Nation-wide age references for sitting height, leg length and sitting height/height ratio and their diagnostic value for disproportionate growth disorders

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Nation-wide age references for sitting height, leg length, and sitting height/height ratio, and their diagnostic value for disproportionate growth disorders

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Keywords

Sitting height; leg length; standards; Marfan syndrome; hypochondroplasia

Abstract

Introduction: To detect whether growth is proportionate or disproportionate, sitting height (SH), leg length (LL), and the ratio between SH and height (H) are usually measured. However, the diagnostic value of the SH/H ratio for detecting disproportionate growth disorders has not yet been evaluated. Furthermore, the SH/H ratio is dependent on height, so that specific age references and appropriate cut-off limits have to be prepared per population. The dependence of SH/H on height also suggests that a correction of the cut-off limits of SH/H for relative height might improve the diagnostic value.

Objectives: To obtain age references for SH, LL and SH/H ratio in the Netherlands; to evaluate how SH standard deviation score (SDS), LL SDS, SH/H SDS and SH/LL SDS are related to height SDS; and to study the usefulness of height corrected SH/H cut-off lines to detect Marfan syndrome and hypochondroplasia.

Methods: Cross-sectional data on height and sitting height were collected of 14,500 children of Dutch origin in the age range 0-21 years. Reference SD charts were constructed by the LMS method. Correlations were analyzed in 3 age groups. SH/H data from patients with Marfan syndrome and genetically confirmed hypochondroplasia were compared with height-corrected SH/H references.

Results: A positive association was observed between H SDS and SH SDS and LL SDS in all age groups. There was a negative correlation between SH/H SDS and height SDS (r=0.16 and –0.23). In short children with a height SDS below <-2 SDS, a cut-off limit of +2.5 SD leads to a more acceptable percentage of false positive results. In exceptionally tall children, a cut-off limit of -2.2 SDS can be used. Alternatively, a nomogram of SH/H SDS versus H SDS can be helpful. The sensitivity of the height-corrected cut-off lines for hypochondroplasia was 80% and for Marfan syndrome only 30%.

Conclusions: In exceptionally short or tall children, one has to take into consideration the dependency of the SH/H ratio (SDS) on height SDS in the evaluation of body proportions. The sensitivity of the cut-off lines for hypochondroplasia is fair.

Introduction

In the diagnostic work-up of children with exceptionally short or tall stature, the visual inspection and objective measurement of body proportions can give important clues. [1-3] The usual method of judging body proportions of children is to calculate the ratio between sitting height and height (SH/H) or sitting height and leg length (SH/LL) and compare this with age references. Sitting height can also be used as a proxy of statural growth if height cannot be measured, for example because of lower limb deformities.

In short children, most chondrodystrophic syndromes (skeletal dysplasias) are characterized by short limbs. In contrast to achondroplasia, hypochondroplasia can be difficult to diagnose. Hypochondroplasia is an autosomal dominant condition characterized by a disproportionate short stature, with relatively short legs, micromelia, macrocrania and lumbar lordosis, linked to N540K mutations in the FGFR3 gene. Also other conditions, such as Down syndrome and Turner syndrome can present with abnormal body proportions. On the other hand, some other syndromes associated with short stature present with a relatively short trunk. In tall children, it is important to diagnose Marfan syndrome, gonadotropin deficiency and Klinefelter syndrome, because of the clinical consequences. Marfan syndrome is an autosomal dominant disorder of connective tissue characterized by a disproportionate tall stature and relatively long legs. Thus, measuring body proportions deliver vital diagnostic information in the work-up of growth disorders.

It is generally known that tall children have relatively long legs and vice versa.[4,5] Therefore, we conjecture that the interpretation of SH/H ratio should not only be based on age references, but also on height. This would theoretically improve the specificity of the cut-off lines. However, no such conditional references are available. There is also no information available about the sensitivity of the usual cut-off lines of normality (+ or - 2 SDS), either corrected for age only or after an additional correction for height, in detecting the most frequent disproportionate growth disorders."

In this paper we present age references of SH, LL and SH/H ratio for Dutch children, and show their relationship with height. In addition, we compare SH/H of children with known Marfan syndrome and known hypochondroplasia with the new references in order to determine whether the usual cut-off limits in the reference charts are appropriate for detecting these disorders.

Methods

Subjects

Cross-sectional data on height and sitting height were collected in the Fourth Dutch Growth Study in 1996 and 1997. A total of 14,500 children, 7,482 boys and 7,018 girls, of Dutch origin in the age range 0-21 years were included. Sitting height was measured in 6,877 boys and 6,202 girls. Children with known growth disorders and those on medication known to interfere with growth were not included in the sample. Details have been described elsewhere.[6] The sample was nationally representative. Separately, we collected growth data of children with Marfan syndrome; 4 boys (of 3, 6, 9, and 13 y) and 6 girls (of 8 (*n*=4), 12, and 16 y). Through the Laboratory of Clinical Genetics and referring physicians, we anonymously gathered data on individuals with DNA-confirmed hypochondroplasia: 7 children (3 boys (of 4, 6, and 12 y) and 4 girls (of 1, 6, 10, and 12 y)), and 3 adults (1 man of 41 y, and 2 women 24 and 43 y old). In addition we gathered data of a family of a 10 year old girl with a confirmed HCH mutation in the FGFR3 gene that caused a mild hypochondroplasia. None of these patients had been treated with any relevant medication at time of the measurement.

Measurements

Length of infants, until 2 years of age, was measured to the nearest 0.1 cm in the supine position, fully extended with their heels in contact with a baseboard. Crown-rump length, a measure of trunk length, which is conceptually similar to sitting height in older children, was measured until two years of age while the child was lying in supine position on a measuring table. After the thighs were placed in a vertical plane, the footboard was pulled against the buttocks. From 2 years of age onward, standing height was measured to the nearest 0.1 cm by using a calibrated microtoise. Sitting height was measured by bringing the horizontal bar of the microtoise into the most superior midline of the head while the child was sitting in erect position on a flat stool or box. Arching of the back was avoided as much as possible by applying upward pressure to the mastoid processes while the child breathed deeply and held its breath during the measurement. The difference between crown-rump length and sitting height was on average +0.4 cm at 2 years of age. For the ratio crown-rump length/length and sitting height/height the difference was on average +0.03. Leg length was obtained by subtracting sitting height from height. The difference between length and crown-rump length is a corresponding estimate of leg length in infants.

Statistical analysis

References for SH, LL and SH/H for age were constructed with the LMS method. The distribution of the data is summarised by three spline curves, the L, M, and S, that vary in time: the Box-Cox transformation power that converts data to normality and minimises the skewness of the dataset (L), the median (M), and the coefficient of variation (S).[7] The choice of the smoothing factors for the L, M, and S curves was made by creating local detrended QQ plots.[8] The associations between SH SDS, LL SDS, SH/H SDS, SH/LL SDS and height SDS were calculated by (multiple) regression analyses and studied for 3 age groups: 0-<5 y (I), 5-<12.5 y (II) and 12.5-<21 y (III) of age. Two strategies were used to find the optimal cut-off values for height SDS and SH/H SDS. First, an ellipse was drawn around 95% of the data points in the scatterplot of SH/H SDS against H SDS, and points that were located outside the ellipse were classified as unusual. The second method was to select H SDS < -2 or >+2 first, and within that group, we classified all points as unusual that were located at least 2 SDS units away from the regression line of SH/H SDS given H SDS.

Results

Reference SD charts for sitting height (SH) and leg length (LL) (figure 1A and 1B), and sitting height/ height (SH/H) for age (figure 2A and 2B) were constructed for boys and girls aged 0-21 years.[9]

The corresponding L, M and S data are shown in table 1. In infants SH represents 68% of the length, decreasing to 57% at 3 y of age for both sexes. During puberty sitting height represents 52% of the height. Between 10 and 15 years a growth spurt in leg length is observed. The ratio SH/LL decreases from a mean of 2.10 in the first year to 1.05 in boys and 1.11 in girls at 20 year of age.

Table 2 shows the association between body proportions and height SDS. As expected, for both SH SDS and LL SDS a strong positive association with height SDS was found in all age groups. The correlations between SH/H (or SH/LL) SDS and height SDS were all negative and statistically significant (p<0.001).

Table 1. L, M, and S values for sitting height (SH) (cm), leg length (LL) (cm), and sitting height/height (SH/H) ratio for boys and girls of Dutch origin in the age-range 0-21 years.

				BOYS					
AGE		**SH**			**LL**			**SH/H**	
years	**L**	**M**	**S**	**L**	**M**	**S**	**L**	**M**	**S**
0.25	3.072	41.691	0.045	1.061	19.376	0.080	5.220	0.682	0.034
0.50	3.087	45.669	0.044	0.936	22.136	0.078	5.220	0.671	0.034
0.75	3.092	48.035	0.044	0.824	24.605	0.077	5.220	0.660	0.034
1.0	3.087	49.710	0.044	0.729	26.922	0.075	5.220	0.648	0.034
2.0	3.030	53.599	0.046	0.536	35.711	0.071	5.220	0.604	0.034
3.0	2.971	55.952	0.046	0.513	42.289	0.067	5.220	0.572	0.033
4.0	2.886	58.741	0.047	0.530	47.110	0.064	5.220	0.555	0.033
5.0	2.768	61.831	0.047	0.558	51.291	0.062	5.220	0.546	0.031
6.0	2.624	64.916	0.047	0.588	55.143	0.061	5.220	0.541	0.030
7.0	2.474	67.784	0.046	0.617	58.826	0.060	5.220	0.536	0.029
8.0	2.331	70.446	0.047	0.644	62.405	0.060	5.220	0.531	0.028
9.0	2.212	72.642	0.047	0.672	65.720	0.059	5.220	0.525	0.027
10.0	2.115	74.502	0.048	0.703	68.825	0.059	5.220	0.520	0.026
11.0	2.023	76.435	0.048	0.742	71.947	0.059	5.220	0.516	0.025
12.0	1.931	78.893	0.049	0.791	75.332	0.059	5.220	0.513	0.025
13.0	1.868	81.971	0.050	0.851	79.180	0.059	5.220	0.509	0.025
14.0	1.871	85.482	0.050	0.910	82.832	0.058	5.220	0.508	0.026
15.0	1.925	88.994	0.047	0.957	85.618	0.057	5.220	0.510	0.026
16.0	1.985	91.555	0.044	0.990	87.476	0.057	5.220	0.512	0.027
17.0	2.024	93.017	0.042	1.007	88.456	0.057	5.220	0.513	0.027
18.0	2.047	93.854	0.041	1.013	88.821	0.057	5.220	0.515	0.028
19.0	2.059	94.311	0.040	1.014	88.885	0.057	5.220	0.516	0.028
20.0	2.062	94.432	0.040	1.016	88.954	0.057	5.220	0.516	0.029
21.0	2.060	94.654	0.040	1.019	89.144	0.057	5.220	0.513	0.029

					GIRLS				
AGE		SH			LL			SH/H	
years	L	M	S	L	M	S	L	M	S
0.25	1.510	40.669	0.045	0.707	18.895	0.079	4.720	0.683	0.036
0.50	1.445	44.742	0.045	0.673	21.518	0.077	4.720	0.672	0.036
0.75	1.386	46.962	0.046	0.650	23.999	0.075	4.720	0.660	0.036
1.0	1.336	48.719	0.046	0.641	26.364	0.074	4.720	0.648	0.036
2.0	1.234	52.428	0.048	0.719	35.261	0.069	4.720	0.601	0.036
3.0	1.194	54.615	0.049	0.785	42.145	0.066	4.720	0.568	0.035
4.0	1.164	57.761	0.049	0.764	46.801	0.063	4.720	0.553	0.034
5.0	1.147	61.155	0.050	0.713	50.650	0.061	4.720	0.546	0.032
6.0	1.144	64.146	0.050	0.660	54.452	0.060	4.720	0.541	0.031
7.0	1.153	66.810	0.050	0.625	58.309	0.059	4.720	0.536	0.029
8.0	1.176	69.573	0.050	0.624	62.011	0.058	4.720	0.531	0.028
9.0	1.217	72.287	0.049	0.662	65.409	0.058	4.720	0.526	0.027
10.0	1.277	74.730	0.049	0.738	68.658	0.057	4.720	0.522	0.028
11.0	1.357	77.178	0.048	0.850	71.969	0.057	4.720	0.519	0.027
12.0	1.471	80.100	0.047	0.982	75.247	0.056	4.720	0.516	0.027
13.0	1.610	83.126	0.045	1.101	77.896	0.056	4.720	0.516	0.027
14.0	1.735	85.498	0.043	1.175	79.464	0.056	4.720	0.518	0.027
15.0	1.823	87.060	0.041	1.209	80.153	0.055	4.720	0.522	0.027
16.0	1.883	88.108	0.040	1.225	80.491	0.055	4.720	0.524	0.027
17.0	1.907	88.544	0.039	1.234	80.657	0.055	4.720	0.524	0.027
18.0	1.917	88.707	0.039	1.238	80.749	0.055	4.720	0.524	0.027
19.0	1.933	88.994	0.039	1.242	80.827	0.055	4.720	0.525	0.027
20.0	1.953	89.347	0.038	1.248	80.956	0.055	4.720	0.526	0.027
21.0	1.969	89.627	0.038	1.253	81.057	0.055	4.720	0.526	0.027

Table 2. Correlations between SH SDS, LL SDS, SH/H SDS, and SH/LL SDS and height SDS in three age groups.

	Age groups		
Correlation (r)	**0-<5 yr**	**5 - <12.5 yr**	**12.5-21 yr**
SH SDS - H SDS	0.61	0.63	0.80
LL SDS - H SDS	0.50	0.69	0.87
SH/H SDS - H SDS	-0.16	-0.23	-0.23
SH/LL SDS - H SDS	-0.15	-0.22	-0.24
SH SDS-LL SDS	-0.36	-0.08	0.40

This is illustrated in figure 3 presenting a scatter plot of SH/H SDS versus height SDS. The equiprobable ellipse around 95% of the points shows a tendency towards decreasing SH/H SDS with increasing height SDS. Vice versa, shorter children have higher SH/H ratios, thus relatively shorter legs. Data points located inside the ellipse may be considered as normal. Figure 4 shows the ellipse, the regression line and two lines at 2 SDS units away of the regression line. This figure can be used as a nomogram to assess for a given height SDS the normal range of SH/H SDS. To explore if this nomogram is a useful tool to distinguish

patients with Marfan syndrome from constitutionally tall children, or patients with hypochondroplasia from idiopathic short stature, one SH/H observation per patient from these groups of patients were plotted in the figure. The purpose was to find cut-off limits that detect disproportion. Only in 3 out of 10 patients with Marfan syndrome SH/H was located below the conditional - 2 SD line, so this cut-off criterion has a sensitivity of only 30%. In 4 out of 10 patients SH/H SDS was below the unconditional -2 SD line. The ellipse criterion performed better: 6 out of 10 patients with Marfan were located outside the ellipse. When the conditional -2 SD line is taken as diagnostic criterion the likelihood ratio of a positive test (LR+) is 0.3/0.02=15, and the likelihood ratio of a negative test (LR-) 0.7/0.98=0.7. With regard to hypochondroplasia, a total of 8 out of 10 cases were located above the conditional +2 SDS line, corresponding to a sensitivity of 80%. This results in a LR+ of 40 and a LR- of 0.2. We observed that also here the ellipse performed better: all hypochondroplasia cases were located outside the ellipse. Figures 5A and 5B show sitting height/height data of the members of a family with HCH due to a FGFR3 gene mutation on the maternal side. The sitting height/height index of the index case and three of her female relatives is shown in figure 3A, and of her brother and uncle in figure 3B. The HCH mutation in the FGFR3 gene (in codon 540: substitution of asparagine by serine) caused a mild hypochondroplasia with a variable expression pattern. All affected family members had short stature (height <-2 SDS) and a mild increased sitting height/height index, indicating a disproportionate short stature with relatively short legs.

The negative correlation between SH/H SDS and H SDS signifies that for short or tall children the usual cut-off limits for body proportions (+ or - 2.0 SDS) would result in considerable percentages of children who would be considered as disproportionate. This is shown in table 3. If one would strive for a specificity of about 98%, the cut-off limit of SH/H SDS for short children would be +2.5 SDS, and for tall children -2.2.

Table 3. Percentages of short children (height SDS below -1.5 or -2.0) with a SH/H SDS >+2.0 or +2.5, and percentages of tall children (height SDS above +1.5 or +2.0) with a SH/H <-2.0 or -2.5.

Short children			Tall children		
SH/H SDS	**H SDS <-2.0**	**H SDS <-1.5**	**SH/H SDS**	**H SDS >+1.5**	**H SDS >+2.0**
>+2.0	6.8%	3.6%	**<-2.0**	3.5%	5.2%
>+2.5	4.3%	2.5%	**<-2.5**	1.1%	1.7%

Discussion

This study provides new reference charts for Dutch children for SH, LL and SH/H in relation to age. The SH/H ratio changed from 0.68 infancy to 0.52 in adolescence, indicating that in the prepubertal years growth occurs more in the limbs than in the trunk. This is also shown by the decreasing SH/LL ratio from 2.10 to 1.08 at 10 years of age. The use of a ratio might be misleading when two ratios might be equal while the nominator and denominator might be different. This effect is even stronger when a change in the nominator automatically leads to a change in the denominator, for example by using SH/LL ratio. To minimize this risk, we chose for sitting height/height for age reference charts.

During the past two centuries in the Netherlands, as well as in many more industrialized countries, a positive secular growth change has been observed.[6] Various studies have shown that the positive secular change is mainly due to increase in leg length rather than in trunk length (1,4,10-13). Tanner described that between the nineteenfifties and eighties Japanese height increased solely due to change in leg length. Sitting height showed no increase, so the trunk/leg proportions changed much more towards the proportions of North Europeans, though their final height was still 1 SD lower.[14]

Secular trend may explain part of the difference we observed between our study and the Oosterwolde study, a previous (regional) Dutch growth study including sitting height measurements and performed in 1980 and 1990.[15] We found that our reference lines for SH for age and SH/H ratio for age were usually lower than the Oosterwolde study. Despite the fact that the Oosterwolde sample consisted of relatively tall children from the Northern part of the Netherlands, the 1997 Dutch population was even taller. The Oosterwolde study showed that in 10 years (1980-90) the increase in height was more pronounced than the increase in sitting height, so the major secular change must have been in the legs (1). In the three previous national Dutch growth studies no data on body proportions were collected, so that we cannot comment on the secular trend with respect to body proportions. Our present data on sitting height, leg length and height reference values in the Netherlands are higher than in Denmark, UK and Sweden,[16] illustrating our earlier observations[6] that the Dutch population is probably still the tallest in the world (mean height for men 184.0 cm, for women 170.6 cm).
We have shown that in short children a cut-off of 2.5 SDS is better than a cut-off of 2 SDS and that in tall children a cut-off limit of -2.2 SDS can be used. However, we think that instead of using fixed cut-off limits, one can better plot individual observations on the diagram of SH/H SDS versus H SDS. The sensitivity of the conditional ±2 SD cut-off limits for detecting hypochondroplasia and Marfan syndrome on the reference chart was studied by comparing body proportions of these two patient groups to the reference population. Based on the values of the positive and negative likelihood ratios of the conditional cut-off limit, the diagnostic value of assessing body proportions for hypochondroplasia is good. For Marfan syndrome, the LR+ is high,[15] but the LR- is not much lower than one, suggesting that normal body proportions do not exclude Marfan syndrome. We can speculate that the major secular change that has affected leg length in particular has led to the relative lack of utility of the standards in the detection of the Marfan individuals, and that this may not be the case in other countries such as the UK. Besides tall and disproportionate stature, there are other defined characteristics to allow diagnosis of Marfan syndrome, such as arachnodactyly, joint laxity, hernias, scoliosis and chestdeformations, myopia, dislocation or poor fixation of the lens and a high arched plate. For both patient groups the equiprobable ellipse is a better criterion to detect growth disorders than the ±2 SD lines method. Further investigations on larger groups of patients are necessary to further validate the clinical usefulness of abnormal body proportions for the detection of these and other growth disorders.

Eveleth and Tanner[17] described that differences in body proportions are genetically controlled and different for European, African and Oriental populations (Caucasians have tall stature with long legs, in contrast to Orientals). With better environmental circumstances relatively longer legs appear in all ethnic groups. In fact, monitoring leg length might even be a better tool for reflection of environmental improvements than height. Abused children, who have relatively short legs, showed after social interventions a significant recovery of leg length.[18] In our study on body stature, mean height was related to geographical region, family size and educational level of the parents and the child.[6] In the present study geographical region was only a significant predictor in the youngest group (data not shown). No significant differences were found for educational level or gender.

One of the problems in assessing body proportions is that errors in SH measurement are easily made, which can lead to considerable inter-observer variation. We did not study the inter-observer variance for sitting height measurements, but in the Fels Longitudinal Study the mean absolute interobserver difference was 0.5 cm (SD 0.3 cm) for crown-rump length and 0.3 cm (SD 0.2 cm) for sitting height.[19]

In conclusion, new reference charts for sitting height, leg length and body proportion are presented. There was a statistically significant negative correlation between SH/LL and SH/H and height. For practical purposes, in an exceptionally short child a SH/H ratio below +2.5 SDS and in a tall child a SH/H ratio above –2.2 should still be considered normal. The nomogram for SH/H SDS versus H SDS is a useful tool in the work-up of children with growth disorders and provides an objective basis for recognizing disproportionate growth.

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Figure Legends

Figure 1A and 1B
Sitting height and leglength for age for Dutch boys and girls aged 0-21 years, indicating the 0, ±1,±2, ±2.5 SD lines.

Figure 2A and 2B
Sitting height / height ratio for age for Dutch boys and girls aged 0-21 years, indicating the 0, ±1, ±2, 2.5 SD lines.

Figure 3
A scatter plot of SH/H SDS versus height SDS.

Figure 4
A nomogram to assess for a given height SDS the normal range of SH/H SDS, indicating the ellips, the regression line and two lines at 2 SDS units away of the regression line.
▲ Marfan Syndrome ● Hypochondroplasia

Figure 5A
SH/H data of the members of a family, with a HCH mutation in the FGFR3 gene on the maternal side, that caused a mild hypochondroplasia with a variable expression pattern. Figure A shows the SH/H index for the index case, her cousin, her mother, her aunt and grandmother.

Figure 5B
SH/H index for the brother and an uncle of the index case.

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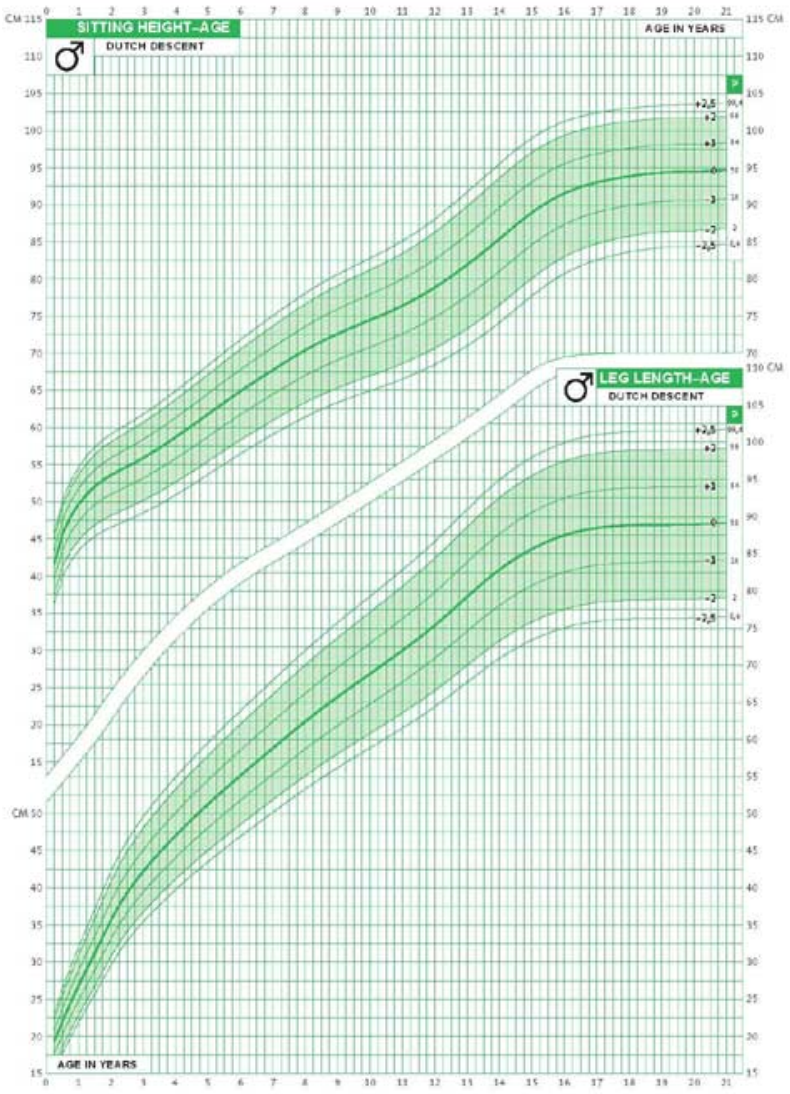

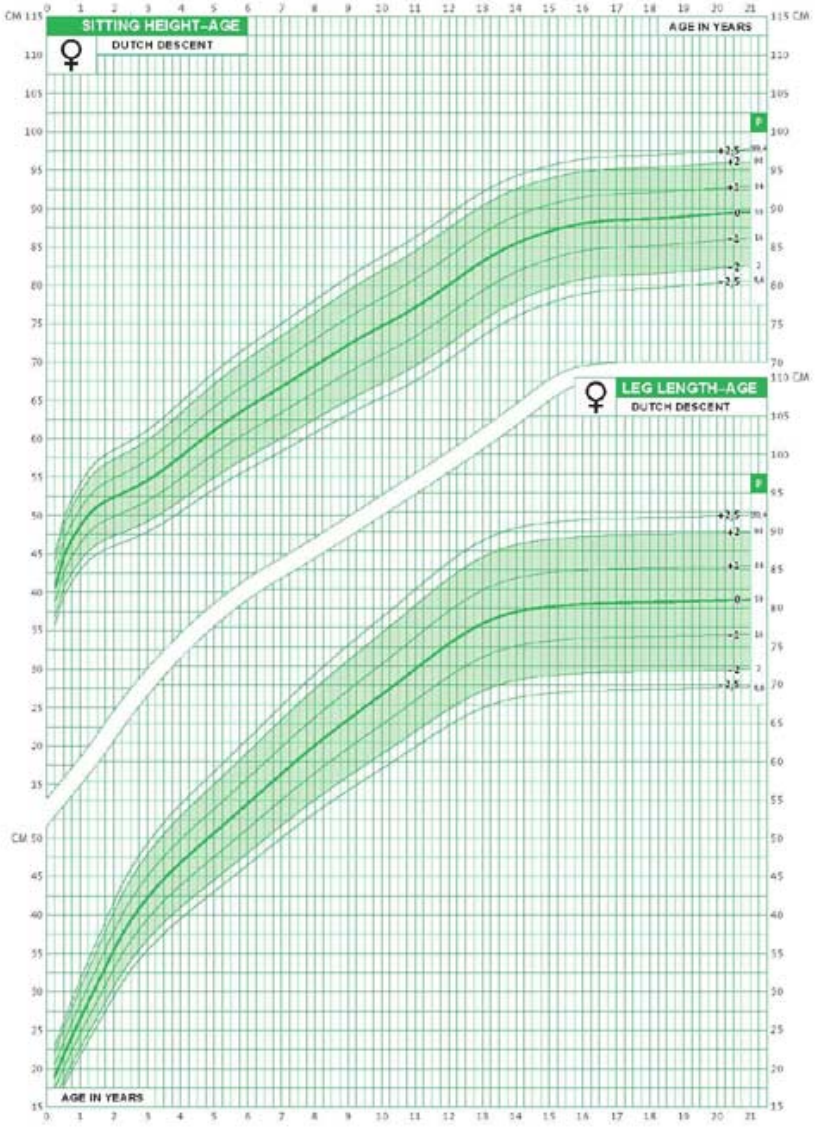

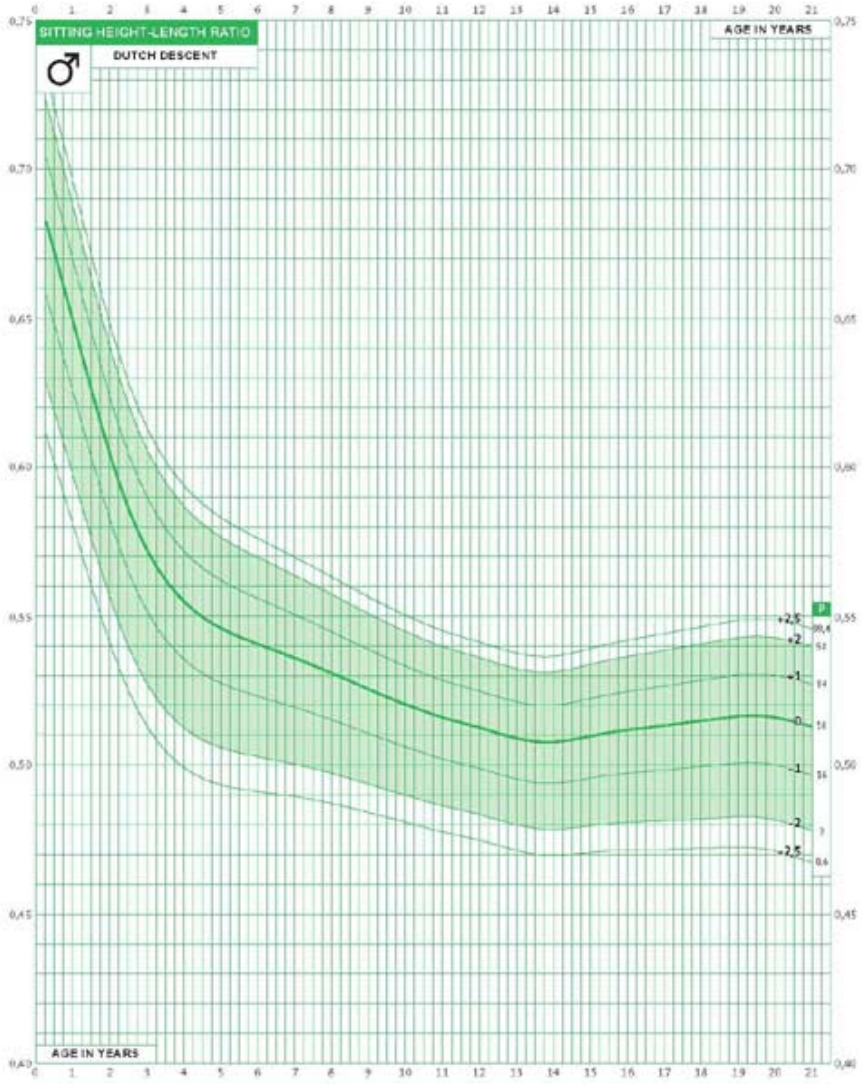

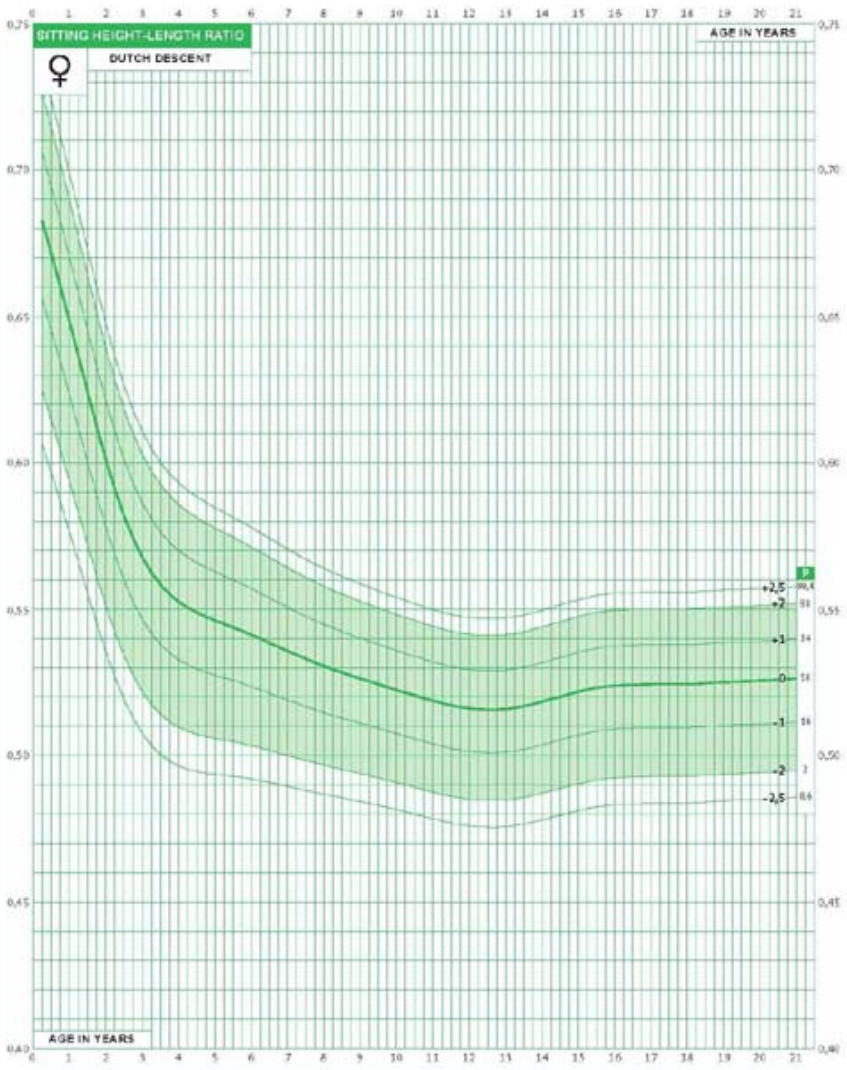

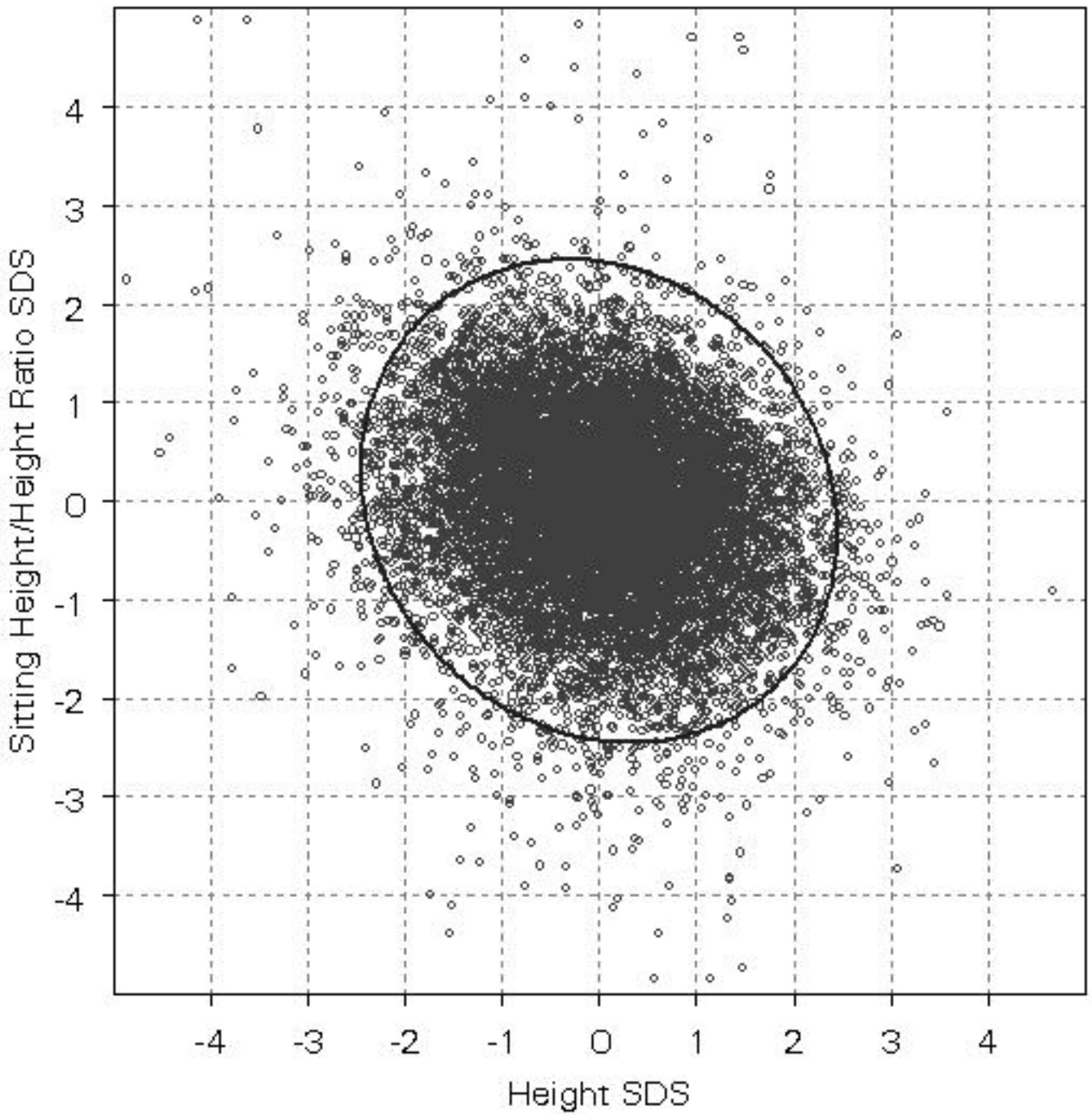
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Height SDS
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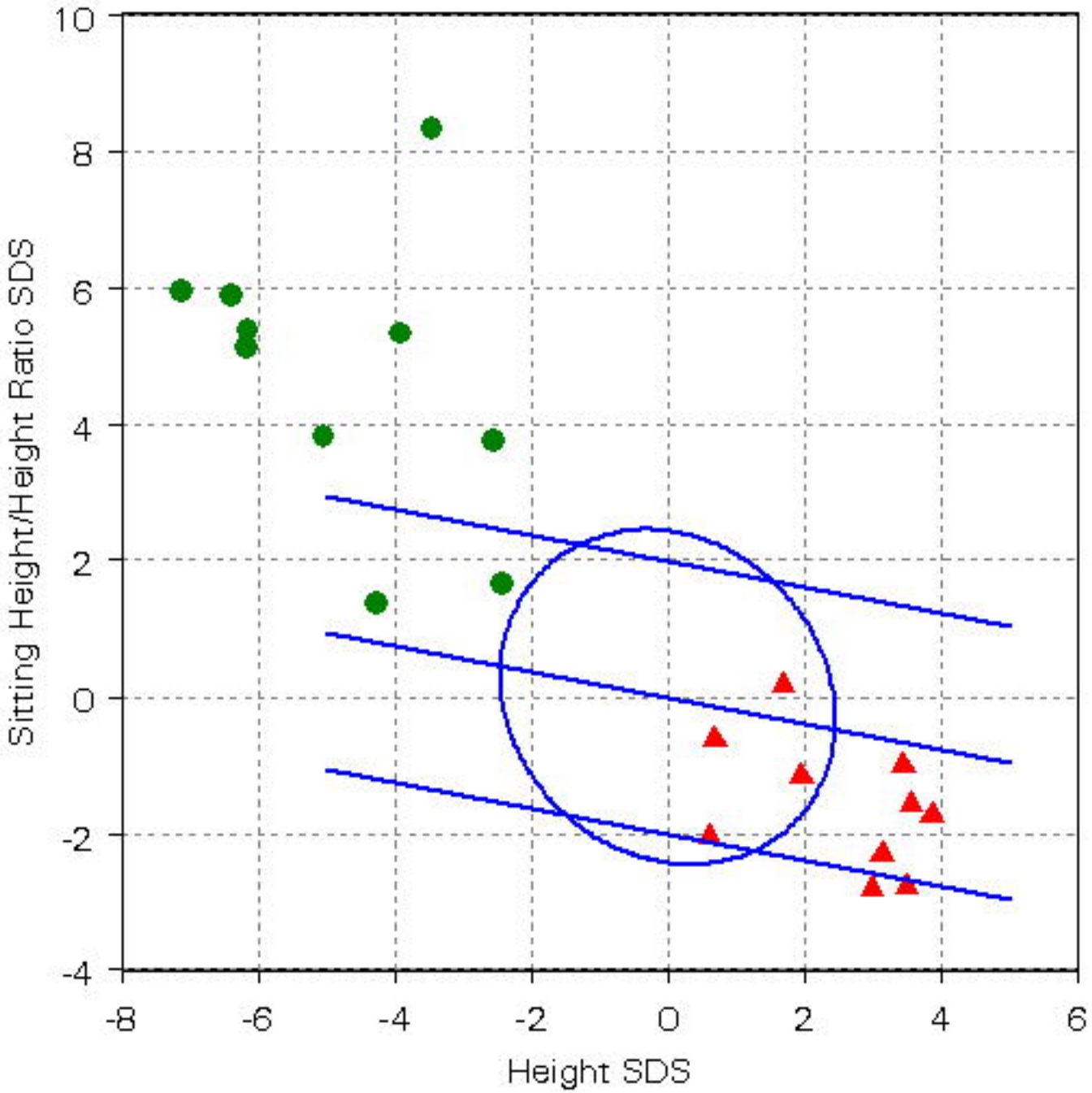
-1
-2
-3
-4
-4
-3
-2
-1
0
1
2
3
4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Sitting Height/Height Ratio SDS
Height SDS

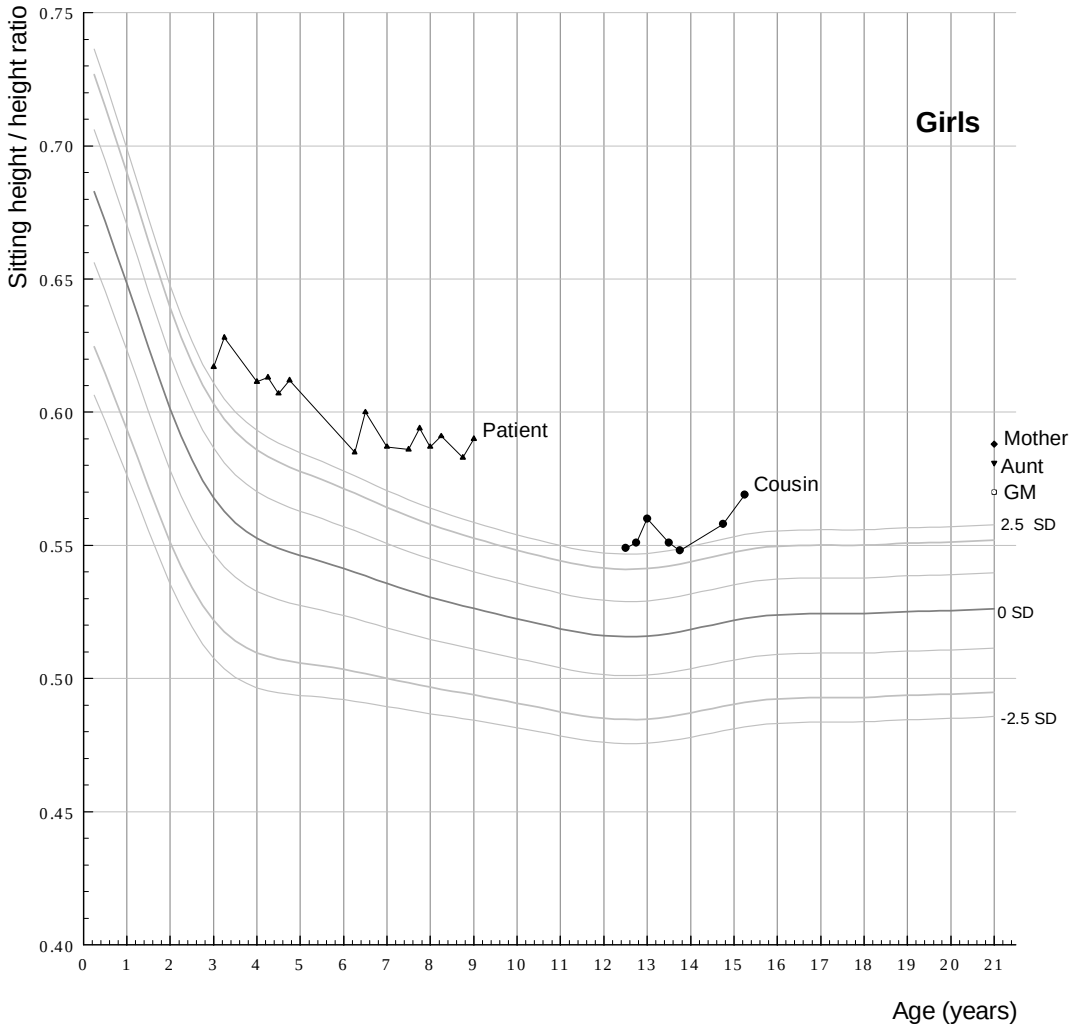

Figure 5A

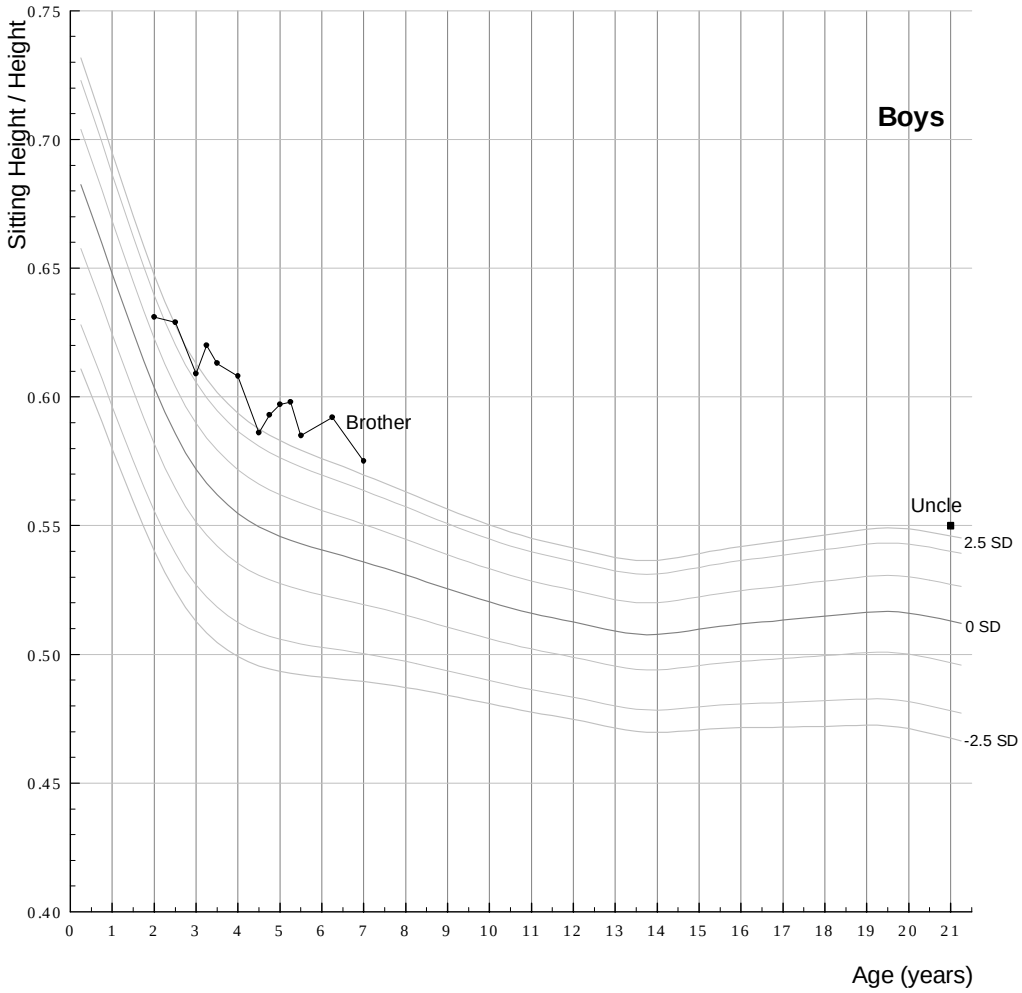

Figure 5B