   WHEN GROWTH DEVELOPS OUTSIDE THE CURVE AREA

While growth curves show an individual's position within the population distribution per age, they may have limited accuracy for following a child's growth pattern that develops outside the central distribution shown by the curve. For instance, Figure 8 depicts the height patterns of four boys with different skeletal dysplasias and extreme short stature. It is apparent that all of them grow far beyond the curve area, but a more precise evaluation is difficult. This hampers predicting a child's growth pattern, monitoring whether additional medical conditions might be present and discussing height development over time with the families. Syndrome-specific growth charts are therefore essential.
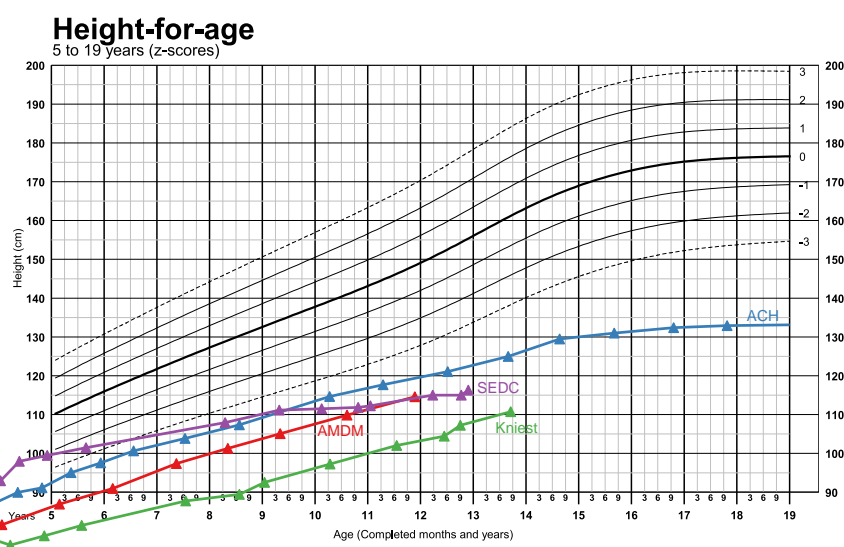
Figure 8 Individual height development in four boys with different skeletal dysplasias: achondroplasia (ACH in blue), acromesomelic dysplasia Maroteaux (AMDM in red), Kniest dysplasia (Kniest in green) and spondyloepiphyseal dysplasia congenita (SEDC in purple). Height position of all boys develops far beyond normal population range, here illustrated on ±3 SD WHO growth chart.[37]

1.4.1   Skeletal dysplasias

Skeletal dysplasia have historically been recognized and grouped based on radiologic evaluations.[57] Clinical entities could therefore be distinguished based on typical features such as for instance short limbs-normal trunk (e.g. achondroplasia, dyschondrosteosis), short limbs and trunk (e.g. pseudoachondroplasia, diastrophic dysplasia, Kniest dysplasia), lethal forms of short-limbed dwarfism (e.g. thanatophoric dysplasia), increased limb length (e.g. Marfan syndrome) or decreased bone density (e.g. osteogenesis imperfecta).[58]

Starting in the later 1990s, technological advances opened up for genetic explanations and confirmation.[57] Skeletal dysplasias can therefore today also be grouped based on molecular defects such as for instance defects in extracellular matrix protein (e.g. collagen type I including osteogenesis imperfecta, collagen type II including Kniest dysplasia, cartilage

oligomeric protein (COMP) including pseudoachondroplasia), defects in metabolic processes including enzymes or transporters (e.g. solute carrier 26A2 (SLC26A2) affected in diastrophic dysplasia), defects in signalling pathways (e.g. fibroblast growth factor receptor 3 (FGFR3) affected in achondroplasia and thanatophoric dysplasia, natriuretic peptide receptor B (NPR-B) affected in acromesomelic dysplasia type Maroteaux) or defects in nuclear protein or transcription factors (e.g. short stature homeobox gene (*SHOX*) affected in Léri-Weill dyschondrosteosis).[59]

The skeletal dysplasia family includes a wide range of genetically heterogeneous groups and entities that can be phenotypically overlapping. A straight-forward correlation between genotype and phenotype might be limited to certain clinical entities. On the other hand, a spectrum of mild-to-severe phenotype for similar genotype can be found in the FGFR3 family (tall stature – hypochondroplasia – achondroplasia – thanatophoric dysplasia), in *SHOX* related dysplasias (tall stature – Léri-Weill dyschondrosteosis – Langer mesomelic dysplasia) as well as in *NPR2* related dysplasias (tall stature – idiopathic short stature – acromesomelic dysplasia Maroteaux).

The 9th and latest edition of skeletal dysplasia nosology from 2015 classifies 436 genetic disorders related to 364 genes into 42 groups.[60] Some groups are based on affected genes covering various separate diagnoses, while other skeletal dysplasias are still grouped by radiographically or clinically similar entities.

Achondroplasia is the most common and easily recognisable skeletal dysplasia with extreme, disproportionate short stature. The condition is caused by an almost uniform heterozygous mutation in FGFR3[61,62] that causes constitutionally increased activity of the receptor.[63] Endochondral growth is regulated by a balance between FGFR3 activity that restricts chondrocyte proliferation, hypertrophy as well as matrix production and growth promoting factors like C-type natriuretic peptide (CNP) and bone morphogenetic proteins (BMP's) among others.[63] In achondroplasia the negative FGFR3 influence overrides the growth promoting signalling mainly in the extremities, leaving the trunk (i.e. spine) to great extent unaffected.[63] Typical clinical features besides extreme short stature and short, rhizomelic limbs are disproportional large head with frontal bossing, prominent buttocks, short fingers and limitation of elbow extension.[64]

1.4.2 Skeletal dysplasia specific growth studies

Specific growth references exist for more frequent growth disorders such as Turner syndrome[65] and Down syndrome,[66,67] but for many conditions knowledge of growth development is limited since the prevalence is very or extremely low making it unfeasible to construct growth and body proportion syndrome-specific references. In addition, many skeletal dysplasia conditions comprise quite heterogeneous diagnoses with considerable variability in phenotype both within and between families. Individuals with mild phenotypes, for instance in Léri-Weill dyschondrosteosis or hypochondroplasia, might then never be detected. Growth studies for these diagnoses are therefore not necessarily representative for

the genetic disorder if based on only the severe phenotype cases (and affected family members). In addition, mutation based references[68] may comprise a wide range of clinical entities/ severity.

There is remarkably little systematic information available on auxological variables in different skeletal dysplasias. Table 2 gives an overview of published growth references, growth studies and case reports including auxological data for selected skeletal dysplasias.

Table 2 Summary of growth studies of skeletal dysplasias or case reports with anthropometric data

Study	Sample origin	Variables collected	Setting of data collection	Sample size and data collection period	Presentation of results	Comment
Achondroplasia, ACH						
Murdoch et al., 1970[69]	USA	Height	Questionnaire, national and district meetings of the Little People of America (LPA)	73 males/ 75 females majority born 1917-1966	Birth length, adult height, parental ages Individual data in appendices	Diagnosis made by medical geneticists, many cases confirmed by radiology
Nehme et al., 1976[70]	USA	Height Sitting height Leg length Sitting height/ Height (crown rump to crown heel ratio) Femur, tibia, fibula Hand, wrist Weight Foot length	Clinical measurements at Children's Hospital Medical Centre, Boston Massachusetts	11 males/ 7 females aged 5 mo to 18 yrs 70 examinations	Average height and sitting height development, 1-18 yrs in boys and girls (charts only) Standard deviation of height, sitting height, ratio sitting height/ height, length tibia and femur, 1-18 yrs (chart only) Relative height, sitting height, ratio sitting height/ height, length tibia and femur and weight per sex and age group 0-3 yrs, 4-10 yrs, 11-14 yrs, 15-18 yrs (table)	Diagnosis based on radiological features
Horton et al., 1978[71]	USA	Height Height velocity Head circumference Upper/lower body segment	Short stature clinics at medical institutions in Torrance, Seattle and Houston, 1976 National LPA Convention	189 males/ 214 females longitudinal data: height 189/ 214 height velocity 26/ 35 upper/ lower 75/ 95 head 114/ 145	Sex-specific mean ±2 SD references for head circumference, height and height velocity, 0-18 yrs and for upper and lower segment, 2-18 yrs (charts only)	
Wynne-Davies et al., 1981[72]	UK	Height Arm span	Visits traced from records of 8 hospitals	48 individuals	Height scatter plot, 0-35+ yrs, sexes combined (chart only) Span scatter plot, 0-35+ yrs, sexes combined (chart only)	Diagnosis based on radiological features
Hunter et al., 1996[73]	USA UK Australia	Chest Circumference height	Follow-up visits by the same examiner, request for volunteers or conventions of LPA	365 individuals 936 measurements; 497 concurrent height + chest circumference measurements	Sex-specific mean ±2 SD references for chest, 0-7 yrs, 0-2 yrs and 46-108 cm height (charts only)	
Hunter et al., 1996[74]	USA UK Australia Canada	Weight Height Sitting height Skinfold thickness (scapular, abdominal, triceps	Extracts from hospital files, personal interviews	409 individuals 1,147 measurements 516 male/ 631 female	Sex-specific mean ±1 SD references for weight, 44-144 cm height, mean ±2 SD weight for 44-104 cm height, mean ±2 SD weight for 104-146 cm height (charts only) Correlation weight and height versus several indices of body fat at different age groups (table) Mean skinfold thickness (scapular, abdominal, triceps), 18-20+ yrs (chart only) Rohrer Index, 6-18 yrs (chart only) Quetelet Index, 27-72 months (chart only)	3 extreme obese individuals were excluded from the analysis
Tachi-bana et al., 1997[75]	Japan	Height Height velocity	National survey & repeated height records	64 males/ 71 females measurements per age group males/ females:	Sex-specific mean ±2 SD references for height and height velocity, 0-18 yrs (charts only)	

Study	Sample origin	Variables collected	Setting of data collection	Sample size and data collection period	Presentation of results	Comment
				height:3-51/ 3-55 height velocity: 3-47/ 3-50	Sex-specific mean for height, 0-17.75 yrs (table)	
Hoover-Fong et al., 2007[76]	USA	Weight Length/ height Head circumference Upper/ lower body segments Arm span Inner/ outer canthal distance Chest circumference Hand length Middle digit length	Data extracted from clinical records of patients seen by one of the authors (CI Scott) at Al DuPont Hospital for Children 1967-2004	301 of 334 children 1,964 weight measurements	Sex-specific P5-P95 curves for weight, 0-36 mo and 2-16 yrs (charts only)	Diagnosis made by one observer by clinical, radiographic and/or molecular means
Hoover-Fong et al., 2008[77]	USA	BMI Height Weight Upper to lower Body segment ratio Height velocity	Longitudinal data extractions from clinical records of patients seen by one of the authors (CI Scott) at Al DuPont Hospital for Children 1967-2004	155 males/ 125 females number of measurements males/ females: BMI: 937/ 870, height: 1,018/ 937, weight: 960/ 893, upper/ lower ratio: 629/ 584, height velocity: 764/752	Sex-specific P5-P95 curves for BMI, weight, height and height velocity, 0-16 yrs (chart only) P5-P95 curves for upper/lower segment ratio, 2-16 yrs (chart only)	
del Pino et al., 2011[78]	Argen-tina	Height Weight Head circumference	Measurements made by the same observer during 1992-2009, Department of Growth and Development, Garrahan Hospital	114 males/ 114 females number of measurements males/ females: height: 867/ 908, weight: 863/ 935, head circumference: 481/ 567	Sex-specific P3-P97 references for height, 0-18 yrs, weight, 0-17 yrs, head circumference, 0-6 yrs (charts and LMS tables)	Diagnosis based on clinic and X-ray criteria; molecular proof in 67/228 cases Exclusion: chronic disease, shunt, leg-lengthening
Hoover-Fong et al., 2017[79]	USA	Height	Mixed longitudinal data abstracted from medical records from a single clinical practice (CI Scott)	162 males/131 females with 1,005/ 932 measurements	Sex-specific P5-P95 chart, 0-36 mo and 2-16 yrs Tables for mean and SD per month	
Tofts et al., 2017[80]	Australia	Height Weight Head circumference, BMI	Measurements from clinical visits retrospectively extracted from the electronic medical records 1970-2015	69 males/ females 3,352 data points	Sex-specific P10-P90 chart, 0-18 yrs for height, weight, head circumference and BMI (chart only)	Age corrected for prematurity Excluded from weight and BMI analysis if clinical diagnosis of overweight
del Pino et al., 2018[81]	Argen-tina	Sitting height Leg length Sitting height/ height Sitting height/ leg length Head circumference/ height	Measurements made by the same observer at growth clinic 1992-2016, Growth and Development department in Garrahan Hospital	171 males/ 171 females with 1,379/ 1356 measurements	Sex-specific P3-97 references for sitting height, leg length, sitting height/ leg length, sitting height/ height, head circumference/ height ratio, 0-21 yrs (charts and LMS tables)	Diagnosis made on the basis of clinical examination and X-ray criteria; molecular testing 163/ 342
Hypochondroplasia						
Wynne-Davies et al., 1981[72]	UK	Height Arm span Data related to head to pubis, pubis to heel	Visits traced from records of 8 hospitals	24 individuals	Height for age scatter plot on height reference of normal and achondroplasia population (chart only) Span for age scatter plot on reference of general population (chart only)	Diagnosis based on radiographs

Study	Sample origin	Variables collected	Setting of data collection	Sample size and data collection period	Presentation of results	Comment
					Head to pubis and pubis to heel for age scatter plot on reference of general population (chart only)	
Appan et al., 1990[82]	UK	Height Sitting height Subischial leg length Pubertal onset	Seen between 1974 and 1988 in the Middlesex hospital, London	56 males/ 28 females 18 individuals were seen only once, 66 twice or more often	Sex-specific mean and SD for height velocity, 2.5-17.5yrs	Diagnosis made on clinical and radiological criteria
Grigeli-oniene et al., 2000[83]	Sweden	Height Sitting Height/height Arm span Head circumference	Referred to Karolinska Hospital for disproportional short stature and radiological features	12 males/ 11 females	Comparison of body proportions (height, sitting height/height, arm span and head circumference) in SDS, p.Asn540Lys vs. no mutation (chart only)	Presence of at least 3 radiological features based on criteria by Hall and Spranger
Pinto et al., 2014[84]	France	Height Weight	Followed at the Bone Dysplasia Center of Necker Enfants-Malades Hospital	22 males/ 18 females without growth hormone treatment	Sex-specific mean and SD for height velocity, 4-18yrs (table) Sex-specific mean curve for height, sitting height, subischial leg length, 3-18yrs (boys)/ 2-13yrs girls (charts only)	Diagnosis based on radiographs

Acromesomelic dysplasia type Maroteaux, AMDM

Study	Sample origin	Variables collected	Setting of data collection	Sample size and data collection period	Presentation of results	Comment
Langer et al., 1977[85]	USA	Height Weight Head circumference Arm span Upper/lower segment		6 males/ 4 females (2 males/ 7 females in previous literature)	Case report - clinical data (partly longitudinal) ages varying from 0 to 35 yrs	Diagnosis based on radiographs
Khan et al., 2012[86]	Pakistan	Height		9 males/ 7 females	Case report - clinical data of 6 consanguineous Pakistani families ages varying from 9 to 38 yrs	Diagnosis based on radiographs and mutation analysis of *NPR2*
Sriva-stave et al., 2016[87]	India	Height Weight Head circumference		4 males/ 1 female	Case report - clinical data of a consanguineous Indian family ages varying from 1 to 7 yrs	Diagnosis based on radiographs and mutation analysis of *NPR2*
Wang et al., 2016[88]	Korea	Height Arm span		3 males	Case report - clinical data of 3 boys from non-consanguineous Korean families	Diagnosis based on radiographs and mutation analysis of *NPR2*

Pseudoachondroplasia, PSACH

Study	Sample origin	Variables collected	Setting of data collection	Sample size and data collection period	Presentation of results	Comment
Dennis and Renton, 1974[89]	UK	Height Weight Head circumference Upper segment lower segment Arm span	Referred to Hospital for sick children, London	1 male/ 3 females	Case report - clinical data of four siblings ages varying from 3 to 10 yrs	Diagnosis based on radiographs
Hesel-son et al., 1977[90]	South Africa	Height Arm span	Investigated at Groote Schuur hospital and Cape Town university	7 males/ 6 females	Case report - clinical data of 13 individuals ages varying from 3 to 30 years	Diagnosis based on radiographs at ages 2-11yrs
Horton et al., 1982[91]	USA	Height	Records at genetic clinics of medical institutions in Kansas City, Seattle, Houston, Baltimore and Torrance	28 males/ 33 females	Mean ±1 SD references for height, 0-18 yrs (chart and table)	Inclusion based on strict clinical and radiological criteria

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Study	Sample origin	Variables collected	Setting of data collection	Sample size and data collection period	Presentation of results	Comment
Wynee-Davies et al., 1986[92]	UK	Height Span Upper/lower segment	Ascertained through 7 skeletal dysplasia and genetic centres Personal examination and clinical records in some cases	20 males/ 12 females	Description of stature and body proportions and other clinical features Height of familial cases on growth curves from Horton et al., 1982	
Mc-Keand et al., 1996[93]	USA	Height	Ascertained through University of Texas Medical Genetics patient population and supporting organisation LPA Questionnaires (transcribed from original data and phone contact)	33 males/ 44 females	Description of demography, family history, body measurements, skeletal complication, skeletal operations, general health problems, chronic conditions later in life, reproduction and social status	Diagnosis made by medical geneticist and/or a radiologist specialising in skeletal dysplasias
Song et al., 2004[94]	Korea	Height Arm span Limb height Trunk height Tibia/femur Radius/ Humerus		5 males/ 7 females	Case report - clinical data of 12 individuals ages varying from 3 to 36 years	Diagnosis made by orthopedic surgeons and pediatric radiologists based on clinical/ radiological features and mutation analysis of COMP
Yu et al., 2016[95]	China	Height Arm span Upper/lower segment	Visits at Sixth People's Hospital	4 males/ 2 females	Case report - clinical data of 6 individuals ages varying from 3 to 20 years	Diagnosis made by radiographic observations and mutation analysis of COMP
Tariq et al., 2017[96]	Pakistan	Height		9 males/ 8 females	Case report - clinical data of 4 generation consanguineous family	Diagnosis made by radiographic observations and mutation analysis of COMP
Multiple Epiphyseal Dysplasia, MED						
Haga et al., 1998[97]	Japan	Height Long bone epiphyses and spine Metacarpo-phalangeal length	Followed at Shizuoka Children's Hospital, National Rehabilitation Center for Disabled Children and University of Tokyo	8 males/ 7 females	Individual's height, 0-18 yrs in males and females (charts, table) Metacarpophalangeal length: individual's SDS for distal phalanx, middle phalanx, prox. phalanx and metacarpals (table) Plots of epiphyseal height versus metaphyseal at >4yrs	Diagnosis criteria: irregular epiphyseal growth or deformity in >2 epiphyses in the long bones, little or no spinal involvement, normal intelligence, normal facial appearance
Seo et al., 2014[98]	Korea	Height	Review of medical records (first presentation and latest follow-up)	95 individuals	Average height (z-score) in MATN3 and COMP	MATN3, COMP mutation molecularly confirmed
Diastrophic dysplasia, DTD						
Horton et al., 1982[91]	USA	Height	Records at genetic clinics of medical institutions in	38 males/ 34 females	Mean ±1 SD references for height, sexes combined, 0-18 yrs (chart and table)	Inclusion based on strict clinical and radiological criteria

Study	Sample origin	Variables collected	Setting of data collection	Sample size and data collection period	Presentation of results	Comment
			Kansas City, Seattle, Houston, Baltimore and Torrance			
Mäkitie and Kaitila, 1997[99]	Finland	Height Relative weight Weight for height Head circumference	Referrals to the Children's Hospital or Genetic Clinic in Helsinki Birth records, child health centre, schools and hospitals	53 males/ and 68 females 104 families	Sex-specific P10-P90 references for height, 0-20 yrs (chart and table) Sex-specific P10-P90 references for weight, 60-145/135 cm height (table) Sex-specific relative height, 0-20 yrs (chart) Sex-specific P25-P75 references for relative weight, 60-150/140 cm height & 10-60/45 kg weight (boys/girls) (chart) Correlation to relative adult height at birth, 1yr and 5 years Assessment of intrafamilial variability Pubertal growth component evaluation based on the Infancy Childhood Puberty (ICP) model	Diagnosis based on clinical features, radiological findings and family history
Barbosa et al., 2010[100]	Portugal	Height	Referrals to Medical Genetics Services after screening in 4 main Portuguese Services of Medical Genetics and 4 Orthopaedics Services	8 DTD, 4 rMED and 2 mDTD (mild DTD, intermediate phenotype between DTD and rMED) All SLC26A2 positive	Height position of each individual relative to Finnish DTD reference; e.g. <10th centile	Diagnosis made based on clinical protocol, photos and X-rays

Cartilage Hair Hypoplasia, CHH

Study	Sample origin	Variables collected	Setting of data collection	Sample size and data collection period	Presentation of results	Comment
Mäkitie et al., 1992[101]	Finland	Height Sitting height Weight Head circumference Arm span	At visits Children's Hospital, Helsinki Birth records, child health centres, schools and hospitals	44 males/ 56 females 81 families; 17 families incl two or three affected siblings	Sex-specific P10-P90 references for height, weight and sitting height, 0-20 yrs (chart and table) Median relative height, 0-20 yrs (chart) Sex-specific P25-P75 references for relative weight, 60-130 cm height & 10-45 kg weight (chart) Relative sitting height for adult height SDS (chart) Median relative sitting height and subischial leg length, 0-20yrs (chart) Pubertal growth component evaluation based on ICP model	Diagnosis based on radiological and clinical criteria.

Spondyloepiphyseal dysplasia congenita, SEDC and other phenotypes of COL2A1 mutations

Study	Sample origin	Variables collected	Setting of data collection	Sample size and data collection period	Presentation of results	Comment
Horton et al., 1982[91]	USA	Height	Records at genetic clinics of medical institutions in Kansas City, Seattle, Houston, Baltimore and Torrance	34 males and 28 females	Mean ±1 SD references for height, 0-18 yrs (chart and table)	Inclusion based on strict clinical and radiological criteria
Nishi-mura et al., 2005[102]	Japan	Height	Medical records and questionnaires completed by physicians	COL2A1 mutation in 32 males and 26 females of 77 individuals with radiological fit of known COL2A1 phenotype	A list of birth details (weight and length, gestational age), height and age at examination and height/ arm span ratio for all individuals with COL2A1 mutation	Based on radiological criteria, clinical phenotypes were divided into SED spectrum, Kniest, Stickler dysplasia type I and uncommon/ atypical type II collagenpathies

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Study	Sample origin	Variables collected	Setting of data collection	Sample size and data collection period	Presentation of results	Comment
Terhal et al., 2012[68]	Europe Australia Lebanon Israel South America	Height Weight Head circumference	Recruitment through two laboratories that offer DNA analysis of *COL2A1* gene Standard checklist filled in by referring physician and growth curve	33 males/ 46 female 381 height measurements with glycine substitutions 27 children with other mutations in COL2A1 gene 96 height measurements	M ±1.6 SD references for height, 0-20 yrs based on data from individuals with glycine substitutions (only chart)	Exclusion criteria: individuals with loss-of-function mutations, with perinatally lethal phenotype, with developmental disability, severe birth asphyxia, abnormal karyotype, with growth hormone treatment, who were born <30 weeks GA, or measurements <2 yrs of age if born <36 weeks GA
Léri-Weill Dyschondrosteosis, LWD – SHOX-deficiency						
Ross et al., 2001[103]	USA	Height Lower segment Arm span Forearm length Pubertal development Age of menarche Metacarpal-phalangeal profiles Radial length	Subjects referred for short stature or Madelung deformity	11 males/ 32 females	Individual age, height SDS, upper/lower segment SDS; arms span SDS and right radius SDS (table) Height SDS scatter plot, 0-60 yrs (chart)	No GH treatment
Ross et al., 2005[104]	USA	Height Lower segment Arm span Forearm length Arm/ leg circumference Pubertal development Bone age	Clinic subjects referred for short stature or LWD in a parent	14 males/ 20 females with age range 1 to 10 yrs	Sex-specific mean ±SD for age, bone age, height SDS, weight SDS, BMI SDS, head circumference SDS, Arm span SDS, arm span-height (cm) and upper segment/lower segment (table for cohort) Individual clinical data incl age, bone age, height SDS, upper segment/lower segment and arm span SDS (table)	Only LWD individuals with confirmed SHOX abnormalities, none with growth hormone treatment
Salmon-Musial et al., 2011[105]	France	Height Parental height Sitting height Length/ circumference of upper and lower segment	Medical records for children enrolled in the Department of Pediatric Endocrinolgy of the University Hospital in Lyon	8 males/ 14 females from 18 families		
Osteogenesis Imperfecta, OI						
Vetter et al., 1992[106]	Germany Austria Switzerland Italy Turkey	Height Motor performance IGF-I	Seen at 1-year interval for clinical evaluation	127 patients with types I, III and IV OI	P5-P95 height references, 0-10 yrs for type I, III and IV OI (charts only) P5-P95 weight references, 0-10 yrs for type I, III and IV OI (charts only) Median IGF-I serum concentrations per age group 1-2 yrs, 2-6 yrs, 6-8yrs, 8-10yrs and OI type Summary of incidence of several extraskeletal symptoms in ages 1-4yrs and 5-10 yrs OI type	Diagnosed in the first two years of life

Study	Sample origin	Variables collected	Setting of data collection	Sample size and data collection period	Presentation of results	Comment
Lund et al., 1999[107]	Denmark	Height Sitting height Arm span Subischial leg length Weight Head circumference IGF-I IGFBP-3	Referred to the department of clinical genetics at Rigshospitalet in Copenhagen Mean of 3 repeated measurements	42 males/ 44 females with types I, III and IV OI	Scatter plots for height SDS, head circumference SDS, height SDS-mean unaffected family member SDS, subischial leg length SDS-sitting height SDS, arm span/height ratio 0-70yrs and IGF-I SDS, 2-10yrs (charts) Height SDS, difference to target height SDS and unaffected family members SDS, IGF-I SDS, IGFBP-3 SDS, arm span SDS, arm span/ height ratio, subischial leg length SDS-sitting height SDS, head circumference SDS, difference head circumference SDS and height SDS per OI type, per collagen type defect (quantitative or qualitative) for children and adults respectively (tables)	Exclusions: patients with non-OI bone disorder, liver disease, endocrine disorder OI according to Sillence characterisation
Zeitlin et al., 2003[108]	Canada	Height Weight (areal)BMD	At the Shriners Hospital for Children in Montréal, Canada during 1992 and 2001	125 OI patients that were treated with cyclical intravenous pamidronate	Mean ±SD for entire study population, 1yr and 4 yrs treatment group per type OI (table) Mean ±SD at start of treatment and after 1yr of treatment per type OI (table) Scatter plot incl regression line for height for age, 0-20 years per OI type (chart and equation) Height for age regression line and scatter plots of individuals with at least 4yrs pamidronate treatment, 0-20 yrs per OI type and sex (chart only) Final height after treatment (individual data)	
Engel-bert et al., 2004[109]	Nether-lands	Height Weight Head circumference, Sitting height Leg length/sitting height ratio	Followed in the Dutch national centre for diagnosis and treatment of children with OI between 1996 and 2000	49 children, none treated with bisphosphonates	Mean ±SD at start and end of study for height, weight, head circumference, sitting height, leg length/ sitting height ratio per OI type	
Aglan et al., 2012[110]	Egypt	Height Weight Head circumference Arm span Sitting height	Recruitment from limb malformations and skeletal dysplasia clinic (LMSDC), Medical Services Unit, NRC	55 males/ 69 females before initiation of bisphosphonate treatment	Scatter plot height SDS, 0-22 yrs (chart only) Scatter plot weight SDS, 0-22 yrs (chart only) Scatter plot head circumference/ height ratio SDS, 0-22 yrs (chart only)	Clinical and radiological evaluation to determine Sillence type
Germain-Lee et al., 2016[111]	USA	Height or arm span Weight Height velocity	Medical records of patients who were seen in OI Clinic at Kennedy Krieger Institute from 2004 to 2013	144 children and 199 adults in OI type I, III, IV and V	Mean for height SDS in children and adult per IO type (chart and table incl range) Mean for height SDS in children <11yrs and >11-20yrs (chart and table incl range) Scatter plot for height, 0-20yrs (individual series) in children with type I and III OI (chart only) Scatter plot for weight, 40-200cm height (individual series) in children with type I, III and IV OI (chart only)	OI according to Sillence characterisation , type V according to Glorieux

1.5   A GROWTH CHART AS A MATRIX

Keeping in mind the differences between references based on cross-sectional and longitudinal data, no child can be expected to follow a specific centile or SD postion[112,113] but rather its own growth curve.[114] A catch-up/ catch-down in length during the first two years of life is reported for more than 50 percent of normal infants.[115,116] In older ages, a catch-up can follow periods of restricted growth.[114] Centile crossings is also a common phenomenon.[116,117] Evaluations of individual height series in the *First Zürich Longitudinal Growth Study* showed little evidence that a child strictly follows a certain centile.[117] Differences between a child's maximum and minimum height SDS were calculated to define his/her growth channel. In about 2/3 of children this covered more than one SDS and only 1/4 kept within a growth channel of less than 0.5 SDS during prepubertal ages.[117]

Differences in tempi are most apparent during pubertal ages but a child can be expected to crosses centiles already during childhood if s/he is an early or late mature.[115] The child's size at a given time point is thus not necessarily always of most interest, but rather the changes in size over ages, i.e. the growth pattern.[33]

1.6   ILLUSTRATING GROWTH POSITION CHANGES OVER TIME

As noted earlier in section 1.3.4, centile curves are not meaningful when expressing changes in a child's height position over time.[33,53] Using SDS scales, on the other hand, changes can be compared over ages[118] and also allows comparison of several anthropometric variables. For instance, Figure 9a summarises weight, length and BMI development in the girl previously illustrated in the Swedish growth chart (Figure 7). Similarly, a closer look at the effect of growth hormone treatment in a boy with hypochondroplasia, Figure 9b, suggests a temporary height gain from improved sitting height position rather than from leg length.
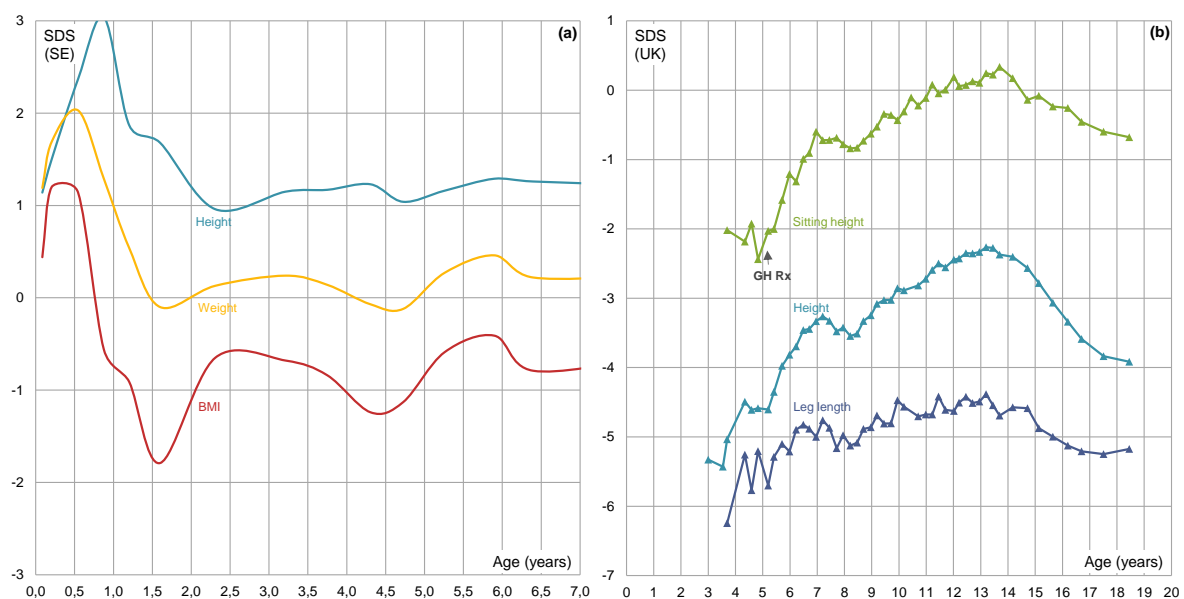

Figure 9 SDS charts to illustrate development of several anthropometric variables: (a) height, weight and BMI development in the girl shown in the growth chart in Figure 7 and (b) sitting height and leg length SDS in a GH-treated boy with hypochondroplasia.

1.6.1 Turner syndrome as an example

This SDS presentation is thus valuable to capture progression and magnitude of positional changes, which also allows comparison between cohorts.[118] Height in girls with Turner syndrome from different ethnic background follows the same pattern but differs in absolute height (Figure 10a). Growth might thus be similar in girls with Turner syndrome when taking into account differences in height of the respective background population. Ethnic differences strongly influence adult height in girls with Turner syndrome, which generally is 20 cm lower than the background population mean.[119]

Similarly, comparing height development in Turner syndrome to girls with idiopathic short stature (ISS) indicates that tempo in both short stature conditions might be different, Figure 10b. Both groups improve height position towards the end of the growth period since the background population reaches final height earlier. Final height position in girls with ISS from this reference and in whom pubertal growth is not compromised by ovarian failure is about -2.7 SDS with temporary position of -3.6 SDS due to decreased growth tempo.

Spontaneous growth in Turner syndrome has been described by several authors; for review see Bertapelli et al.,[65] most recent studies also including girls with hormone treatment.[65] Spontaneous puberty is reported for only 10-17 percent,[120,121] thus leaving the majority of girls with Turner syndrome without pubertal growth spurt and prolonged growth period.[122] In those, only 96 percent of final height is achieved at 16 years of age.[25,121,123] Adult height in those with and without spontaneous puberty is, however, the same.[121]
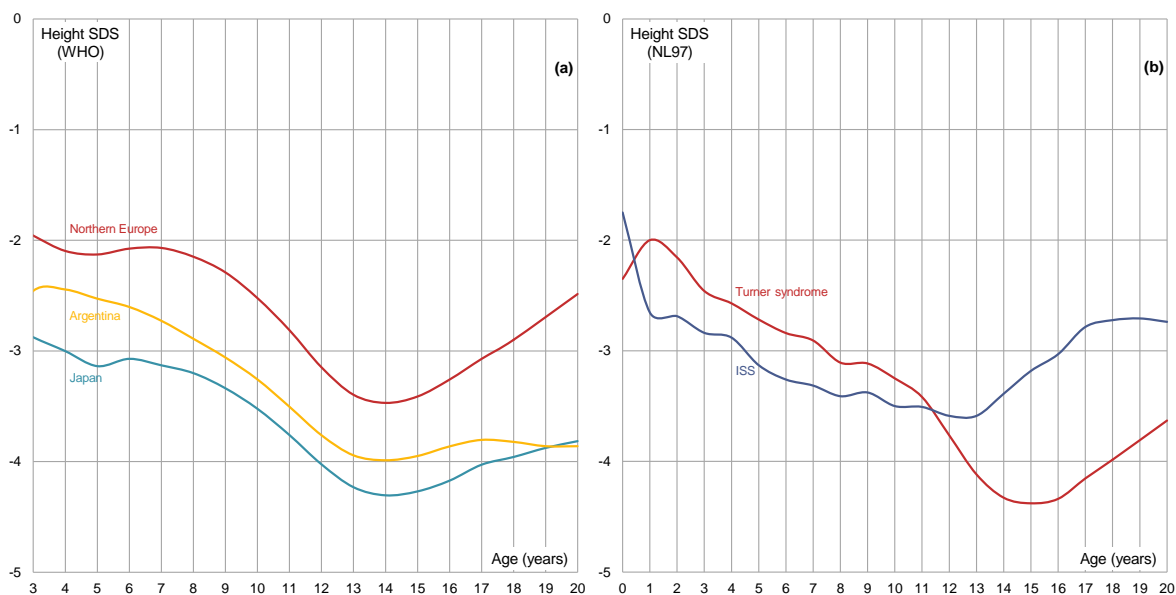

Figure 10 Height SDS (a) in girls with Turner syndrome from Northern Europe[124] (red), Argentina[125] (yellow) and Japan[126] (blue) relative to WHO reference[37,45] and (b) in girls with Turner syndrome[124] (red) compared to with idiopathic short stature (ISS, purple)[127] expressed relative to Dutch reference.[14]

A closer look at body proportions in Turner syndrome suggests that leg length is more severely affected than sitting height (Figure 11). Tempo of leg length growth seems to be slower compared to children of normal height, which might explain the improvement of leg length position after 13 years of age when legs of normal girls have achieved final size. A

pubertal spurt in height and sitting height is not observed. Height position is temporarily compromised during pubertal ages but sitting height (and thus height) improves after 17 years of age. Note, however, that the cohort in the illustrated example was treated with estrogen, which could also stimulate the late catch-up.
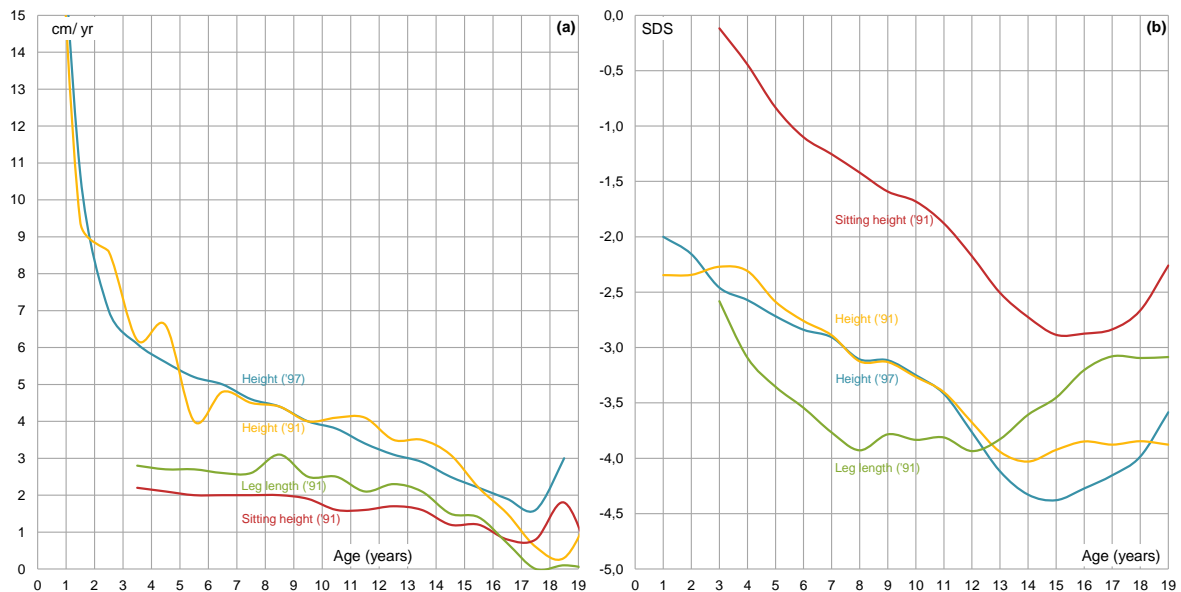

Figure 11 Development of height, sitting height and leg length in non-GH treated girls with Turner syndrome[124,128]: (a) as yearly increments and (b) as SDS relative to Dutch normal reference.[7,14] Note that this cohort was treated with estrogen.

Skeletal phenotype in Turner syndrome includes short stature with mild body disproportion due to short legs, cubitus valgus and aberrant facial morphology. It has been suggested that except for SHOX haploinsufficiency, deficiency of the proteoglycan biglycan is connected to a skeletal phenotype and is also responsible for vascular/ cardiac symptoms that are typical in Turner syndrome.[129] Biglycan is functional for extracellular matrix assembly and maintenance, interacting with collagen type I, II, III and IV and seems also to regulate TGF-beta and BMP4 activities.[130] The expression level of biglycan as determined by number of X-chromosomes is clearly related to height with short stature with short legs in Turner syndrome and tall stature with long legs in triple X syndrome.[131] In contrast to Léri-Weill dyschondrosteosis (LWD), also having SHOX deficiency, Madelung deformity is rarely seen in Turner syndrome and facial phenotype, including mouth anatomy, is usually normal in LWD. In addition, arm span is normal for height in girls with Turner syndrome[132] but shows substantial deficit in LWD.[133]

1.6.2 The importance of SD

A position in the growth chart can easily be calculated by $z = (\text{Measurement-Mean})/\text{SD}$ for the same age in the reference material given that the variable follows a normal distribution.[8] For measures such as weight and BMI, where skewness has to be accounted for, LMS values, introduced in section 1.3.3, can be used. SDS can then be calculated by $z = ((\text{Measurement}/M)^L-1)/LS$, which is $z = (\text{Measurement-}M)/MS$ if L=1.[8]

The SDS value is thus influenced by the mean value of the reference material and especially the size of the SD. As noted earlier in section 1.3.1, variability during pubertal ages may be lower in longitudinal references since differences in tempo and pubertal timing can be adjusted. The effect of this adjustment on the SD can be seen in Figure 12a. In other words, a great deal of variability during pubertal ages is related to tempo, which cannot be accounted for in cross-sectional studies but which influences calculation of SDS position. SD development in the normal population references used in this PhD project are therefore shown in Figure 12b-d. The size of SD in the Swedish growth charts[134] is modified while references from the WHO,[37] the fourth Dutch nation-wide survey[14] and the UK[135] are clearly based on cross-sectional data. Nevertheless, it is crucial to note that SDS during pubertal ages per se can be misleading[136] since comparisons are based on chronological ages. These are, however, a poor proxy for biological age during pubertal ages, as seen earlier in Figure 3.
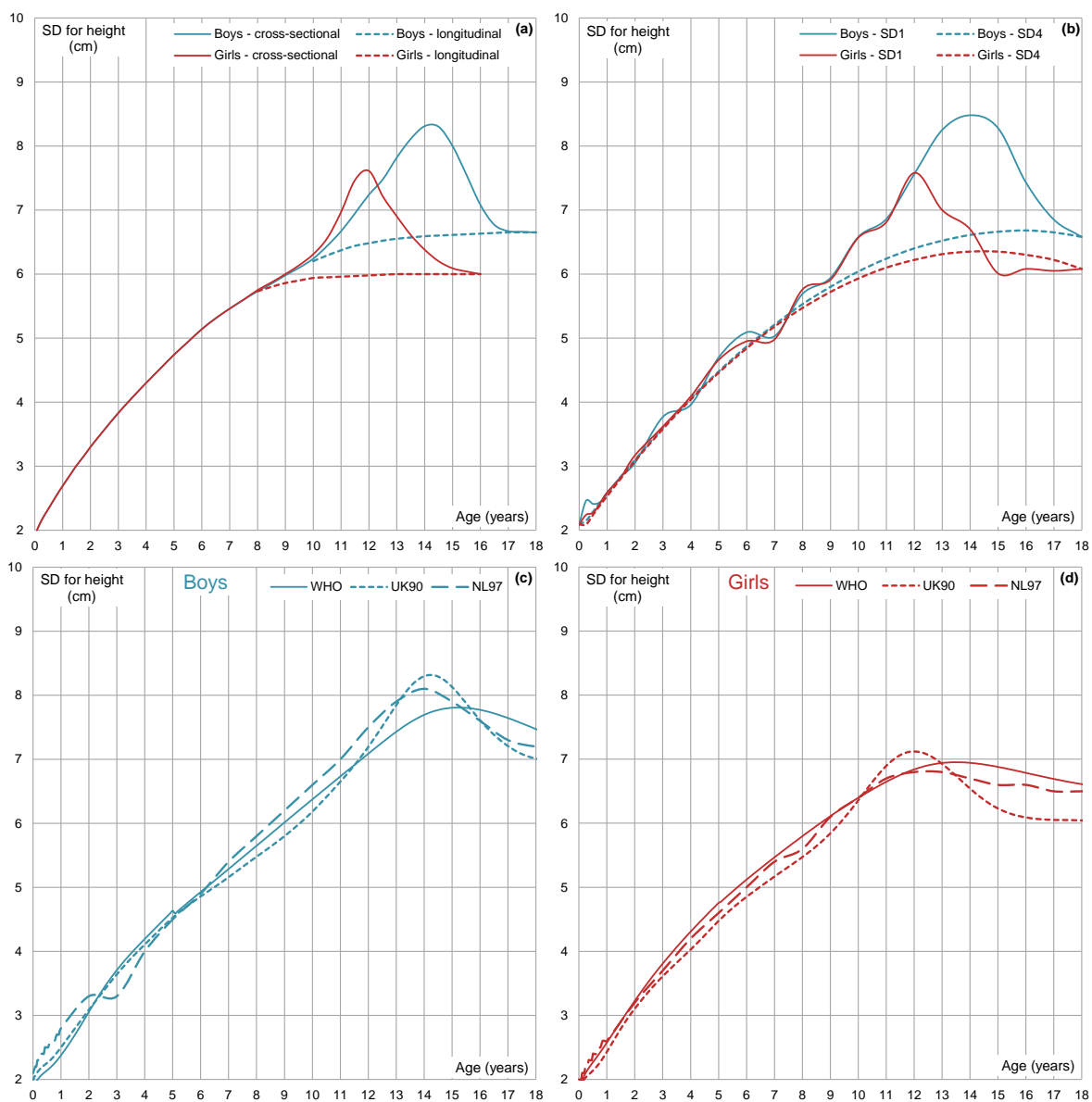

Figure 12 Development of SD for height in boys (blue) and girls (red): (a) differences in SD if conditional (longitudinal, dashed) versus unconditional for tempo (cross-sectional, line) in traditional British height references;[34,35] (b) differences in Swedish height reference[134] with SD1 referring to empirical SD and SD4 referring to SD used in growth charts; (c-d) SD in WHO (WHO),[37] national British (UK90)[135] and Dutch (NL96)[14] references.

Similarly, average size of the reference material influences resulting SDS value. The observant reader might have noticed that height position of the Northern European Turner reference (marked in red) in Figure 10a does not match the same illustration in Figure 10b. This is because the curves are based on different background populations. The WHO reference[37,45] seems suitable for comparing different ethnical groups of the same condition while a Dutch reference[14] might be more meaningful for comparing two short stature conditions from the same background population.

1.7 GROWTH PROMOTING THERAPY

Orthopedic limb lengthening may be a common procedure for increasing height in extreme short stature. It is no standard treatment in children with achondroplasia in Sweden and Northern Europe but is commonly used in Southern Europe (Florian Innig, BKMF, personal communication 2018). This surgical procedure is, however, tedious and not necessarily without complications.[137] Height gain of 20 cm might be achieved.[138]

Growth hormone treatment (GH Rx) often has modest effects in most severe short stature skeletal dysplasias[139] including achondroplasia.[140] Reports on adult height are limited to one study from a small Japanese sample with achondroplasia (8 boys/ 14 girls) where height gain from GH Rx alone was less than 4 cm. Short-term height gain of 0.5 SDS[141] and 0.6/0.8 SDS[142] have also been reported, with[141] and without[142] changes in body proportions.

Future therapies for achondroplasia may target FGFR3 signalling and non-FGF signalling pathways.[143] These include soluble FGFR3 that bind and sequester FGF ligand, anti-FGFR3 antibodies that block ligand binding to the receptor and subsequent downstreaming signalling pathways, tyrosine kinase inhibitors and CNP or CNP analogues that antagonize and inhibit FGFR3 downstreaming signalling.[143]

Growth promoting therapy in milder short stature conditions, such as Turner syndrome, still focuses on GH Rx. Adult height is typically increased by roughly 7 cm,[144] or using supraphysiologic doses almost double.[145] Benefits from GH Rx in Turner syndrome is similar to ISS, SGA and SHOX deficiency.[146] Clinical practice nowadays shifts towards starting GH Rx at earlier ages and less severe height position[147] and clinical guidelines for girls with Turner syndrome suggest GH Rx to be initiated at "about 4 to 6 years and preferable before 13 years, if growth is poor or is likely to be compromised."[148] Treatment response is, however, variable and unpredictable,[149] which makes it difficult for pediatric endocrinologists to communicate realistic treatment outcomes to patients and their families.

In summary, detailed descriptions of growth and body proportions development from birth to adulthood is valuable as background for any growth promoting intervention. Similarly, evaluation of growth promoting therapy using growth charts can support clinical decisions and facilitate communication with families.

2 AIMS

The aim of this study was to construct auxological tools for following growth in children with extreme and/ or disproportional short stature and to evaluate medical intervention that promotes growth.

More specifically,

- <u>Growth in achondroplasia:</u>
  To construct sex- and age specific growth references for height, weight, head circumference and body mass index and to discuss the development of these anthropometric variables in an European achondroplasia cohort.

- <u>Body proportions in achondroplasia:</u>
  To construct sex- and age specific references for sitting height, leg length, arm span and foot length and to discuss the development of body proportions in achondroplasia.

- <u>Growth in other skeletal dysplasia resulting in extreme short stature:</u>
  To describe the growth pattern of individuals with skeletal dysplasia and extreme short stature in the achondroplasia growth charts.

- <u>Evaluation of growth hormone therapy:</u>
  To characterise girls with Turner syndrome with typically good and poor response in height.

3 MATERIALS AND METHODS

The aim of this PhD project can be divided into two parts; one concentrating on growth and body proportion in children with skeletal dysplasias resulting in extreme short stature (Paper I-IV) and the other on evaluating GH Rx in girls with Turner syndrome (Paper V). The following sections will follow the same division.

3.1 GROWTH AND BODY PROPORTION REFERENCES IN SEVERE SHORT STATURE

The first part of this PhD project focuses on constructing references from a European achondroplasia cohort (Paper I-II), on implementing those as clinical charts (Paper III) and suggesting these for following children with other extreme short stature conditions (IV).

3.1.1 Collecting data for achondroplasia and other short stature conditions

Data from children with skeletal dysplasia including achondroplasia was collected by different means and sources.

The majority of measurements were conducted by the same observer (LN) mainly during routine visits at the skeletal dysplasia clinic at the Department of Pediatrics at Karolinska University Hospital in Stockholm, Sweden, and at annual meetings of the German Association for People of Short Stature and their Families (Bundesverband Kleinwüchsige Menschen und ihre Familien e.V., BKMF). Measurements followed a standardised technique. Infants and young children were measured in supine position with legs extended and both heels against a moveable board. Stretched standing position was measured from approximately two years of age using a statiometer (Hyssna Measuring Equipment AB, Sweden) with the child looking straight ahead and back and heals against the wall. Sitting height was measured in a similar way with the same equipment; until about two years of age in supine position (i.e. as crown-rump length), and for older ages sitting straight on a stool, with back, buttocks and head against the wall looking straight ahead. Head was measured at its maximum circumference using a nondistensible tape. A calibrated digital scale was used to record weight of the child that was in light clothes. Arm span was determined as the longest distance between finger tips and was measured on the wall by two observers using stretching technique. Data series were retrospectively complemented with entries from birth, child health and school records. Additional measurements made by the same observer were available from an earlier study.[142]

Data was also collected from colleagues in Denmark, Finland, Norway and Sweden and in collaboration with Sweden's Association of Short stature (Föreningen för kortvuxna, DHR). Colleagues from Spain, Argentina and the USA contributed with measurements from children with short stature conditions other than achondroplasia that they followed in their skeletal dysplasia clinics.

Diagnosis was based on genetic and/or clinical and radiological investigation, which seemed sufficient for the achondroplasia cohort (Paper I-II). For analysing growth in other skeletal dysplasia (Paper IV), genetic confirmation was crucial for diagnosis, which is why we restricted the scope of this study to diagnoses with distinct radiological and clinical criteria. The following diagnoses were finally included:

- Acromesomelic dysplasia type Maroteaux (AMDM): an autosomal recessive skeletal dysplasia. The inactivating mutations in *NPR2*, the gene encoding for the CNP receptor NBR-B disturb the counteracting balance between FGFR3 and NPR-B signalling. This allows for a dominance of FGFR3 activity making the development of height position in the achondroplasia chart fundamentally interesting.
- Pseudoachondroplasia (PSACH): an autosomal dominant skeletal dysplasia caused by heterozygous mutations in the gene encoding cartilage oligomeric matrix protein (COMP). Height position progressively decreases after the first year of life resulting in an adult height within the achondroplasia range, thus making this unique growth pattern interesting.
- Hypochondroplasia: an autosomal dominant skeletal dysplasia caused by mutation in the gene encoding for FGFR3, thus sharing the similar genetic background with achondroplasia. Note that several children with radiological/ clinical hypochondroplasia diagnoses are not linked to FGFR3,[150] suggesting genetic heterogeneity. We therefore focused on those with genetically confirmed hypochondroplasia.

3.1.2 Construction of achondroplasia references and growth charts

All 4,375 measuring occasions were recorded and age, BMI, subischial leg length (SILL) and sitting height/ height ratio (SH/H) were calculated. Measurements from adults aged 20 to 40 years were coded as 20 years of age. Individual data series were plotted for children with several visits to identify possible data entry or measuring errors. These were corrected if possible or excluded. Infant measurements were excluded for those born prematurely, i.e. before gestational week 37 (n=6). Additional exclusion criteria were growth-promoting therapy (n=51) such as leg lengthening (height, SILL, weight, BMI) or growth hormone (all measures) and other conditions affecting growth (n=4). Head circumference measurements from children with shunts were excluded (n=9). Measurements from individuals (n=28) with *eight-plates*[151] applied for correcting/ preventing varus or valgus deformity of the legs were not excluded.

Since the sample comprised a mix of cross-sectional and longitudinal data, we could not adjust individual data series for differences in tempo and to average age at peak height velocity, discussed in section 1.3.1. The data set was therefore treated as a cross-sectional cohort. The final data set was additionally trimmed for each child contributing only one measurement to pre-defined age groups; i.e. at birth, at one week and monthly thereafter until one year of age, bi-monthly for second year of life, quarterly until four years and yearly thereafter. This was done to avoid that individuals with extensive number of measuring

occasions contributed disproportionally to the fitted curves. Final number of data points for data analysis was for height 3,818, for weight 3,693, for head circumference 2,616, for BMI 3,526, for sitting height 1,310, for leg length 1,272 and for arm span 1,148. Descriptive statistics for these pre-defined age groups were obtained as estimates of the empirical (measured) data that could be used for comparison to the fitted values.

Sex-specific growth references were modelled in the GAMLSS[51] package in R Studio version 3.2.3, which includes the LMS method as special case.[8] Model fit was evaluated based on QQ-plots and primarily on appearance of the fitted curves.
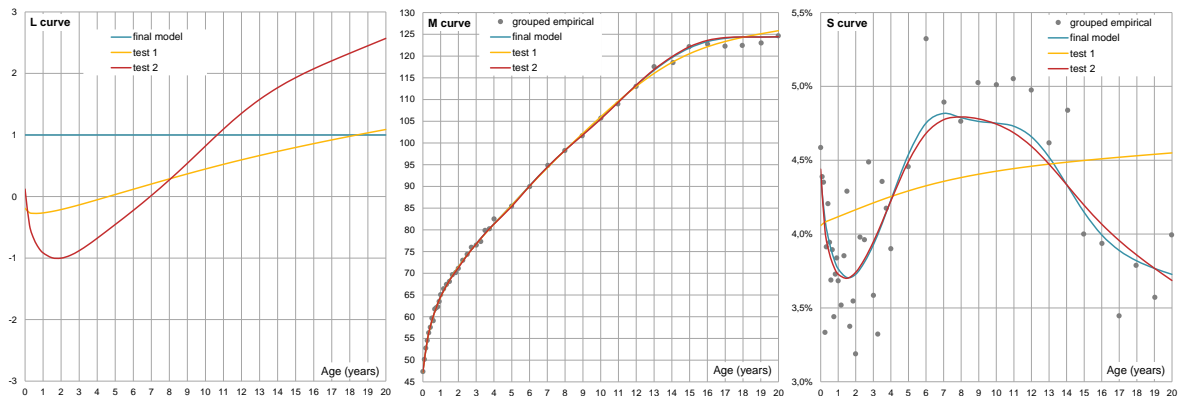
Figure 13 Development of L, M and S curves in test models for determining model distribution for height in girls

More specifically, test models were initially run to investigate the distribution of each anthropometric variable such as for height (Figure 13). These test runs comprised distributions of two parameters (i.e. normal distribution), three parameters (i.e. Box-Cox normal) and four parameters (i.e. Box-Cox power exponential),[52] which were then compared based on versions of AIC and, visually, on fitted ±2 SD curves. Note that four parameter distribution models already seemed impractical for future use of the resulting references, since SDS calculation would be more complicated.
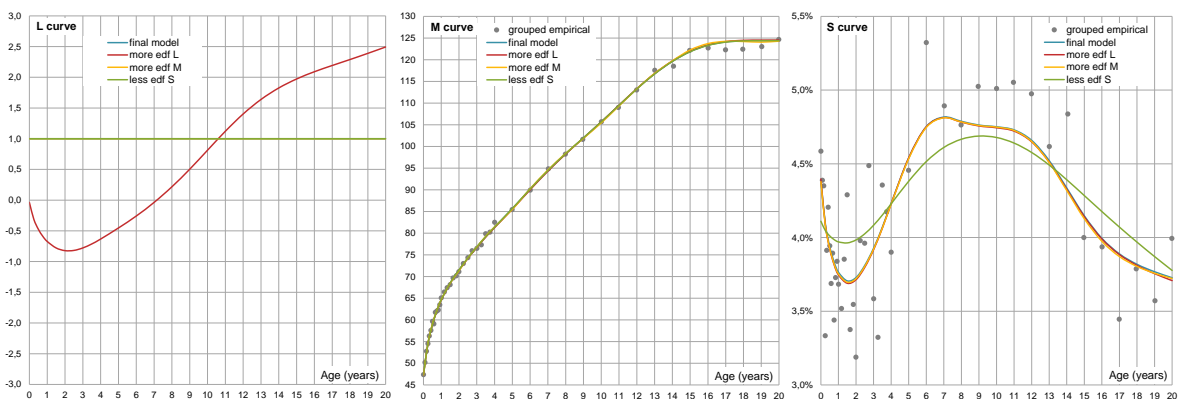

Figure 14 Development of L, M and S curves in models searching for the final height model in girls

Based on the best test run model, further models were fitted to determine a suitable final version that would represent empirical data but, at the same time, give a smooth curve. Increasing complexity of the model, i.e. higher edf values, was visually evaluated based on

appearance of resulting ±2 SD curve (Figure 15) keeping in mind model fit in terms of low information criterion (Table 3) and model diagnostics (Figure 16).

Table 3 Summary of models and information criteria exemplifying model selection for height in girls

	Information criterion			edf			transformed age
	GAIC (#2)	GAIC (#3)	GAIC (#log(n))	L	M	S	
test runs							
final model	10691.05	10709.05	10792.34	0 (fixed L=1)	9	5	0.75
test 1	10729.09	10743.05	10807.64	0.1	7	0.1	0.5
test 2	10689.01	10715.22	10836.48	1	14	4	0.6
Finding final model							
final model	10691.05	10709.05	10792.34	0 (fixed L=1)	9	5	0.75
more df M	10694.17	10718.18	10829.23	0 (fixed L=1)	15	9	0.75
more df L	10689.77	10711.77	10813.56	2	9	5	0.75
less df S	10696.88	10711.88	10781.28	0 (fixed L=1)	9	2	0.75

Considering the small sample size, model selection based on a conservative SBC (GAIC (#log(n)) might be appropriate, yet on the other hand, the cross-sectional design, i.e. not having data for each individual at each age, might prefer a liberal criterion (GAIC(#2)). Note therefore that versions of GAIC were used as guidance for finding appropriate smoothness of the curve while final model selection was based on appearance.
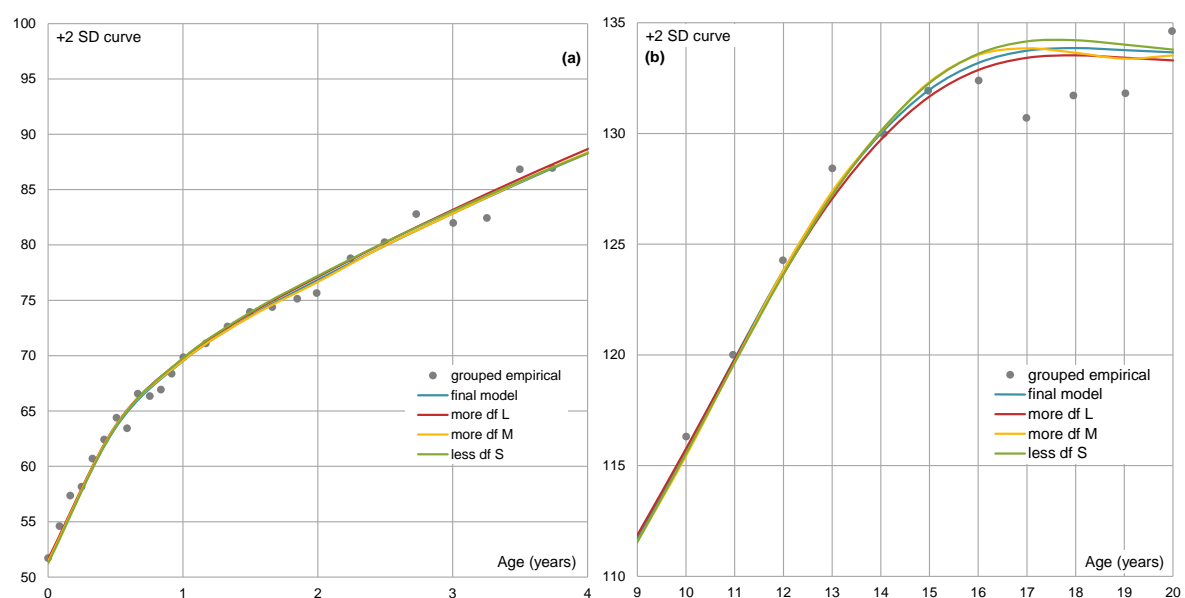

Figure 15 Resulting +2 SD curves for height models in Table 3. Note that +2 SD lines during infancy period are based on 3 months data for this illustration, thus not representing final curve pattern.

All anthropometric variables besides weight and BMI were assumed to follow a normal distribution and were therefore fitted accordingly to a LMS model with constant L=1. For weight and BMI, all three LMS parameters were modelled for age. Note that, due to high

velocity in head circumference during infancy, more weight was given to the measurements during the first years of life, which was done by an age transformation of $x=x^{0.35}$.
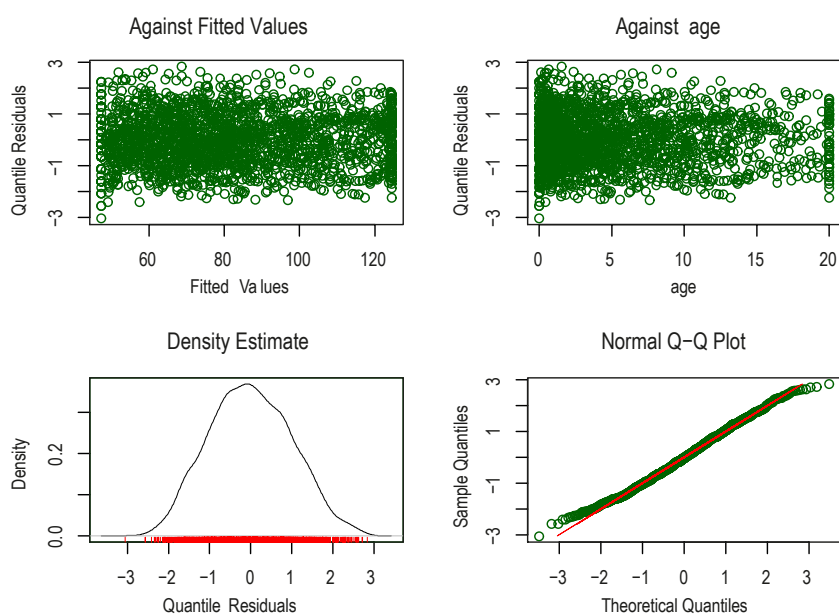

Figure 16 Example of model diagnostics for final model in Table 3: residuals plotted against fitted values and age and normal QQ-plot.

From the resulting references, changes between full chronological ages were calculated as proxy for growth velocity since the data was too limited to construct velocity references. These yearly increments give thus only an indication of velocity and were compared to equivalent estimates from other achondroplasia and normal population references.

The clinical growth charts were technically constructed in collaboration with PC PAL, a medical software company with focus on growth modules for medical systems.

3.1.3 Analysing growth and body proportions in short stature skeletal dysplasia

Another focus of this PhD project was to provide insights into how height and body proportions develop with age in achondroplasia and other skeletal dysplasias with severe short stature. It was therefore natural to illustrate the progress of obtained reference values as well as individual patterns as SDS charts. Development of height could thus be compared to sitting height and leg length and also timing and magnitude of growth restriction could be described.

The WHO reference[37,45] was used for all comparisons of height. Since this material does not cover head circumference up to adult size nor body proportions, SDS for head circumference, sitting height and leg length was estimated from national British references.[135,152] This seemed adequate since adult height both references is comparable. A weakness of the British body segment reference is that it is based on a rather small South-English sample and that subischial leg length was obtained from subtracting sitting height from previous height references.[152] Furthermore, these do not cover sitting height/ height ratio and arm span, which had to be complemented by Dutch references.[7,153] It is worthwhile noting that there is only

one reference,[153] based on three cross-sectional surveys, with distribution parameters to calculate SDS for all growth and body proportion measures used in this study. Comparing sitting height/height ratio of this reference to values in the fourth Dutch nation-wide survey[7] showed surprising deviations and possible unreliable patterns. Furthermore, it could also be argued whether it is fair to compare extreme growth development to a reference from a very tall population.

Growth and body proportion data for children with AMDM, PSACH and hypochondroplasia were also converted to SDS relative to the achondroplasia reference. Individual data series were illustrated as SDS chart and superimposed on the clinical achondroplasia chart.

3.2 GROWTH HORMONE TREATMENT IN GIRLS WITH TURNER SYNDROME

The second part of this PhD project focused on characterising good and poor response to growth hormone treatment (GH Rx) in girls with Turner syndrome, for which data was retrieved from the *Swedish National Register for growth hormone treatment of children and adolescents*. The register export covered details on treatment start and stop, on birth and parents, as well as visit specific data on height, weight, sitting height, pubertal stages, GH and other medication.

Visit specific data was first coded for predefined milestones such as date at treatment start, first year follow-up, pubertal onset as Tanner breast stage >B1 and adult height. Both pubertal onset and adult height were evaluated based on individual data series to ensure that details of the selected visit were congruent with subsequent measurements. Adult height was defined as height velocity <1cm/ year during a minimum time interval of six months. Parental height was calculated as MPH SDS.

SDS calculations were based on the Swedish reference[134] for height and the Dutch references for sitting height, leg length and sitting height/ height ratio[7]. As noted in section 1.6, it might be misleading to calculate SDS during pubertal ages, which was, nevertheless, needed to obtain a height position at GH Rx start. On the other hand, the majority of girls with Turner syndrome lack spontaneous puberty and are therefore most often pre-pubertal at GH Rx start. The pre-pubertal height references in the Swedish growth chart were therefore expected to give a more realistic estimate of height positions during typically (for general population) pubertal ages. Tabled mean and SD values for this reference were therefore estimated from the growth chart. Height and age coordinates obtained using Adobe Illustrator were modelled by 2nd degree polynomial regression where R-squared was used as indicator for model fit.

Treatment response was evaluated as total height gain from GH Rx estimated as delta height SDS from therapy start to adult height. Since defining poor response by arbitrary cut-offs, such as <0.5 SDS,[154,155] could lack empirical background, we used the entire distribution of total height gain to define the different response groups, as seen in Figure 17. Five percent of values at each end of the distribution were considered as non-representative outliers and were thus excluded. The nearest 25 percent were chosen as typically high (*good*) and low (*poor*) responses leaving 40 percent in the middle representing "average" or *intermediate* response.

Note that resulting response groups were overlapping when summarised as histogram (in Figure 17). For instance delta height of 0.56 SDS could be classified as *intermediate* and as *poor*. Responses of the same size, 0.5 SDS defined as 0.375 to 0.625 SDS, were thus assigned to the same group (*poor*). Resulting number of observations in the *good* and *poor* group resulted therefore not exactly in 25 percent each.
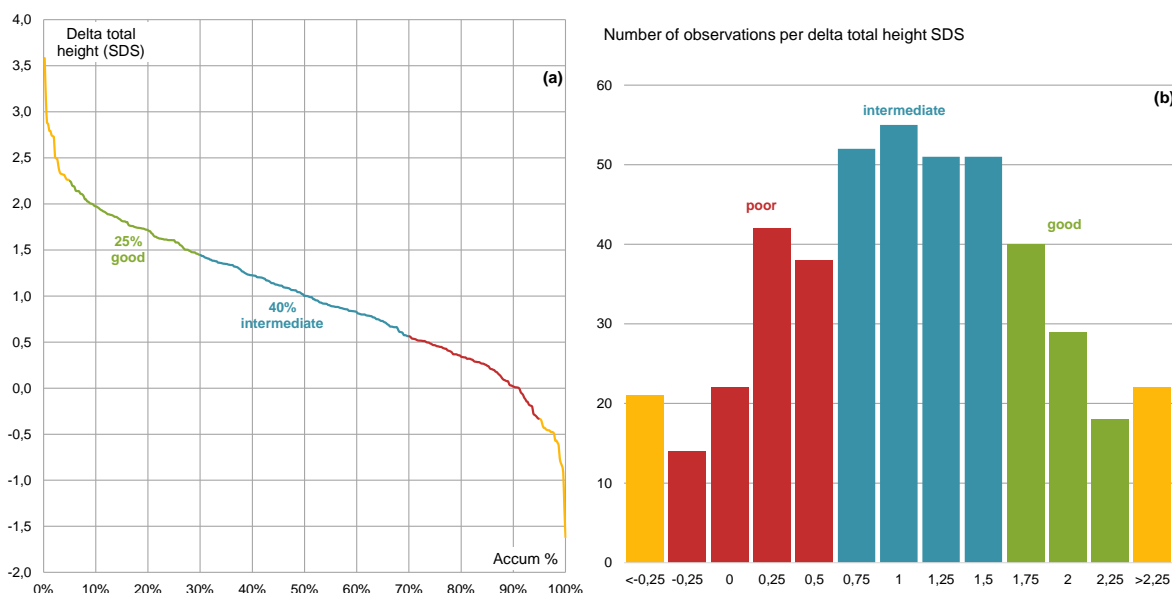

Figure 17 Distribution of total height gain SDS used to define good and poor response: (a) as cumulative percentages and (b) as histogram

Variables previously suggested to be predictive for treatment success were summarised as descriptive statistics and as scatter plots, which were helpful to identify possible sub-groups. Special focus was thus given to:

- MPH as indicator of familial height including the child's deviation from it
- Age and height position at GH Rx start
- Initial treatment response defined as height gain from first treatment year
- GH dose (µg/kg/day) at 12 months of treatment as proxy for dose
- Age at pubertal start divided into those with spontaneous and with induced puberty

In addition, simple SITAR-models were run for each of the response groups. Obtained average curve would illustrate the growth pattern of both response groups and model parameters could be used to compare differences in size, tempo and velocity.

3.3 ETHICAL CONSIDERATIONS

These studies were approved by the Regional Ethical Review Board at Karolinska Institutet, Stockholm, Sweden. The board of the *Swedish National Register for growth hormone treatment of children and adolescents* also approved the project on evaluating good and poor response to growth hormone treatment.

4 RESULTS AND DISCUSSION

This section will discuss selected findings of both parts of this PhD project; i.e. growth and body proportions in extreme short stature (Paper I-IV) and response to GH Rx in Turner syndrome (Paper V). Some challenges in this kind of auxological studies are also touched upon.

4.1 GROWTH AND BODY PROPORTIONS IN ACHONDROPLASIA

Achondroplasia-specific references are available from various ethnical groups and geographic regions (see Table 2), which makes it possible to study variation and possible effect of background populations on height. A description of the growth pattern including ages when growth position is compromised (i.e. timing) and how much growth position is lost (i.e. magnitude) is generally missing. Existing evaluations of height in achondroplasia is limited to comparisons of birth length and adult height to normal population. Reports on body proportions in achondroplasia have been scarce and calculating SDS only recently became available with references from Argentina[81].

We therefore decided to construct growth and body proportion references from a European cohort. Illustrating these also as SDS charts creates insights into timing and magnitude of growth restriction caused by the specific FGFR3 mutation.

4.1.1 Height development in achondroplasia

Figure 18 illustrates how height in achondroplasia develops from birth to adulthood in the present study and in others previously listed in Table 2. Height seems to develop similarly with comparable adult height in most studies, but it is difficult to evaluate possible differences during infancy or childhood, or in tempo.
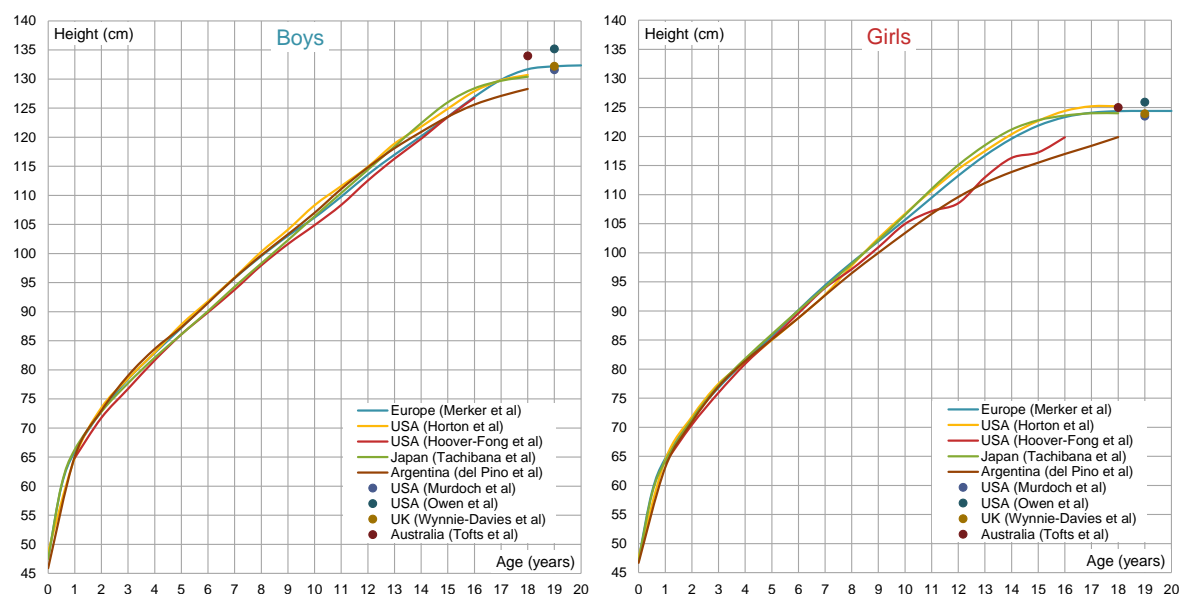

Figure 18 Height for age in boys (left) and girls (right) with achondroplasia in cohorts from Europe, North America, South America, Asia and Australia. Note that height during the first year of life might appear linear, which is a result of values being available only for full chronological ages.
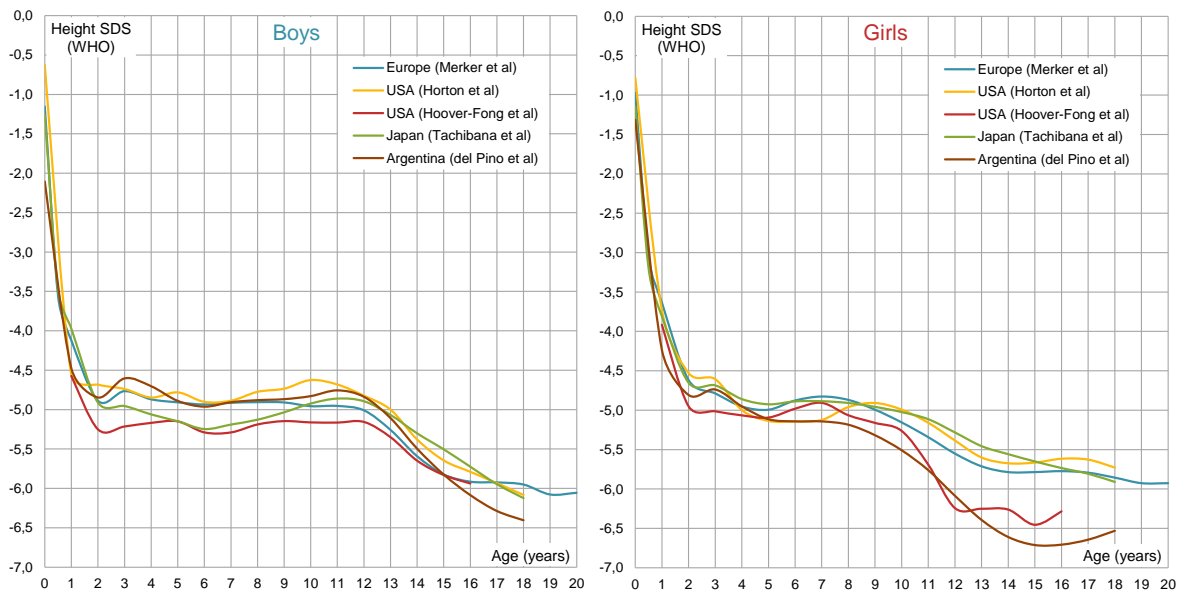
Figure 19 Development of height position in achondroplasia relative to normal population in boys (left) and girls (right) in cohorts from Europe, North America, South America and Asia

Height development expressed as SDS, Figure 19, gives thus better information about tempo and possible ethnical differences. All studies show identical patterns with comparable tempo. Birth length is only marginally affected, which speaks for normal intrauterine growth. Postnatal height position decreases abruptly to almost -4 SDS at one year of age and -5 SDS at two years of age. Major "loss" in height position occurs during the infancy period and the position during childhood ages is generally maintained at about -5 SDS. Adult height is remarkable similar among the cohorts (summarised in Table 4), despite differences in data collection periods, height of background populations and age for reporting adult height. Adolescent height in girls from Argentina and the USA might be an exception. On other hand, note that the first achondroplasia studies from the USA[69,71] report same female adult height as found in this European cohort. Japanese adults with achondroplasia are as tall as their peers in other parts of the world. Secular trends or influence of background population is thus not or is only marginally detectable in achondroplasia.

Table 4 Adult height in different achondroplasia cohorts

| Region/ study | Age | Adult height, cm (mean ±SD) | | | Sample size (male/ female) |
		Boys	Girls	Sex difference	
Northern Europe	20+	132.3 ±4.9	124.4 ±4.6	8 cm	91 (36/55)
USA[69]	16+	131.6 ±5.6	123.5 ±6.0	8 cm	108 (52/56)
USA[71]	18	130.7 ±6.5	125.2 ±6.0	6 cm	n/a
USA[79]	15.8	126.7 ±10.1	119.9 ±10.4	7 cm	16 (7/9)
USA and Canada[156]	19+	135.2 ±5.6	125.9 ±3.9	9 cm	27 (16/11)
UK[72]	n/a	132.2 ±1.6	123.9 ±1.1	8 cm	n/a*
Japan[75]	17.8	130.4 ±5.9	124.0 ±5.3	6 cm	n/a
Argentina[78]	15+	128.3 ±7.7	119.9 ±7.2	8 cm	54 (21/33)
Australia[80]	18	134 ±n/a	125 ±n/a	9 cm	6 (2/4)

* visually read from figure n=17 (3 male/ 14 female >17.5 years)

36

Yearly increments, Figure 20, as proxy for growth velocity, is thus decreased already during the first year of life but progresses subsequently in parallel to the normal height reference. A slight pubertal spurt can only be seen in the Japanese reference for girls, which might be explained by different fitting techniques. In this Japanese achondroplasia study, individual data series were first fitted by eye to obtain height values at full chronological ages from which references were then constructed.[75]
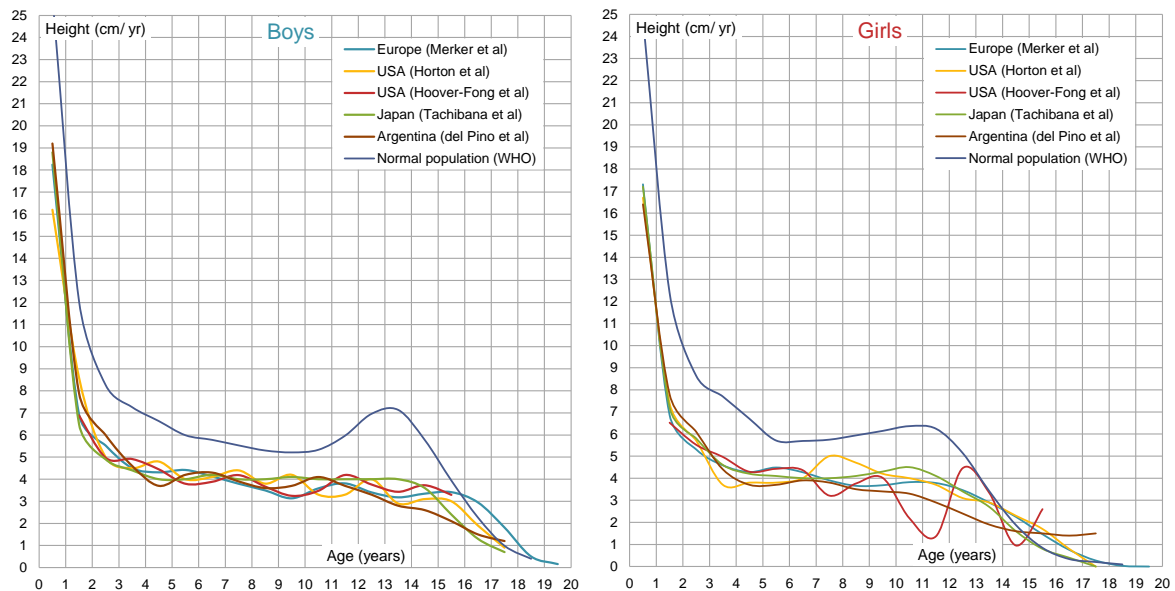

Figure 20 Height in achondroplasia as yearly increments for boys (left) and girls (right) in cohorts from Europe, North America, South America and Asia compared to normal population

Additionally, height position decreases by another SD during pubertal ages (Figure 19), which possibly could be explained by extensive height gain in the normal population and a smaller absolute pubertal height component in achondroplasia[157]. Pubertal timing is generally normal in achondroplasia, and a growth spurt is also present,[71,157] but smaller in absolute terms.[157] Evaluations of individual height patterns in our material show a clear acceleration during normal pubertal ages; i.e. 12 years for boys and 10 year for girls. Total height gain from these ages to final height is 18.5/ 17.8 cm respectively in boys and girls (data available for 17 boys and 24 girls) or 14.2/ 14.5 percent of adult height. Corresponding pubertal height gain calculated from the mean values of our achondroplasia height reference is 18.7 cm for both sexes or 14.2/ 15.1 percent of respective adult height. This is comparable to 15.6/ 15.0 percent in the WHO reference.[37]

4.1.2 Leg length and arm span development in achondroplasia

As noted in section 1.1, secular trends in height are to a great extent related to leg growth.[4,5] In the normal population, only 30 percent of final leg length is attained at one year of age (Figure 1), compared to 55 percent of sitting height (as proxy for trunk length). Growth velocity for legs is thus normally higher than for trunk during prepubertal ages. Short legs and arms with limited growth capacity are, however, a typical feature of achondroplasia.
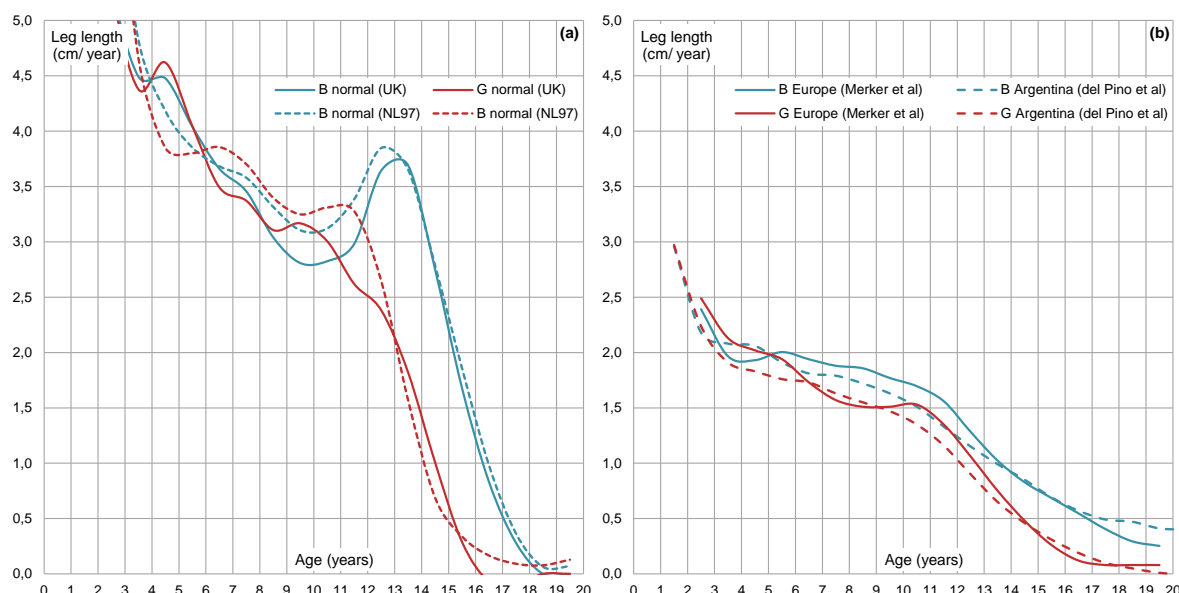
Figure 21 Leg length as yearly increments in (a) normal population references[7,152] and (b) achondroplasia cohorts in Europe and South America. Note that comparison to existing achondroplasia US studies is not included since these traditionally measure upper/lower body segment instead of sitting height and subischial leg length.

Leg growth, expressed as yearly increments in Figure 21, in achondroplasia is pronouncedly lower compared to that of the normal population. Leg length is almost 14 cm shorter at two years of age and almost 40 cm at adult ages (Table 5). Half of this final deviation is reached between four and six years. Leg length might also be affected by genu varum development, which may be caused by knee joint laxity and an uneven growth of tibia and fibula. Overgrowth of distal fibula[158] might cause varus development of the tibia.[159]

Table 5 Deviation of body proportions, in cm, in achondroplasia from normal population at selected ages

Age	Leg length		Arm span		Sitting height	
	Boys	Girls	Boys	Girls	Boys	Girls
2 years	-13.3	-13.6	-13.8	-13.4	-1.5	-1.8
4 years	-18.7	-18.6	-24.7	-24.2	-0.9	-1.6
6 years	-23.3	-23.3	-35.3	-33.6	-1.2	-1.5
9 years	-27.8	-28.5	-41.0	-45.1	-2.0	-2.1
18 years	-39.5	-35.5	-64.5	-63.4	-6.2	-3.9

Similarly, arm span is about 14 cm shorter than normal at two years of age and almost 65 cm at adult ages. In other words, an adult with achondroplasia has roughly 35 percent less range of motion compared to a normal adult despite similar sitting height/ trunk length. "Personal area" and reach of arms is thus severely restricted, which limits the possibility to managing daily tasks, including dressing and taking care of personal hygiene.[160,161] An inability of full elbow extension might also be contributing to this situation and is frequently reported in achondroplasia.[58,162]

Note that shoulder breadth constitutes a higher proportion of arm span during younger ages, thus contributing to less affected arm span (Figure 22). Absolute size and magnitude of growth restriction can therefore not be compared but growth pattern and tempo appear otherwise similar in leg length and arm span. Growth is severely compromised already in

early ages with leg length at about -7 SDS already at two years and arm span decreasing from -3 SDS to -6.5 SDS during prepubertal ages.
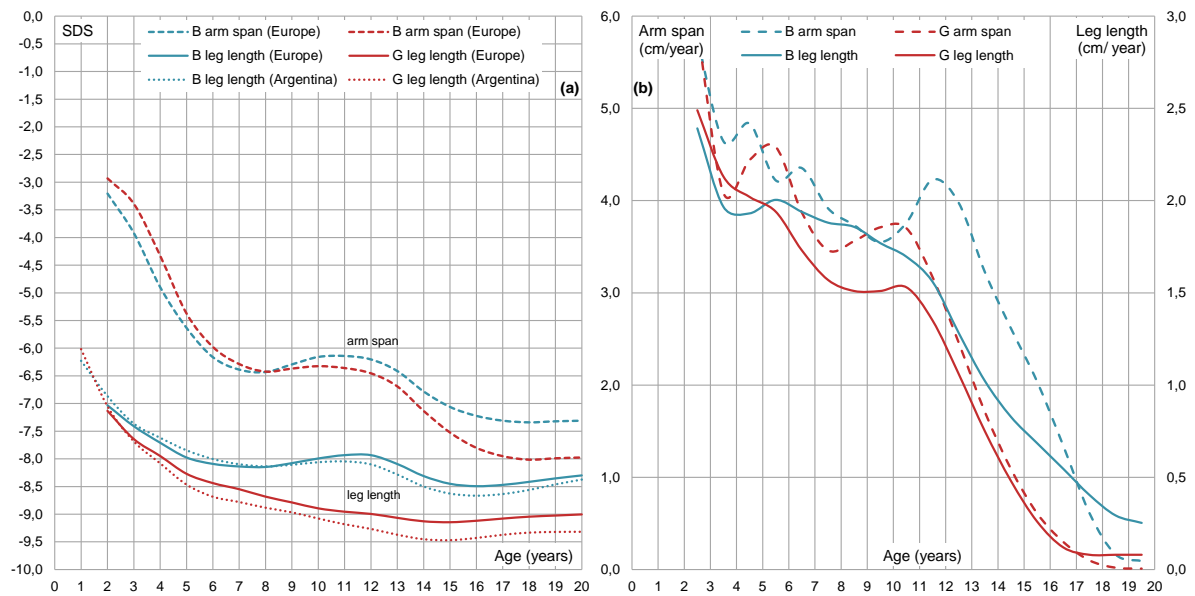

Figure 22 Development of leg length and arm span in achondroplasia: expressed (a) as SDS and (b) as yearly increments. Note different scaling for both variables as shoulder breadth contributes to arm span.

4.1.3 Head circumference in achondroplasia

Head circumference is only marginally increased at birth but accelerates postnatally faster compared to the normal population. Over 90 percent of adult head circumference is already achieved at two years of age, Figure 23, almost one year earlier than normal. Tempo of head growth is thus increased in achondroplasia.
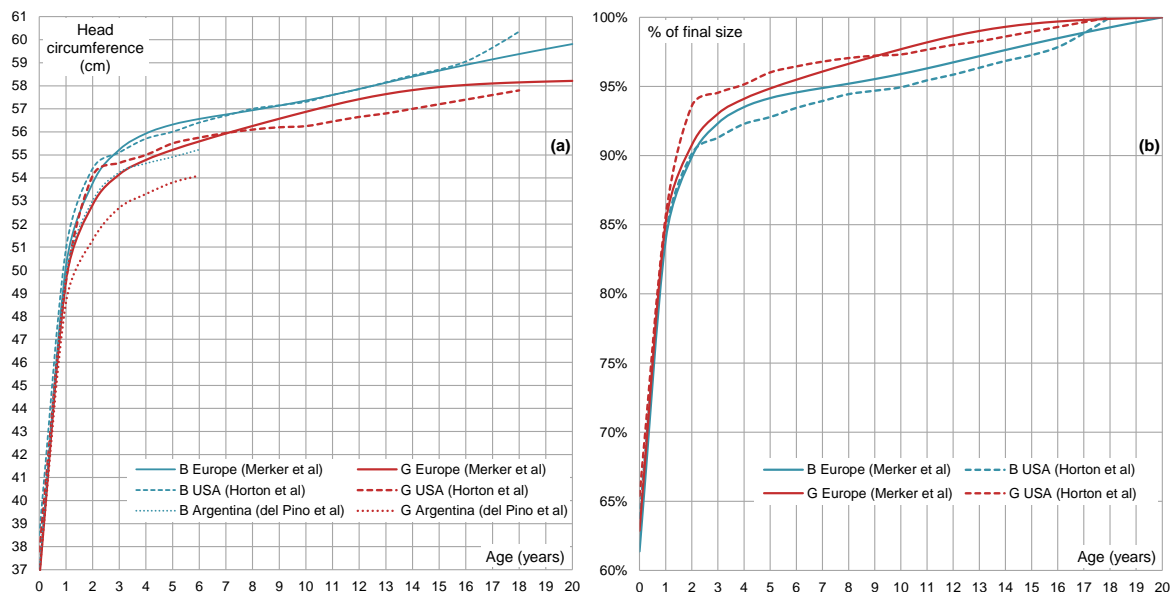
Figure 23 Head circumference in achondroplasia cohorts from Europe, North America and South America: (a) as development of mean and (b) as percentage of final size

The typical macrocephaly is probably a result from FGFR3 influence on CNS growth while growth of the skull bone is a secondary adaption. Increased brain tissue volume is also

confirmed by MR imaging in school children with achondroplasia.[163] Activating mutations in FGF receptors give a reduced skull base with premature closure of synchondroses causing a narrow foramen magnum.[59] Additionally, narrow foramina in the skull base might cause an increased venous pressure and a communicating hydrocephalic situation due to increased liquor pressure.[164] Note that decreased or abolished FGFR3 signalling, as in human CATSHL syndrome, results a microcephalic development.[165,166]

4.2 CLINICAL CHARTS FOR FOLLOWING HEIGHT AND HEAD CIRCUMFERENCE

The clinical charts are compiled in an achondroplasia growth chart booklet. This booklet comprises besides the charts also checklists of medical areas for prospective surveillance, adapted from guidelines for health supervision in achondroplasia.[167,168]
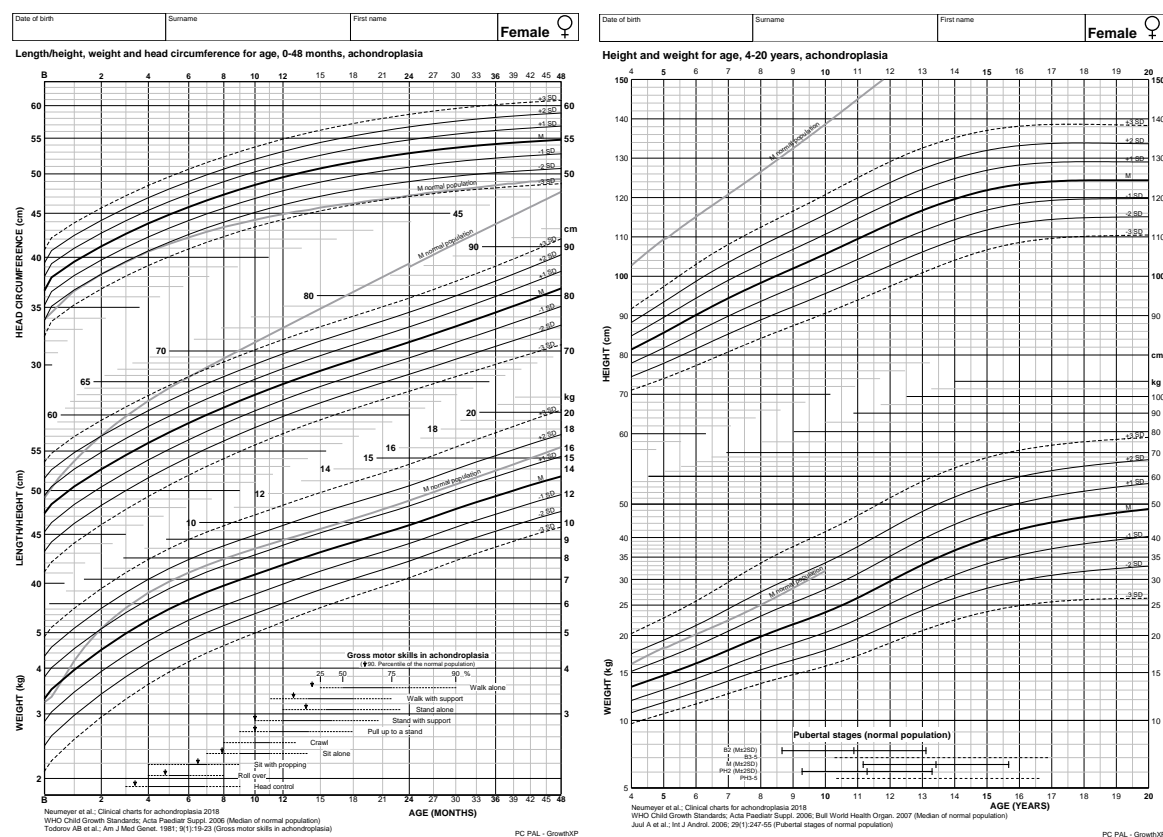

Figure 24 Clinical achondroplasia growth charts for ages 0 to 48 months and 4 to 20 years

The growth charts layout in Figure 24 combines head circumference, height and weight for ages 0 to 48 months as well as height and weight for ages 4 to 20 years. This is achieved by using a non-linear age axis for the period 0 to 48 months and a log scale for the y-axes. Gross motor development is usually delayed in achondroplasia and should be monitored,[169] which can be done in a scheme adapted from Todorov et al.[169] Similarly, as pubertal timing is regarded as normal in achondroplasia,[71,157] pubertal development can be recorded in a scheme constructed from a recent Northern European reference of normal children.[170]
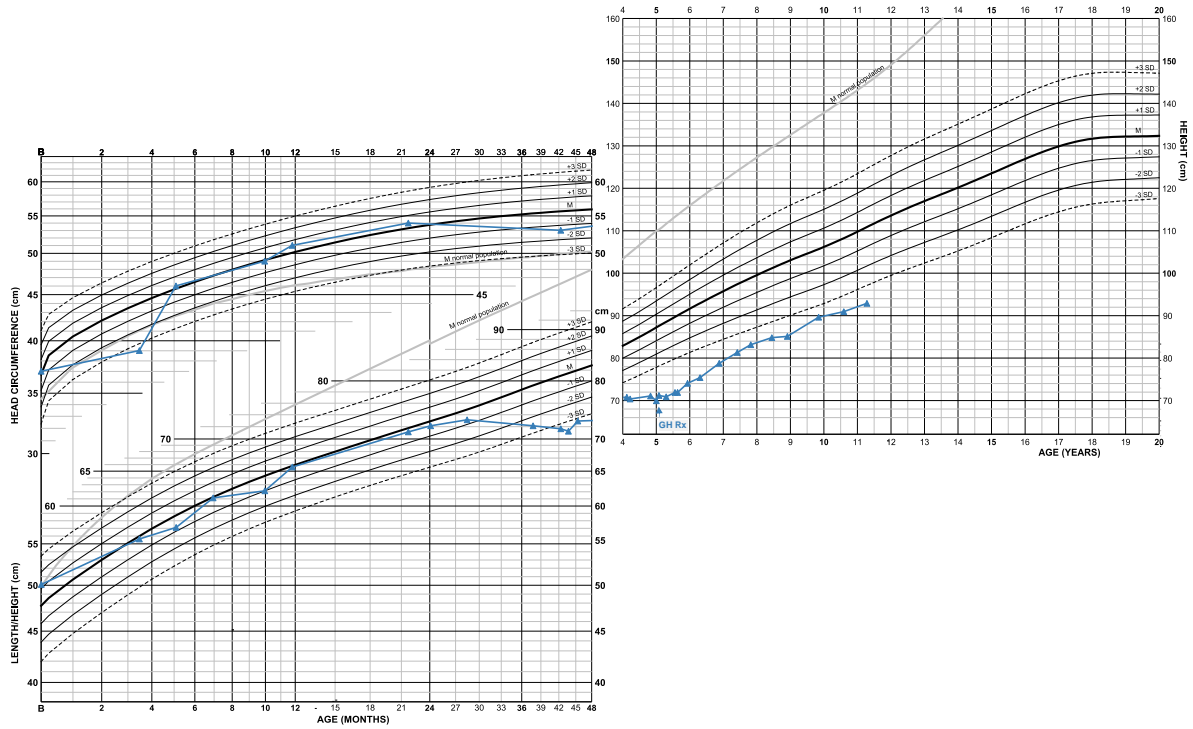
Figure 25 Height and head circumference development in a growth hormone deficient boy with achondroplasia on clinical achondroplasia chart with start of growth hormone treatment at five years of age
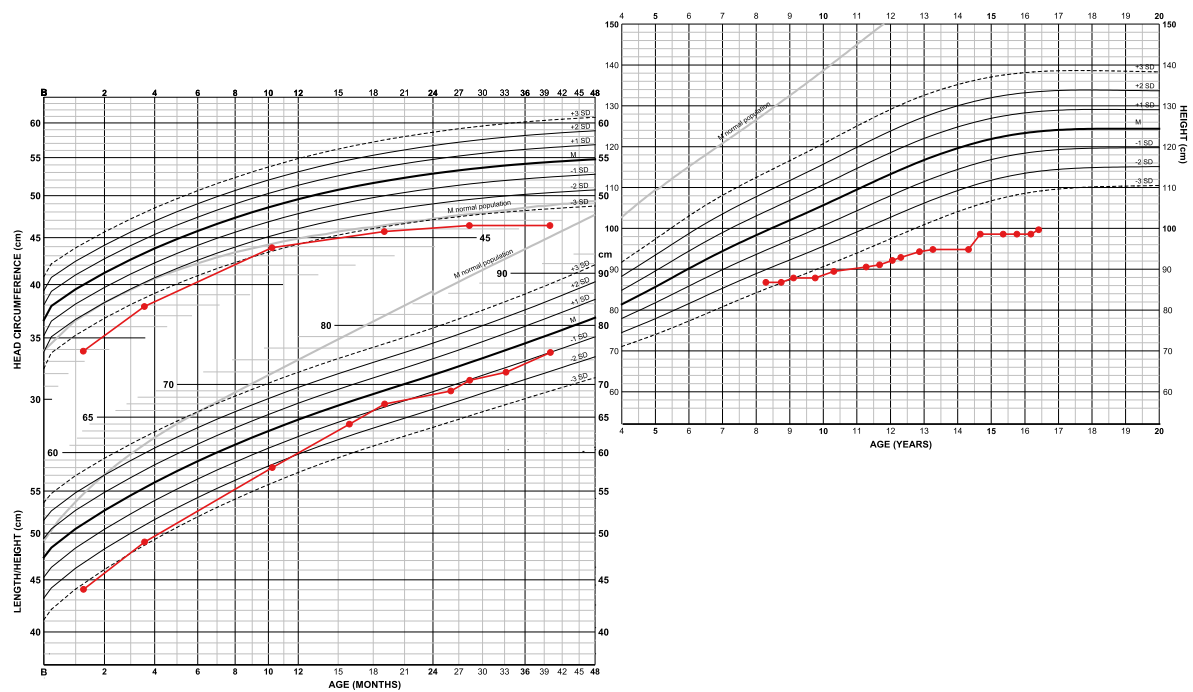

Figure 26 Height and head circumference development in a girl with combination of achondroplasia and Kabuki syndrome on clinical achondroplasia chart

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These charts aim at supporting clinical surveillance of children with achondroplasia since possible complicating medical conditions affecting growth should be monitored just as in children of normal height. Two examples of aberrant growth pattern are shown in Figure 25 and Figure 26. The first case is a boy with probable growth hormone deficiency, possibly also connected to failure to thrive. Substantial improvements in height position can be observed after initiation of growth hormone therapy. The second case is a girl with a head circumference clearly developing below normal achondroplasia ranges, indicating that an additional syndromic condition might be present. Her pubertal growth is clearly subnormal and final height might also be reached earlier. Genetic evaluations in this case confirmed a combination of achondroplasia and Kabuki syndrome.

4.3   DIFFERENT GROWTH PATTERNS WITH COMPARABLE ADULT HEIGHT

Height development in some skeletal dysplasia with severe short stature might result in comparable adult height (Figure 27). Although the growth pattern might differ, the magnitude of growth inhibition can cover similar ranges. Height position in pseudoachondroplasia, for instance, seems to decrease gradually from birth to adult ages while birth length is severely affected in children with defects in SLC26A2 (diastrophic dysplasia) and in collagen type 2 (spondyloepiphyseal dysplasia congenita), indicating that prenatal growth is affected.
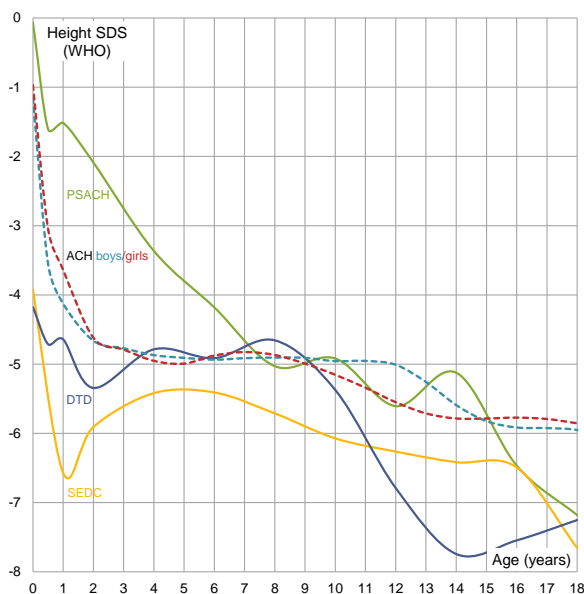

Figure 27 Development of height SDS in references for pseudoachondroplasia (PSACH), diastrophic dysplasia (DTD), spondyloepiphyseal dysplasia congenita (SEDC)[91] **and for boys and girls with achondroplasia**

Considering that the growth pattern of achondroplasia is now rather well studied and known, our references could be adopted as a matrix for following children with other extreme short stature conditions. Positions for height and other measured variables can then be expressed in relation to normal population and achondroplasia references.

4.3.1 Pseudoachondroplasia

The distinct height pattern of PSACH, seen in Figure 27, is also observed in most of the children in our cohort (Figure 28). Prenatal and initial postnatal growth is normal, but slows down later in infancy. Height position is thereafter gradually lost during the entire growth period. It is unusual that a height position is maintained for a longer period, but an abrupt decline as typical for achondroplasia is not seen. It is unclear whether adult height is related to timing of this slow decrease or if a later onset results in a faster decline. However, it is clear that SDS cannot be used to compare individuals of different ages and that adult height predictions from current height positions are not meaningful in PSACH.
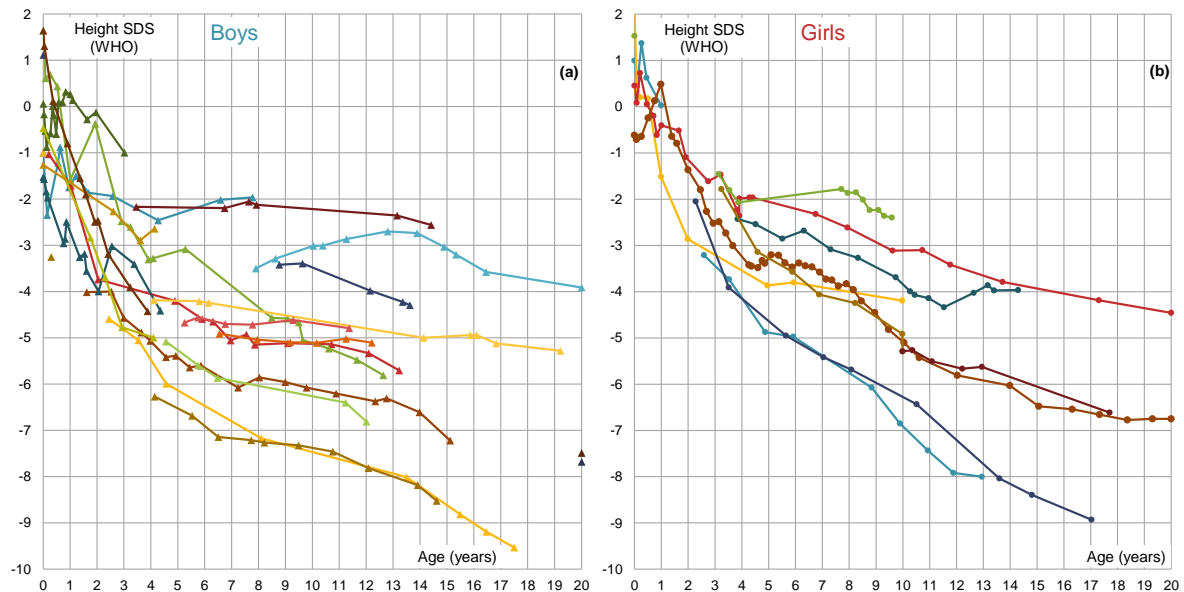

Figure 28 Height SDS development in (a) 20 boys and (b) 9 girls with pseudoachondroplasia

Sitting height position progresses within normal ranges in some of the children and becomes profoundly short in others (Figure 29). For leg length the group differences become more distinct although leg growth is affected in all children. In one group leg length develops between -3 and -7 SDS at a constant position, which means that legs continue growing at a normal tempo. Legs in the other group grow slower and continuously decrease even beyond -7 SD. A milder shortness and body disproportion is typical for multiple epiphyseal dysplasia (MED) type 1 that could be regarded as the least affected variant of PSACH.
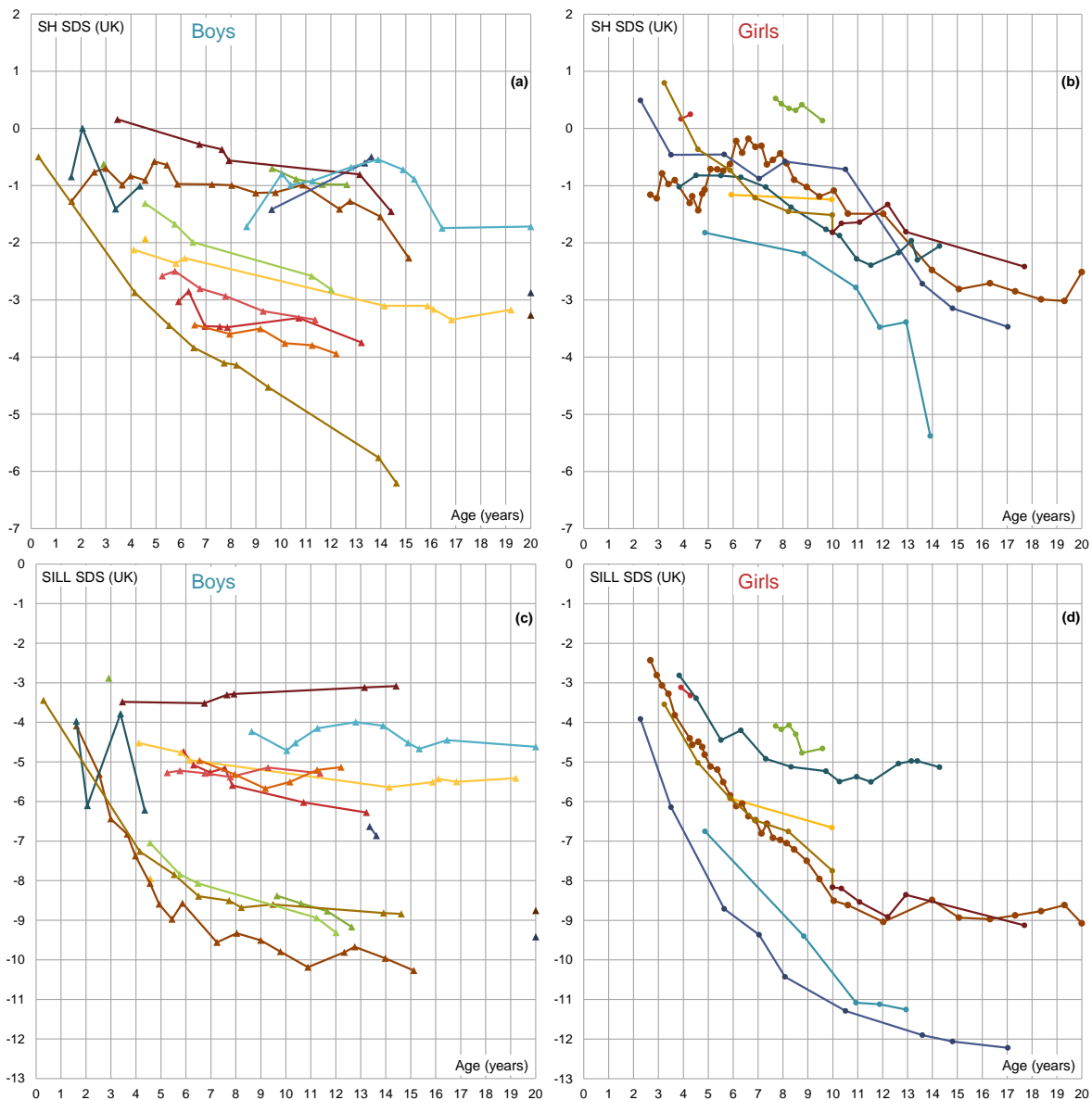
Figure 29 Body proportion development in boys (left) and girls (right) with pseudoachondroplasia: (a-b) sitting height SDS and (c-d) leg length SDS

More than 150 mutations in *COMP* have been reported but the correlation to auxological phenotype is poorly understood and height inhibition varies both between and within families. For instance, height in affected family of a four generation consanguineous Pakistani family, marked by black contour lines in Figure 30, varies between normal (within ±2 SD) and extreme short stature (-4 to -6 SDS). Two relatives with homozygous missense variants are -10 SDS short.[96]

Produced by proliferating and hypertrophic chondrocytes, COMP is a vital coordinating constituent of extracellular matrix of the epiphyseal growth plate[171] and normally assembles in endoplasmatic reticulum (ER) with other matrix proteins for subsequent secretion. A mutant COMP may cause retention of this complex resulting in cellular stress promoting apoptosis of chondrocytes together with deficient amount and quality of extracellular matrix of the growth plate.[172–174]
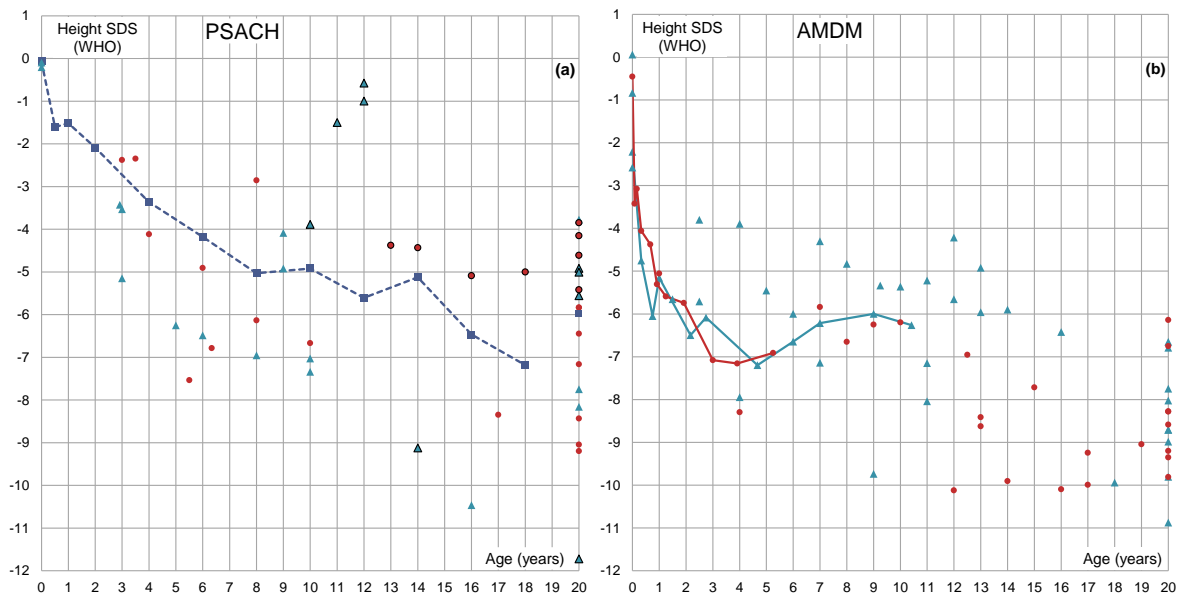
Figure 30 Height SDS in pseudoachondroplasia (PSACH) and acromesomelic dysplasia type Maroteaux (AMDM) cases reported in the literature: (a) 29 boys (blue triangles) and 27 girls (red circles) with PSACH[89,90,92–96,175,176] including sex-combined PSACH reference (purple).[91] Scatter symbols with black contour lines indicate membership in a large Pakistani family with PSACH all with missense variants in COMP.[96] (b) 27 boys (blue triangles) and 19 girls (red circles) with AMDM[85–88,177–179] with lines indicating longitudinal data series.

4.3.2 Acromesomelic dysplasia type Maroteaux

Height development in AMDM resembles that in achondroplasia. A major growth inhibition occurs during the first year of life and the height position is maintained during prepubertal ages. Body disproportion is not necessarily pronounced since sitting height is more affected than in achondroplasia. Head circumference also grows within normal population ranges.
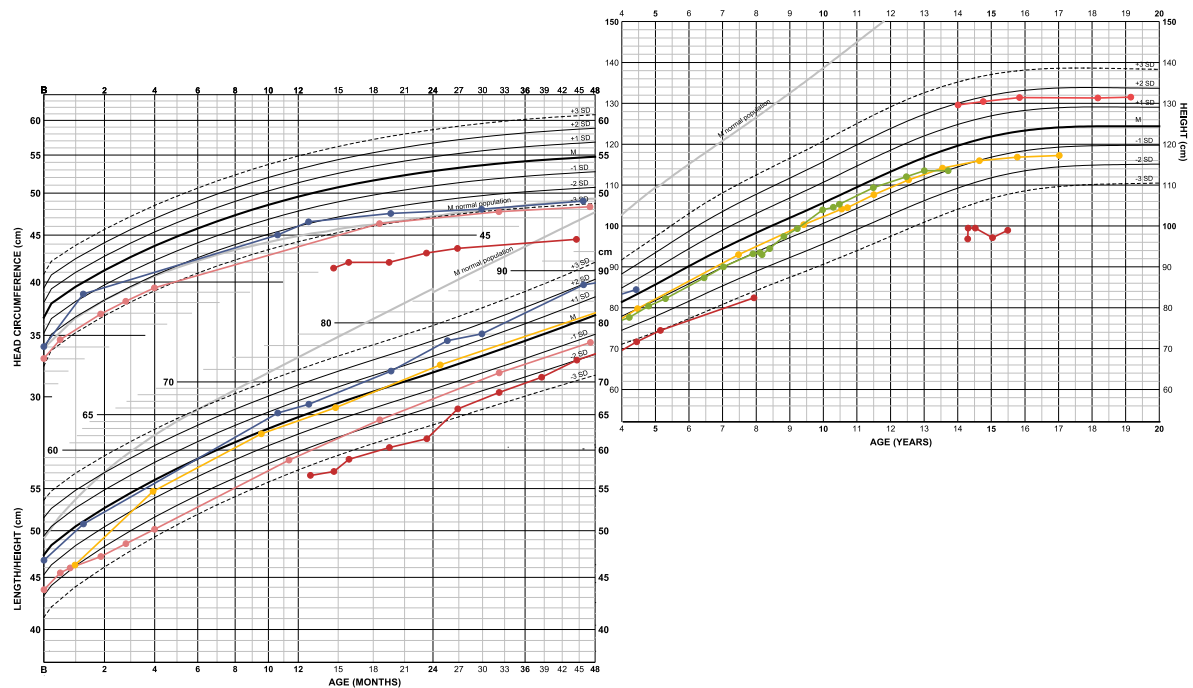

Figure 31 Head circumference and height development of six girls with acromesomelic dysplasia type Maroteaux on clinical achondroplasia growth chart

Thus, defects in the CNP/NPR-B signalling reflects its importance in growth balancing FGFR3 activity. Biallelic loss of *NPR2* function results in AMDM, whereas heterozygosity may reduce adult height by only 1-1.5 SDS.[180,181] About 30 mutations in *NPR2* have so far been reported for individuals with AMDM with varying auxological phenotypes. Many of those results in a reduced number of CNP receptors expressed on the chondrocyte cell surface while other variants of NPR-B might have reduced CNP binding capacity.[88,182] It is yet unknown whether any degree of residual function of the receptor is related to the variability in clinical and auxological phenotypes.
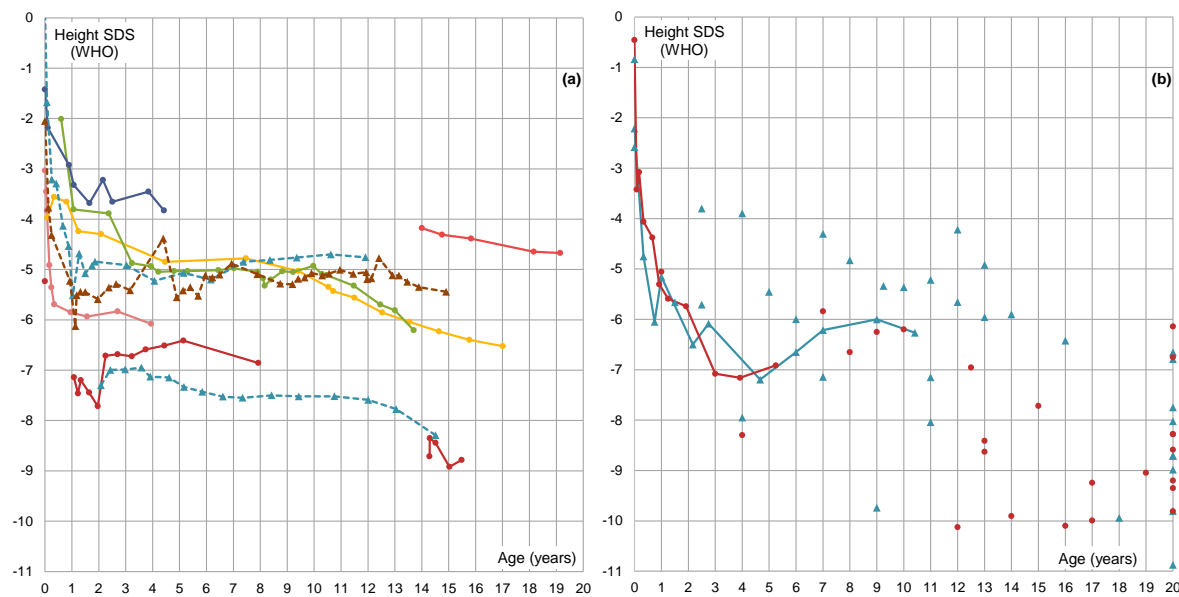

Figure 32 Height SDS in acromesomelic dysplasia type Maroteaux: (a) longitudinal series of three boys (triangles) and six girls (circles) in this study and (b) 27 boys (blue triangles) and 19 girls (red circles) reported in the literature[85–88,177–179] **with lines indicating longitudinal data series.**

It is clear that the phenotype in our cohort, although positive for *NPR2* mutation, is not as severely affected as reported in the literature, where adult height ranges from -6 to -11 SDS (Figure 32). Growth pattern from birth to adulthood is, however, difficult to map from occasional measurements in available case reports. Longitudinal data series will be needed to investigate growth during pubertal ages as well as ages for attaining adult height.

4.3.3 Hypochondroplasia

Hypochondroplasia is thought to be one of the most common skeletal dysplasias although reports of individual cases and details on growth are limited in the literature. Diagnosing is maybe problematic since radiology might not always be obvious and agreement on diagnostic criteria is not consistent.[183] Also, a pathogenic variant in *FGFR3* is only found in about 70 percent of all cases, p.Asn540Lys being the most common at about 60 percent.[150] No mutation in *FGFR3* is thus found in a substantial number of cases despite similar radiological and clinical phenotypes as typical for p.Asn540Lys.[150,184]

Children with p.Asn540Lys often grow at about -3 to -4 SDS and adult height ranges from -1 to -5 SDS (Figure 33). The negative influence from FGFR3 signalling is emphasized in homozygous (p.Asn540Lys) or compound heterozygous (p.Asn540Lys/ p.Gly380Arg)

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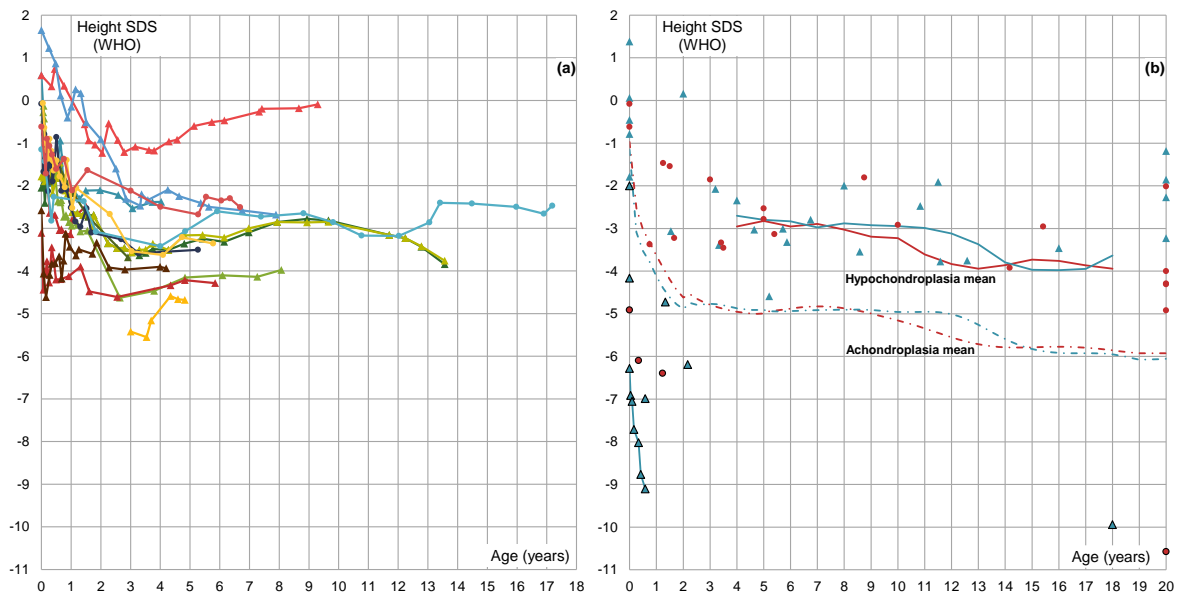mutations in *FGFR3* resulting in severe height retardation (indicated by black contour lines in Figure 33).

Figure 33 Height SDS development in hypochondroplasia: (a) 11 boys (triangles) and 4 girls (circles) with FGFR3 p.Asn450Lys mutation and (b) boys (blue triangles) and girls from the literature[83,150,184–190] **including homozygous or compound heterozygous mutation in FGFR3 (black contour lines)**[191–196] **as well as mean height for hypochondroplasia**[84] **and achondroplasia.**

The clinical and radiological phenotype of hypochondroplasia and achondroplasia is overlapping,[184,197] which can also be seen in Figure 34 showing the growth patterns of four boys, three with genetically confirmed hypochondroplasia and one with achondroplasia. Note that head circumference is comparable in all four cases. Body disproportion in two boys (with p.Lys650Asn in yellow and p.Asn540Lys in red) are, due to longer legs, not as pronounced as in the rare p.Tyr278Cys (in blue) and in p.Gly380Arg (in green).

In this specific example, phenotype of the boy with p.Lys650Asn might be relatively mild but other amino acid substitutions in this protein position can result in severe phenotypes. For instance, mutations changing lysine (basic amino acid) to glutamic acid (acid amino acid) results in thanatophoric dysplasia type II (p.Lys650Glu). A change to methioniene (hydrophobic amino acid) may instead result in SADDAN (Severe Achondroplasia with Developmental Delay and Acanthosis Nigricans) or thanatophoric dysplasia type I (p.Lys650Met). Exchange to glutamine or asparagine (both hydrophilic amino acids) may result in milder hypochondroplasia phenotypes (p.Lys650Gln/Asn).[185]
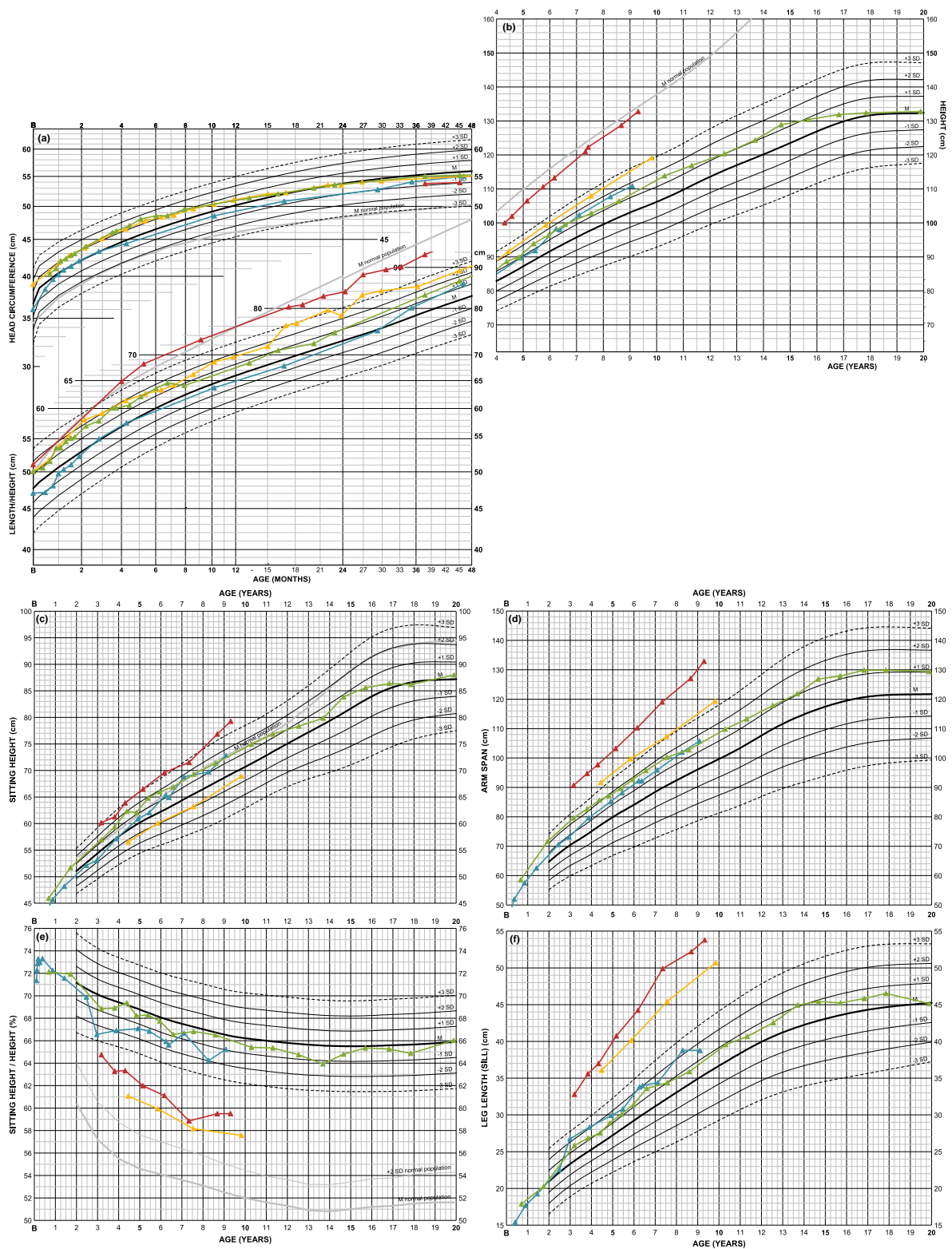
Figure 34 Height and body proportion development in four boys with confirmed FGFR3 mutations; hypochondroplasia p.Lys650Asn (in yellow), p.Asn540Lys (in red) and p.Tyr278Cys (in blue) and achondroplasia p.Gly380Arg (in green) in clinical achondroplasia charts

4.4 WEIGHT AND BMI IN SEVERE SHORT STATURE

Much of the value of BMI, as measure of relative weight, lies in its development over time rather than in absolute position in the BMI chart, which may also be distorted in conditions with extreme short stature and/or body disproportion. Short legs will naturally cause increased BMI value with achondroplasia as typical example. The meaning of the position in the normal BMI curve may then be unclear.

Table 6 Mean height values and corresponding ages in the normal population

Height (cm)	90	100	110	120	130	140
Ca age in normal population	2.5	3.5	5.0	7.0	8.5	10.5

Thus, the severity of short stature and the severity of disproportion needs to be taken into account suggesting that weight for height curves might be more relevant for clinical evaluation of relative weight. Yet, it should be kept in mind that also such comparisons are not necessarily appropriate since the metabolism changes with age. In other words, the metabolic situation of an adult with height of 130 cm would then incorrectly be compared to that of a prepubertal child as listed in Table 6. Comparing weight for height in achondroplasia to general population reference, for instance, showed that all individuals would be classified as "obese" while measures of skinfold thickness suggested only 13 percent.[198]
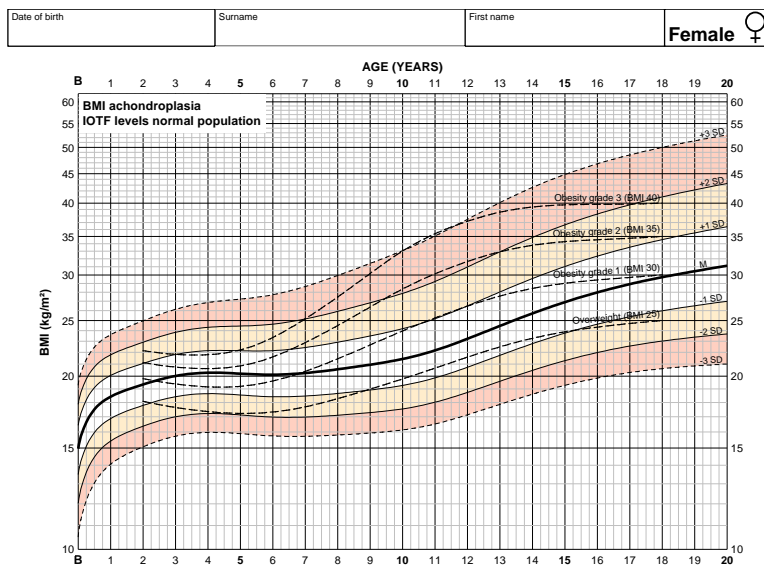

Figure 35 Clinical achondroplasia BMI chart is based on log scales for BMI axis to give the same space to the upper and lower end of the distribution.

Our achondroplasia specific BMI chart, Figure 35, is constructed on o log scale for the BMI axis to balance SD width of both ends of the distribution. As already mentioned, the BMI curve is naturally moved upwards and a BMI infancy peak is missing. Note that BMI does not necessarily take the distribution of fat tissue into account where abdominal fat might have different metabolic impact than fat accumulation in thigh and buttocks, as is typical in achondroplasia. In addition, metabolic variables such as blood glucose, triglyceride, free fatty acid, cholesterol, insulin and thyroid hormone are normal in achondroplasia despite waist/hip ratio indicating abdominal obesity.[156,199] Following waist circumference as a measure of

abdominal-visceral fat might therefore be valuable but syndrome-specific references are not available. Since sitting height usually is only mildly affected, normal population references might just be as useful.

Lastly, skeletal dysplasia specific handicap might also influence the possibility for physical activities, which can promote weight gain. The ability to accumulate fat seems to differ between various skeletal dysplasias, which might be related to the broad spectrum of mutations in genes regulating extracellular matrix proteins, signal transductors or RNA processing molecules. The specific pathological gene product might thus influence the possibility to accumulate adipose tissue. Individuals with certain matrix protein defects, such as for instance in SEDC or osteogenesis imperfecta, seem to have less subcutaneous fat than peers with achondroplasia despite similar or worse physical handicap.

4.5 EXPRESSING CHANGES IN EXTREME BODY DISPROPORTIONS

Body disproportions are pronounced in children with achondroplasia and often in pseudoachondroplasia. Expressing sitting height/ height ratio and its changes can, however, be difficult since SD bandwidth in the normal population reference becomes successively smaller at the upper end of the distribution. Sitting height/height SDS results thus in extreme figures, often above +10 SDS. From a clinical perspective, it might be easier to use multiple SD based on central distribution thus neglecting influence of/ adjustment for skewness.
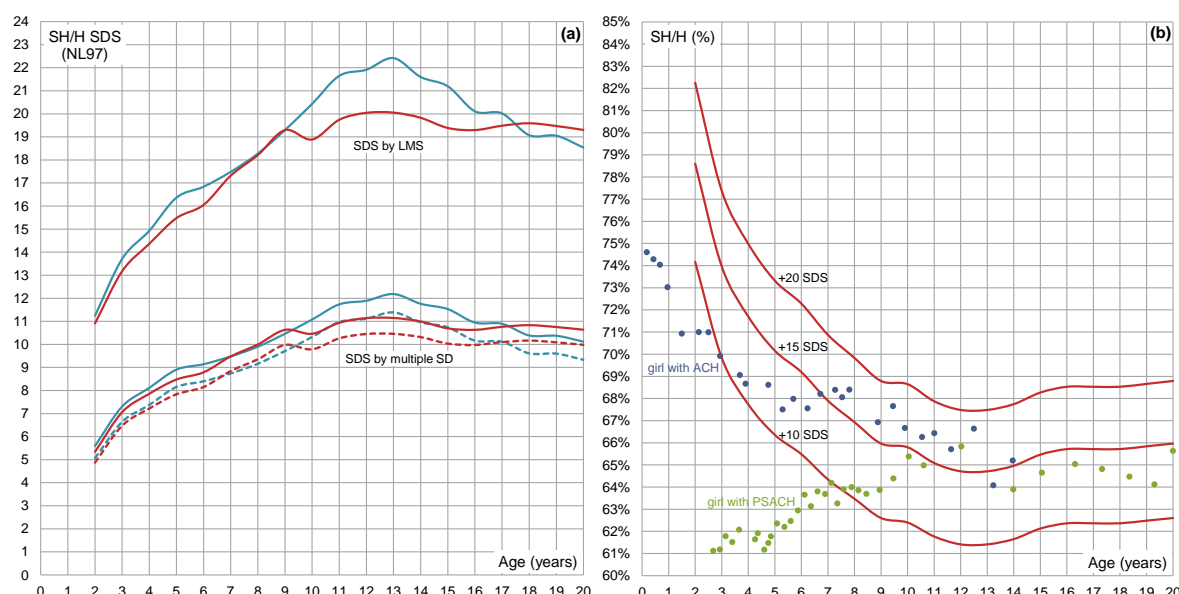

Figure 36 Extremes of SH/H SDS: (a) achondroplasia mean estimated by LMS values and by multiple SD of central distribution; (b) extreme SD levels of normal population SH/H reference[7] (calculated by LMS values) including individual series of a girl with achondroplasia (ACH) and with pseudoachondroplasia (PSACH).

The problem is illustrated in two examples in Figure 36. Estimating SDS for SH/H mean for the achondroplasia reference gives extreme results especially if based on LMS values where SH/H develops from +11 to about +20 SDS. Using SD of the central distribution, for instance SD bandwidth between +1 and 0 SD or the average of the range between ±2 SD, results in high but less extreme values. Note that the progression of the curves is similar with a peak at approximate ages at peak height velocity in the normal population. The other example shows

SH/H development of a girl with achondroplasia and one with pseudoachondroplasia. SD levels of the Dutch normal reference[7] were estimated by LMS values to cover same ranges as for the two clinical examples. At 20 years of age 2.8 percent units cover the area between +20 and +15 SDS and 3.4 percent units the area between +15 and +10 SDS (a range of 5 SD!). Comparable SD bandwidth between +5 and 0 SDS is 5.8 percent units.

4.6 CHALLENGES IN CONSTRUCTING SYNDROME-SPECIFIC GROWTH CURVES

Constructing syndrome-specific growth charts also comprises challenges. Achondroplasia specific studies, including this one, are generally based on rather small samples. Measurements are in many cases collected over decades by one or a few observers, which may result in sound data quality that allows a reasonable estimation of mean/ median, yet variability and tempo (i.e. also yearly increments) might be difficult to capture from these small samples. Data series of an individual can influence both progression and size of the SD curve if s/he somewhat deviates from the remaining observations. Measurements during pubertal ages are a general problem, which affects the mean curve during adolescent and adult ages. Adult height measurements often include data from affected parents and other adults, possibly representing another cohort, which influences resulting yearly increments and mean values of late adolescent/ adult ages. Yearly increments, as shown in Figure 37, can therefore take rather shaky forms and are not necessarily representative.
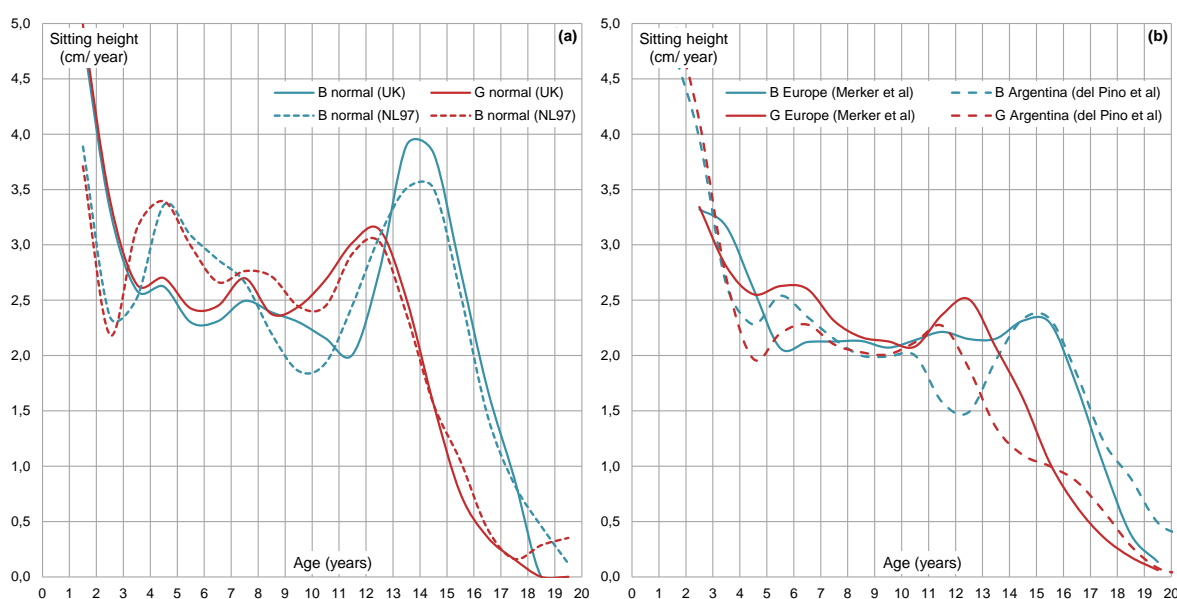

Figure 37 Sitting height as yearly increments in (a) normal population references[7,152] and (b) achondroplasia cohorts from Europe and South America

Also attitudes towards including atypical cases as well as towards smoothing methods influence resulting reference values. Exclusion criteria in syndrome-specific growth studies might comprise chronic disease, growth promoting therapy, significant neurosurgical complications, yet, it is questionable if individuals with atypical growth pattern are (or should be) excluded. For instance, should a boy with difficulties to gain weight be included in a syndrome-specific reference for which measurements are scarce? Differences in

achondroplasia weight references, i.e. no weight gain during puberty or higher weight in females despite shorter height than in males (Figure 38), are unlikely to be explained by natural/ biological causes.
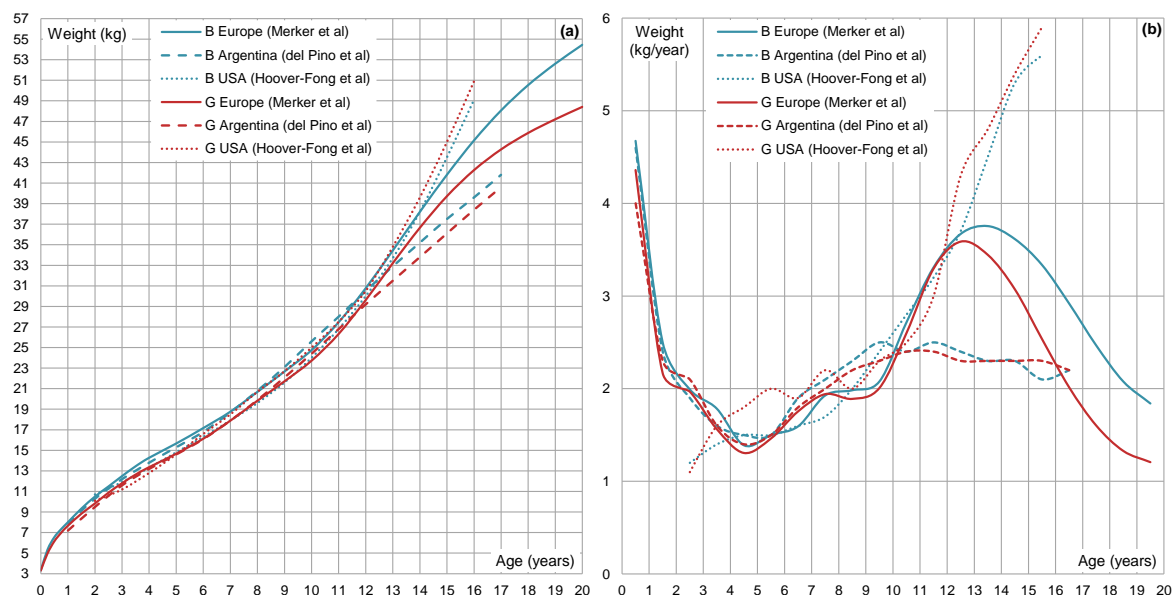

Figure 38 Weight in achondroplasia cohorts from Europe, North America and South America: (a) development of median and (b) as yearly increments of median

In addition, although estimates of variability might be poor in small samples, our clinical achondroplasia charts cover ranges of ±3 SD, which might appear bold. Note however that height, head circumference and body proportions were fitted to normal distribution models with fixed SD bandwidths. This approach follows an ambition to create a growth matrix for following children over time and that is clinically easy to use rather than fitting a perfect model from a small sample, which comprises three or four parameters for SDS calculation.

Lastly, accurate velocity curves are difficult to construct from a small sample with irregular measurement periods. Growth velocity per se is a tricky measure since individuals differ in growth tempo but also since this variable is sensitive to measuring errors and time interval between measuring points. Longitudinal, standardised measurements preferably within three months periods are needed to obtain reliable results.

4.7   AIMS OF SKELETAL DYSPLASIA SPECIFIC GROWTH STUDIES

Keeping in mind these challenges of constructing syndrome-specific growth charts, it might be worthwhile to describe specific phenotypes for research purposes in SDS format. Magnitude of growth retardation and syndrome-specific tempo can then be expressed for instance in relation to the WHO reference. This reference material is internationally acknowledged and has been constructed by state-of-the-art methods. Tabled LMS values are available for a detailed age range and no additional interpolation between completed age intervals is thus needed. In order words, describing the growth pattern of a certain skeletal dysplasia does not necessitate constructing syndrome-specific growth references, which

might be based on measurements from different clinical entities from different background populations and different measuring techniques.

From a clinical perspective, the availability of a standardized growth matrix might be more important regardless its background population. Future height development is a concern for parents when height develops far beyond the normal range. For them and for future planning it is important to get a fair forecast of future height development.

4.8 HEIGHT GAIN THROUGH GROWTH PROMOTING THERAPY

Communicating expected treatment outcomes to parents can be problematic if these are variable. The second part of this PhD project focuses therefore on evaluating growth promoting therapy by characterising good and poor height response to growth hormone treatment (GH Rx) in girls with Turner syndrome.

One of the most important question is how to define and estimate treatment success and whether the therapy goal is to normalise final height relative to the normal background population (i.e. above -2 SD) or relative to familial target (i.e. MPH ±9 cm for girls) or rather to achieve maximal height from treatment.[200] Treatment effects can be evaluated based on comparisons to control groups or to projected adult height,[201] measured in cm or expressed as SDS relative to Turner-specific or to normal population references.
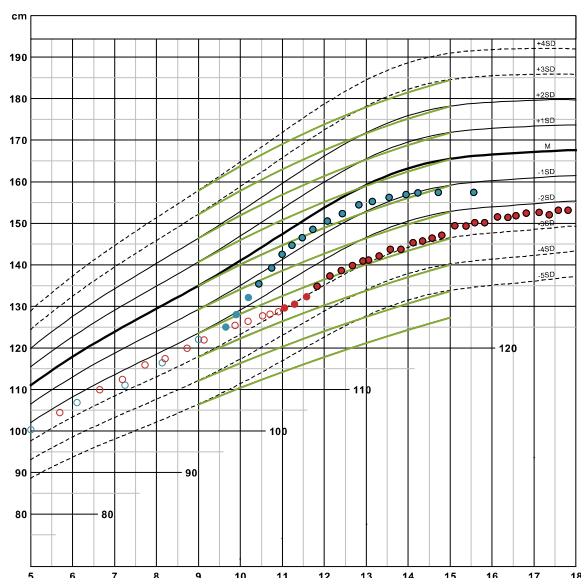

Figure 39 Differences in height SDS during pubertal ages if based on conventional or prepubertal (in green) height references. Height development in two girls prior treatment (circles without fill), under GH Rx (filled circles) and after onset of puberty (black contour lines) is shown. It might also be difficult to differentiate between height gains from GH Rx or from pubertal induction.

Each of these methods comprises drawbacks, as noted in earlier sections. To recall, adult height projections from current height position might be imprecise in younger ages also when using bone age[23,24] and might, if based on historical Turner references, not take into account possible effect of secular trends in height. Also since estimates of variability (or SD) are not necessarily consistent between syndrome-specific references, resulting SDS can vary greatly depending on the choice of reference.[202] Likewise calculating SDS from normal population

references can be misleading during pubertal ages[136] since chronological age, following a conveniently linear scale, is a poor proxy for a growth tempo that is regulated by the ovaries or testes. Two examples in Figure 39 depict this dilemma. The girl marked in blue starts GH Rx at 9.6 years of age and a height position just below the -2 SD line. Height increases by almost 1 SD until pubertal onset at 10.4 years and height position after 12 treatment months could then be compared to -2 SD (prepubertal line) or -1 SD (conventional line). Similarly, the girl marked in red starts GH Rx at 11 years and at a height position of -2.5 (prepubertal line) or -3 SDS (conventional line). Height after one year is -1.9 or -2.9 SDS respectively.

Lastly, it should be noted that the dataset represents a mix of therapy traditions and attitudes that might also have been changing over time. Therapy modalities including GH dose, timing of pubertal induction or possible concurrent treatment are thus not randomly determined, but by the doctor's perception. This complicates analysis of correlations, interactions or effects contributing to total height gain. The focus of this study is thus on describing the variability in terms of good and poor responses in respect to variables that generally are claimed to be predictive for treatment success.
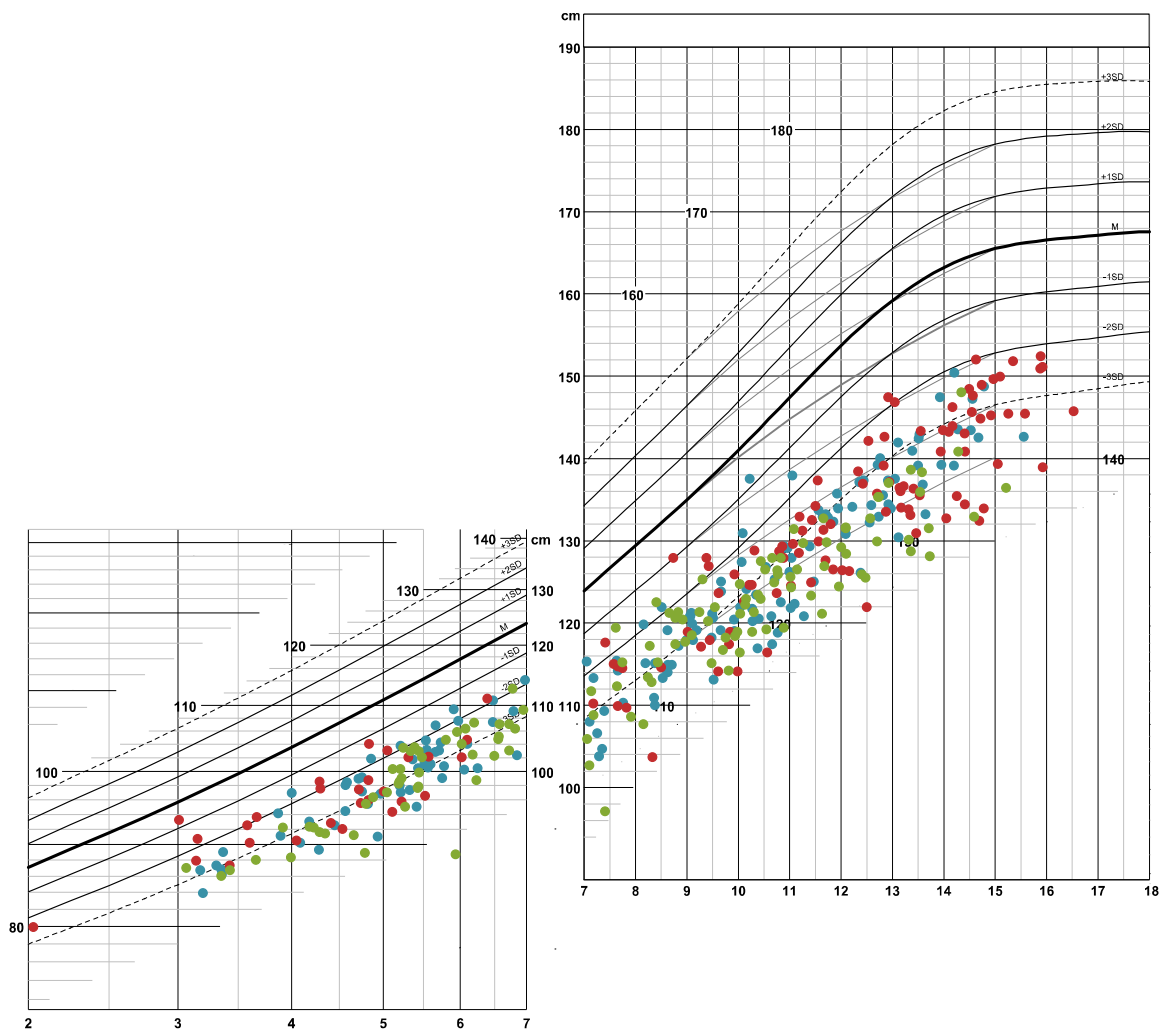

Figure 40 Age and height (cm) in 413 girls with Turner syndrome at GH Rx start on Swedish growth chart with colours indicating three response groups: good (green), poor (red) and intermediate (blue). Note that 5 percent at each end of the response distribution were excluded to avoid possible outliers.

4.8.1 Age at GH Rx start

Age at GH Rx start and treatment duration were the most important, but not independent, factors of final height (in cm) in a large register-based study.[203] Also prediction models, developed for clinical guidance, suggest age at treatment initiation as the most important factor for total height gain (in cm).[204] Measuring height gain from GH Rx start to adult height in cm will of course always favour early treatment initiation.

In this cohort of 455 girls, timing of GH Rx initiation is distributed over almost the whole growth period (Figure 40) with about 50 percent starting treatment during (for normal population) pubertal ages. It is therefore questionable how valuable a comparison across all ages is. In this material more girls with poor response started GH Rx during pubertal ages, especially after 14 years of age (28/126 in poor versus 4/129 in good group). It could thus be argued that height gain potential is limited after certain ages and that earlier GH Rx start per se is not inevitably a predictor for treatment success. Dividing the cohort into those with GH Rx start during typically prepubertal (<9.5 years) and pubertal (>9.5 years) ages shows no clinically relevant effect of earlier GH Rx initiation on total height gain (Figure 41a and Figure 42b).

Figure 41 Pivotal view of good (in green) and poor (in red) response in the younger cohort with GH Rx start <9.5 years. The aim of this presentation is to compare green versus red not x versus y.

Note that these pivotal charts are not inconvenient to read as the perception focuses on the relationship between x and y instead of on differences between green and red scatters. This kind of presentation is, however, interesting for exploring the dispersion of the data in both cohorts without necessarily hunting for statistical significance with more or less clinical/

biological relevance. Corresponding descriptive statistics, in form of median and ranges, are summarized in Table 7.

In the younger group, both good and poor responses start GH Rx at comparable ages and height positions; 6.7 versus 6.1 years of age and -3.0 versus -2.7 SDS. In the older group, on the other hand, good responses is clustered at earlier ages and lower height positions; 11.3 versus 12.9 years of age and -3.1 versus -2.3 SDS. Following a cluster of poor response with late GH Rx start (marked in orange box) suggests that final height is comparable to good response. No clinical relevant difference is neither seen for initial treatment response, MPH or age at pubertal onset between good and poor response in this older group.

Table 7 Median and range for variables previously suggested to be predictive for GH Rx success and partly shown as scatters in Figure 41 and Figure 42

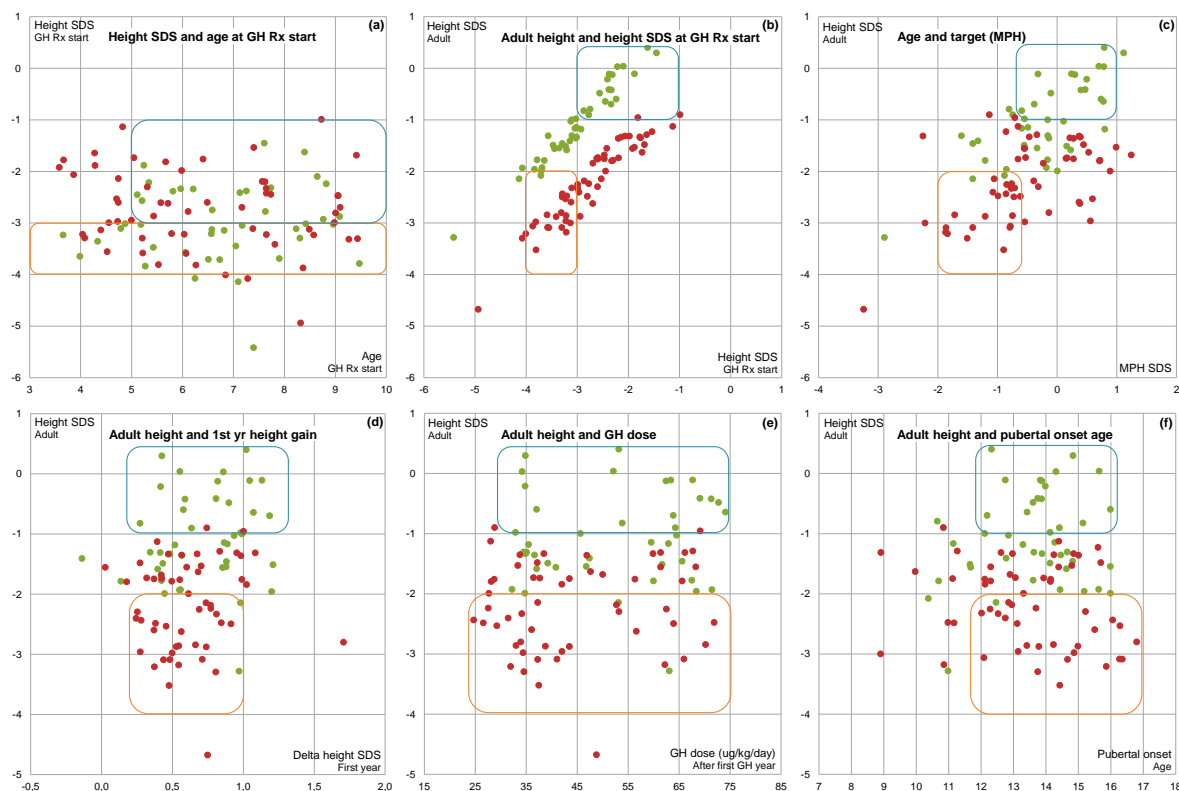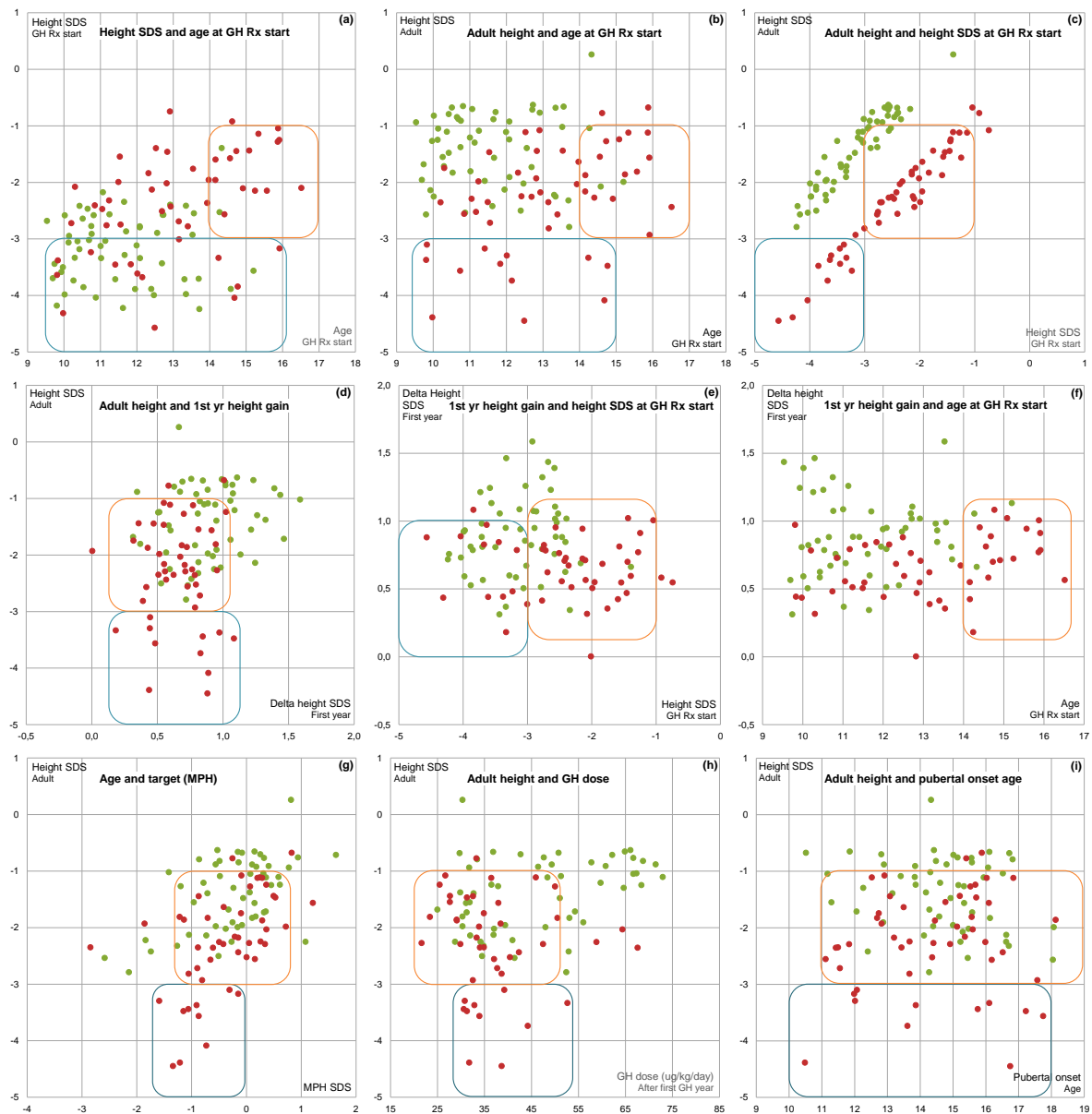| | GH Rx start <9.5 years | | | | | | | GH Rx start >9.5 years | | | | | | |
| | good response | | | poor response | | | | good response | | | poor response | | | |
	n	median	range		n	median	range			n	median	range		n	median	range	
MPH	41	-0.2	-2.9	1.1	57	-0.6	-3.3	1.2		53	-0.1	-2.6	1.6	48	-0.3	-2.9	1.2
GH Rx start																
Age	43	6.7	3.7	9.5	58	6.1	3.6	9.4		56	11.3	9.5	15.2	51	12.9	9.8	16.5
Height SDS	43	-3.0	-5.4	-1.5	58	-2.7	-4.9	-1.0		56	-3.1	-4.2	-1.4	51	-2.3	-4.6	-0.7
ΔMPH SDS	41	-2.8	-3.7	-1.8	57	-2.3	-3.8	0.2		53	-2.8	-3.3	0.4	48	-2.0	-3.3	0.9
Dose (µg/kg/day)																
at 12 months	41	53.2	32.2	74.1	54	39.9	24.7	71.9		53	46.4	25.0	72.9	44	34.0	14.9	67.6
Age at Pubertal onset																
all	43	13.9	10.4	16.0	55	13.4	8.9	16.8		54	14.9	10.5	21.6	50	14.6	10.5	18.1
spontaneous	3	12.8	10.7	14.1	10	11.0	8.9	14.9		13	13.2	10.5	21.6	18	13.0	11.4	18.1
induced	40	13.9	10.4	16.0	45	13.9	10.8	16.8		41	15.0	11.3	18.1	32	15.3	10.5	17.8
Adult height																
Age	43	16.3	15.0	18.9	58	16.3	14.3	18.6		56	17.1	15.4	21.7	51	17.0	15.0	21.3
Height SDS	43	-1.2	-3.3	0.4	58	-2.2	-4.7	-0.9		56	-1.3	-2.8	0.3	51	-2.3	-4.5	-0.7
Height cm	43	159.3	145.5	169.0	58	152.7	136.2	161.8		56	158.8	150.5	169.2	51	152.9	138.4	163.5
ΔMPH SDS	41	-0.8	-2.0	0.3	57	-1.7	-3.5	0.9		53	-1.1	-3.3	0.4	48	-1.9	-3.4	0.5
Body proportions																
At GH Rx start																
SH SDS	37	-1.7	-3.3	0.2	44	-1.4	-3.1	0.4		42	-2.2	-3.4	1.0	37	-1.9	-4.9	-0.4
SILL SDS	37	-3.5	-5.9	-1.8	44	-3.4	-5.0	-2.0		42	-4.0	-6.8	-2.0	37	-3.5	-4.5	-1.7
SH/H SDS	37	2.5	0.0	4.3	44	2.5	-0.5	5.0		42	2.6	0.3	14.8	37	2.3	-0.9	6.2
At adult height																
SH SDS	32	-0.2	-2.2	1.3	44	-0.8	-3.5	0.8		36	-0.6	-1.9	1.0	34	-1.2	-4.0	0.6
SILL SDS	32	-2.0	-3.2	-0.6	44	-2.7	-4.6	-1.2		36	-2.0	-3.1	-0.3	34	-2.5	-4.8	-1.0
SH/H SDS	32	2.0	-0.4	4.6	44	2.6	-0.8	6.6		36	2.0	-0.7	3.6	34	1.9	-0.5	4.5
Delta Height SDS																
total Rx	43	1.9	1.6	2.3	58	0.5	0.0	0.9		56	1.7	1.4	2.3	51	0.2	-0.5	0.4
first year	41	0.8	-0.1	1.2	54	0.6	0.0	1.7		54	0.9	0.3	1.2	47	0.7	0.0	1.1

Figure 42 Pivotal view of good (in green) and poor (in red) response in the older cohort with GH Rx start >9.5 years. The aim of this presentation is to compare green versus red not x versus y.

4.8.2 Height at GH Rx start and MPH

MPH and a normal child's actual height position are important predictors of his/her adult height, as noted in section 1.2, and the same is observed in non GH-treated girls with Turner syndrome. Correlation between parents and girls is comparable to that of the normal population despite constant height loss.[119,205] Regression slopes between earlier height position and adult height varies between 1.13 (R-squared 0.9)[25] and 0.84 (R-squared 0.64)[24] in non GH-treated girls with Turner syndrome. Note that height at GH Rx start is the main determinant in existing prediction model for final height (in cm) but only fifth rank of total height gain.[204] Similarly, taller final height is related to taller parents in some studies,[204,206] but not in others.[145]

In this study, MPH SDS is related to adult height SDS (Figure 41c and Figure 42g) and is in good and poor response respectively -0.2 versus -0.6 SDS in the younger group and -0.1

versus -0.3 SDS in the older group. The natural relationship between earlier height and adult height positions are maintained ((Figure 41b and Figure 42c); regression slopes are well above 0.9 and R-squared around 0.9. Considering that short stature is not a pathologic condition per se, it is tempting to speculate that this natural relationship is not disturbed in Turner syndrome. In an age-matched group with tumor cerebri, in contrast, the slope is 0.8 with R-squared only 0.3 suggesting a "disturbance" by disease and/or its treatment (unpublished data from the *Swedish National Register for growth hormone treatment of children and adolescents*).

Interesting to note is that the curves for good and poor response progress perfectly in parallel to each other, both in the younger and older cohort. The space between the response groups composes the intermediate group; i.e. 40 percent of the central distribution (marked in blue in Figure 17 but not added to Figure 41b and Figure 42c). In other words, the natural relationship between height SDS at GH Rx start and adult height is maintained while upper and lower side of this relationship constitute good and poor treatment response.
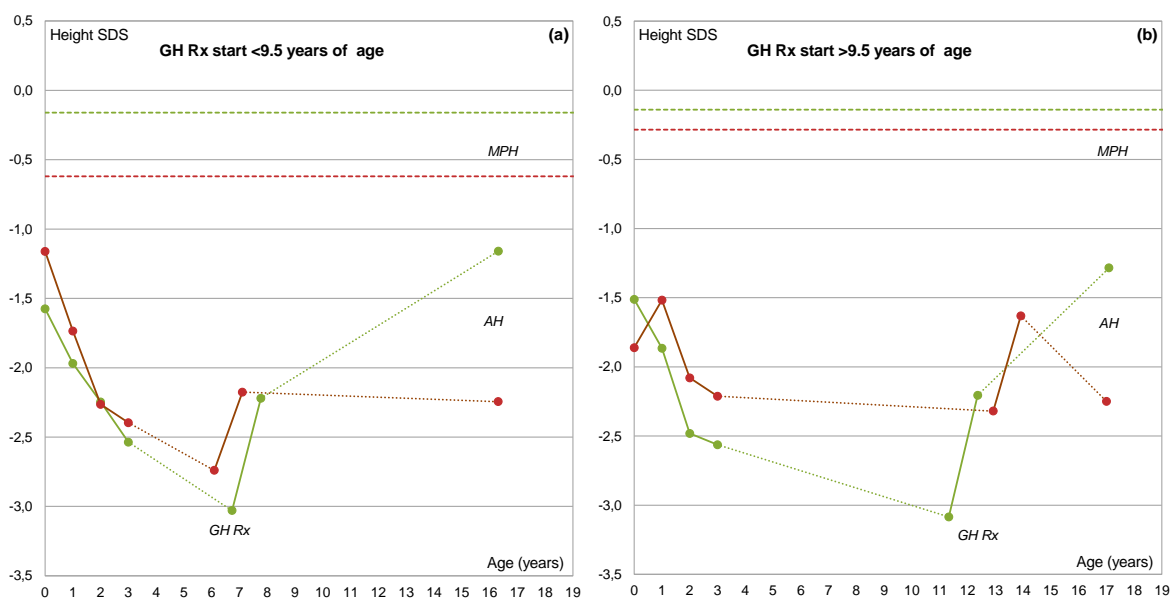

Figure 43 Height position in those with good (green) and poor (red) response at birth and first years of age, GH Rx start, after 12 months GH Rx and at adult height compared to target: in (a) the young cohort with GH Rx start < 9.5 years of age and (b) in the older cohort with GH Rx start >9.5 years of age. Note that height progression beyond selected time periods is not investigated nor expected to be linear and is therefore marked by dashed lines.

4.8.3 Increased tempo versus height position

First year's treatment response in height is generally regarded as determinant for long-term response[207,208] and is therefore valuable for guiding further actions; i.e. for doctors to recommend continuation of treatment, for policy maker to agree to financial support and for families to stay motivated to continuing necessary activities related to GH therapy.

Delta height SDS from first treatment year, Figure 43, is comparable in both response groups of the younger cohort, 0.8 versus 0.6 SDS. Those with good response continue improving their height position and resulting final height is approximately 1 SDS below MPH, which might be within familial target range. A similar initial gain, 0.9 SDS, is seen for good

responses in the older group. Yet, height gain in both poor groups seems to be only temporary. Important to note that in this older cohort height SDS after 12 treatment months could be distorted by effects of pubertal induction making it difficult to differentiate whether the increase in height SDS is due to effect of GH Rx or due to induced pubertal spurt.

4.8.4 Remaining questions

The current study refrains from reporting effects of oxandrolone therapy since this factor was not reported as determinant of height outcome in prediction models from KIGS.[204] Yet, evidence from several RCT's suggests increase in final height by oxandrolone,[42,209] possibly associated to improvements in sitting height rather than leg length.[210] The proportion of such treatment was noteworthy in our cohort, 29/43 versus 34/58 in the younger group and 40/56 versus 20/51 in the older group, and should thus investigated further.

Sitting height/height ratio in untreated girls with Turner syndrome normalises from 56.9 percent at ten years of age (+3.9 SDS) to 53.7 percent at adulthood (+0.8 SDS).[132] In this study, sitting height/height ratio improved for good response in both age groups, from 2.5/2.6 SDS for younger/ older at GH Rx start to 2.0/2.0 SDS at adult height. This development indicates a preference for trunk growth in the good response group whether depending on GH Rx, estrogens or oxandrolone or being inherent by the skeletal dysplasia background in Turner syndrome has to be studied further.

A randomized dose-response trial using three GH dose regimes, 45/45/45, 45/68/68 and 45/68/90 µg/kg/day for first/ second year/ thereafter, showed higher height gain in both higher dose groups leaving IGF-I levels above normal ranges.[145] GH dose is this study is not controlled by a standardised protocol. Total GH dose may be difficult to estimate from register data and it is furthermore probable that GH dose per kg is not maintained for those with good response and that higher GH dose is given to those considered to have insufficient response. This makes it of course not meaningful to group the total cohort in GH dose cohorts. Also in KIGS prediction models, GH dose has little weight for final height or height gain from treatment.[204]

Similarly, data on IGF-I and karyotype was insufficient for analysis in this study. Differences in treatment response associated to karyotype were suggested by one study[211] but not by others.[145,203,204,212,213] Investigating changes in IGF-I levels is essential considering that GH secretion in girls with Turner syndrome is generally normal[201] and that low IGF-I levels instead might be connected to a slower spontaneous tempo in growth.

5 CONCLUDING REMARKS

Growth charts are essential for following children in clinical work and for evaluating growth promoting therapy. Syndrome-specific growth charts are helpful in situations where growth develops far below the normal population range, such as in skeletal dysplasias with extreme short stature.

Growth and body proportion references from the present European achondroplasia cohort, the first with a detailed description of periods with growth restriction relative to normal growth from birth to adulthood, suggest that

- tempo in head size is increased attaining final size earlier than normal
- height position is especially compromised during first years of life
- leg length at adult ages is roughly 50 percent shorter than normal
- arm span at adult ages is almost 35 percent shorter than normal, despite almost normal trunk height, thus severely restricting personal area of access
- pronounced body disproportions distort the BMI value, with a median developing above internationally accepted cut-off levels for overweight

Clinical charts are partly constructed on non-linear age scales and logarithmic scales for y-axes with the intention to

- capture growth pattern during infancy when growth velocity is highest
- enable simultaneous evaluation of length, weight and head circumference development
- give same resolution/space for positional BMI changes within lower versus higher distribution
- facilitate plotting and reading sensitivity.

Presented growth chart compilation will support clinical surveillance of children with achondroplasia and other severe short stature conditions for which syndrome-specific charts are missing. Using achondroplasia growth charts as a short stature matrix suggests

- height inhibition in acromesomelic dysplasia type Maroteaux is also compromised during first years of life and height in some cases resembles that in achondroplasia
- height position in pseudoachondroplasia decreases, after an initial period of normal growth, gradually until adult height, which makes adult height predictions from previous height position impossible
- auxological phenotype in hypochondroplasia is pronounced heterogeneous ranging from almost normal stature to phenotypes similar to achondroplasia.

Syndrome-specific charts are often based on small samples making estimates of variability not necessarily robust. This can affect calculation of changes in growth positions based on SDS. Evaluation of growth hormone treatment in girls with Turner syndrome might therefore better be based on normal population references using prepubertal SD lines for calculating

height position at treatment start during normally pubertal ages. Analysing total height gain from treatment to distinguish between good and poor response shows that

- growth hormone treatment is initiated over the wide range of ages covering childhood and pubertal ages
- early start of GH might not result in better total height gain
- initial height gain might be temporary in a noteworthy proportion of girls with Turner syndrome and is not translated to total height gain
- register data reflects treatment attitudes and traditions making it difficult to assign effects to treatment modalities such as GH dose

For the future, regular measurements of auxological variables including sitting height and arm span are encouraged in order to increase knowledge in growth and body proportion patterns in different skeletal dysplasia entities. Likewise, the background for variability in response to GH treatment in non-GH deficient children needs further investigation.

6 ACKNOWLEDGEMENTS

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