

Growth Charts for Individuals with Rubinstein–Taybi Syndrome

Lex Beets,¹ Cristina Rodríguez-Fonseca,² and Raoul C. Hennekam^{1*}

¹Department of Pediatrics, Emma's Children's Hospital/Academic Medical Center, Amsterdam, The Netherlands

²Spanish Rubinstein-Taybi Association, Madrid, Spain

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Rubinstein–Taybi syndrome (RSTS) is an autosomal dominant disorder characterized by variable degrees of intellectual disability, an unusual face, distal limb anomalies including broad thumbs and broad halluces, a large group of variable other major and minor anomalies, and decreased somatic growth. The aim of the present study was to construct up-to-date growth charts specific for infants and children with RSTS. We collected retrospective growth data of 92 RSTS individuals of different ancestries. Data were corrected for secular trends and population of origin to the Dutch growth charts of 2009. On average, 17.9 measurements were available per individual. Height, weight and body mass index (BMI) references for males and females were constructed using the *lambda, mu, sigma* method. RSTS individuals had normal birth weight and length. Mean final heights were 162.6 cm [−2.99 standard deviation score (SDS)] for males and 151.0 cm [−3.01 SDS] for females. BMI SDS compared to the general Dutch population were −0.06 and 1.40 SDS for males and females, respectively. Head circumference SDS compared to the general Dutch population was −1.89 SDS for males and −2.71 SDS for females. This is the first study to publish growth charts using only molecularly proven RSTS individuals. These syndrome-specific growth charts can be used in managing problems related to growth in RSTS individuals. © 2014 Wiley Periodicals, Inc.

Key words: Rubinstein-Taybi syndrome; growth charts; short stature; microcephaly; body mass index

INTRODUCTION

The Rubinstein–Taybi syndrome (RSTS; OMIM 180849) is a well-known intellectual disability-multiple congenital malformation syndrome with a birth prevalence of 1 in 100,000–125,000 [Hennekam, 2006]. It is caused by mutations in *CREBBP* located at chromosome 16p13.3, or in *EP300* located at chromosome 22q13.2, or microdeletions of these loci [Roelfsema et al., 2005]. Main characteristics are variable degrees of intellectual disability, an unusual face, distal limb anomalies including broad thumbs and broad halluces, and many other possible major and minor anomalies [Rubinstein and Taybi, 1963; Hennekam, 2006].

In 1990 growth in RSTS was studied in 95 patients [Stevens et al., 1990]. It demonstrated absence of a pubertal growth spurt, decreased final adult height in both males and females, overweight

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in boys during childhood and in girls during adolescence, and microcephaly in a minority of adults. The 1990 growth charts had as shortcomings that the diagnosis was a clinical one while at the time misdiagnoses were known to occur [Lowry, 1990], and growth data of individuals with various ethnic background were not corrected. Furthermore, since 1990, the average human height has increased significantly [Schönbeck et al., 2013]. No similar study has been performed since.

The aim of the present study is to provide up-to-date growth charts specific for infants and children with RSTS. These charts should assist pediatricians and other caregivers in providing optimal care to RSTS individuals with problems related to physical growth.

METHODS

Study Design

We contacted Brazilian, Danish, Dutch, French, German, Italian, Spanish, UK, and US RSTS families and/or Support groups who agreed to forward an invitation to participate to all families with an RSTS individual known to them. In the invitation, the purpose and design of the study were explained, and the URL to enter the growth data was provided. The data were collected through a website in which families could enter the data of the RSTS individual. Next to weight, height, and head circumference at various ages, data were

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*Correspondence to:

Raoul C. Hennekam, M.D., Ph.D., Department of Pediatrics, Room H7-236, Academic Medical Center, Meibergdreef 9, 1105AZ Amsterdam, The Netherlands

E-mail: r.c.hennekam@amc.uva.nl

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collected regarding ethnicity, parental height, age at start of puberty, use of growth hormone supplements, and results of genetic studies.

The collected data were reviewed on the password-protected database and if inconsistencies, probable errors or missing data were detected, the family was contacted for further information and correction of data if needed. Only individuals in whom the clinical diagnosis of RSTS was confirmed cytogenetically or molecularly were allowed to enter the study. If data of height or head circumference were collected after 21 years of age these were recorded as final measurement [Schönbeck et al., 2013]. For weight, the first weight collected after the age of 20 years was recorded as final assessment [Roede, 1990]. Body mass index (BMI) was calculated using the formula $BMI = \text{mass}(\text{kg})/(\text{height}(\text{m}))^2$.

The number of available measurements varied widely between patients. Therefore, we included a maximum of 15 measurements per patient, with a minimum of 3 months between two measurements. If available, birth weight and final measurement data were included. To assess whether the number of measurements significantly influenced a chart, we calculated the correlation between mean standard deviation score (SDS) and the number of measurements per patient. We used all data as correlation was low (<0.3).

Correction for Secular Trends

Measurements in the present study population were performed over a period of more than seven decades (1937–2013). Corrections for secular trend were installed for all data between 1937 and 1997. From 1997 onwards, the secular trend has stopped [Schönbeck et al., 2013] and correction is not needed. We used data from the first four Dutch national studies on growth performed in 1955, 1965, 1980, and 1997, respectively [de Wijn and de Haas, 1960; Van Wieringen et al., 1971; Roede, 1990; Fredriks et al., 2000]. We corrected data for height by calculating the SDS for the growth chart applicable for the date when a measurement was performed. Every measurement performed before 1955 was interpreted as being performed in 1955, as no earlier national Dutch growth study has been performed. It has been indicated that differences in height due to the secular trend are extremely limited in the first 5 years of life [Fredriks et al., 2000], so data were corrected only if obtained after the first 5 years of life. In the Netherlands, a secular trend for weight has not been found from 1980 on [Roede, 1990; Fredriks et al., 2000; Schönbeck et al., 2013], so data were not corrected if obtained after 1980. Dutch head circumference does not show a secular trend, and correction of data was not needed [Van Wieringen et al., 1971; Roede, 1990; Fredriks et al., 2000; Schönbeck et al., 2013].

Correction for Population of Origin

Since the population from the Netherlands is (one of) the tallest in the world and since we wanted to compare our internationally derived growth charts with existing Dutch growth charts, we corrected the data from RSTS individuals from other countries. We calculated the SDS from the growth chart of the country which the RSTS individual originated from and then converted this to the height in the 2009 Dutch growth charts [Cacciari et al., 2002; Ogden et al., 2002; Sobradillo et al., 2004; Schönbeck et al., 2013; Tingaard et al., 2014]. We used growth measurements of RSTS individuals

from other countries that had been gathered after 1990 only. Comparisons showed that head circumferences in the participants from the various populations did not differ significantly and could be used without adaptation [Fredriks et al., 2000; Ogden et al., 2002; Tingaard et al., 2014]. There are significant differences in weight in the general population in the various countries from which the RSTS participants originated [Fredriks et al., 2000; Ogden, 2010; Schönbeck et al., 2013; Tingaard et al., 2014]. We realized correction was extremely complicated and data would therefore remain of uncertain reliability. Therefore only data from Dutch RSTS individuals were used to constitute the weight for age charts and BMI charts.

Growth Chart Generation

We used the Growth Analyzer software Version 4.0 (Ed. Dutch Growth Foundation, Rotterdam, Netherlands) to construct 3, 10, 25, 50, 75, 90, and 97th centile curves for height, weight, and BMI, specific for gender. This software has proven to be valid for producing syndrome-specific growth charts [Malaquias et al., 2012; Ruijter et al., 2014]. For the comparison between RSTS and standard Dutch growth charts for height, we constructed growth charts of -2.5 , -2.0 , -1.0 , 0 , 1 , 2.0 , and 2.5 SDS, since the Dutch growth charts were constructed the same way. The program uses the “LMS” method, which is based on the principle that anthropometric data can be converted to a standard normal distribution by a Box-Cox transformation for any given age. Three smoothed age-related curves are used to transform data: the L-curve describes the most suitable power coefficient at each age (Box-Cox power) and it is needed to convert the data to a Gaussian distribution. The M-curve is the median or 50th centile curve for the measurements, the S-curve is the coefficient of variation which is the standard deviation expressed as a fraction or percentage of the mean [Cole, 1990]. A table of corresponding smoothed L, M, and S values is accessible and these values can be used to calculate any required centile or SDS curve using a simple formula that involves the L, M, and S values at any given age: $SD\text{-score} = ((X/M)^L - 1) / L \times S$, in which X is the measurement of interest (height, weight, BMI, and head circumference). The values of L, M, and S are constrained to change smoothly with age using a penalized maximum likelihood approach. The estimated degrees of freedom (EDF) of curves for L, M, and S can be manipulated based on examination of goodness of fit testing and choice of EDF values allows the user to balance between charts that are empirically valid and aesthetically pleasing as well as biologically plausible [Cole and Green, 1992].

All data were recorded in Statistical Package of Social Sciences (SPSS), version 20 SPSS Inc., Chicago, IL. Mean height, weight, head circumference, and BMI were compared with the healthy Dutch population (0 SDS) using one-sample *t*-test.

RESULTS

Demographics

In a retrospective study, we collected growth data from 92 RSTS patients (46 males). Fifty-four patients were of Dutch, seven of Spanish, three of Italian 11 of Danish, and 17 of American ancestry.

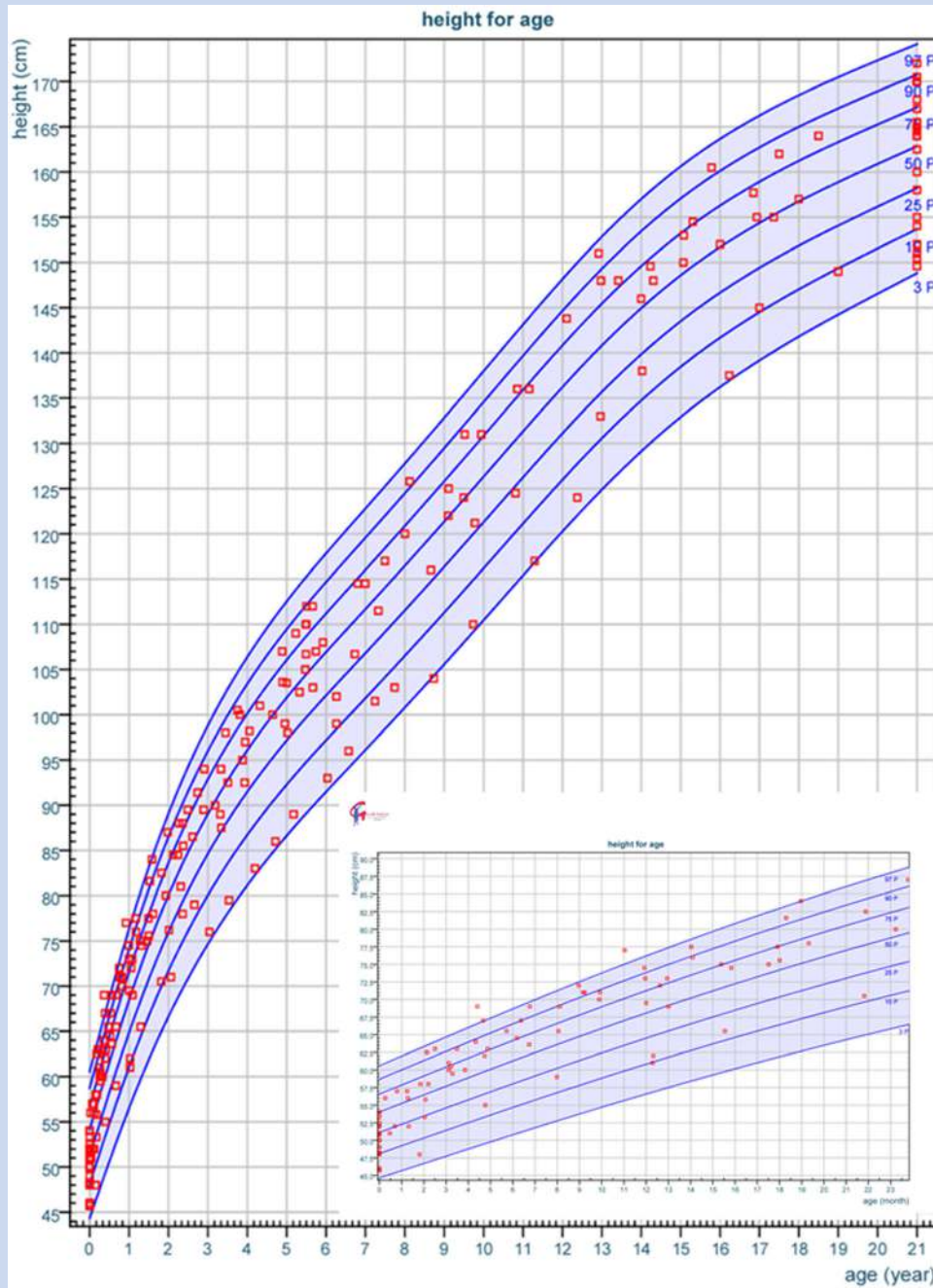


FIG. 1. Growth in height for boys with RSTS, ages 0–21 years, showing individual data points. The inset shows an enlarged graph of length/height for boys 0–24 months of age.

Only patients with the RSTS confirmed by cytogenetic or molecular analyses were included. Eighty-seven patients had a mutation in *CREBBP*, two patients had a mutation in *EP300*. No patient had been treated with growth hormone supplements.

Length and Weight at Birth

Information on length and weight at birth was available for 39 females and 37 males. Since 1985, birth length in The Netherlands is

infrequently measured because of a supposed increased risk for development of hip dysplasia [De Jonge, 1986]. Therefore there is no Dutch reference curve available for length at birth, and growth curves of Swedish neonates are being used in clinical practice [Niklasson and Albertsson-Wikland, 2008]. We have no information about gestational age of the patients, but as gestational age in RSTS is completely comparable to those of the general population, it will be unlikely this has a significant influence in a group of this size [Hennekam et al., 1990]. Indeed, RSTS neonates had normal

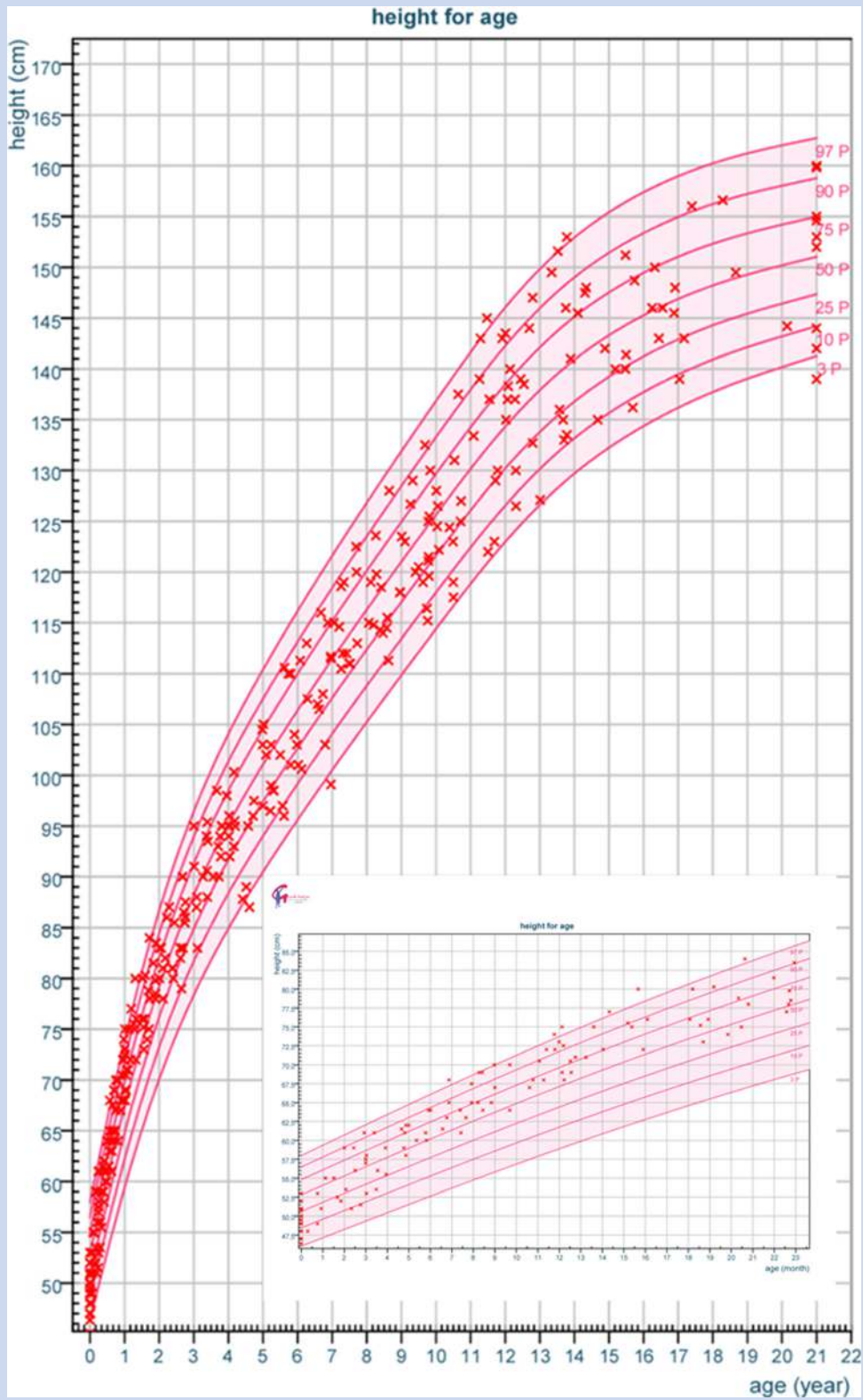


FIG. 2. Growth in height for girls with RSTS, ages 0–21 years, showing individual data points. The inset shows an enlarged graph of length/height for girls 0–24 months of age.

weight at birth (3.070 ± 525 g, corresponding to -0.9 SDS ± 1.01 SDS), and mean length at birth (50.2 cm ± 2.7 cm, corresponding to -0.1 SDS ± 1.42 SDS).

Growth Charts for Height and Weight

On average, 6.7 height measurements, 7.3 weight measurements, and 2.9 head circumference (HC) measurements were available per RSTS individual. The height EDF parameters were L1 M5.6 S2.6 and L2 M5.6 S2 for boys and girls, respectively. Mean final height for males was 162.6 cm (± 6.4 cm) and for females 151.0 cm (± 6.0 cm). Compared with the general Dutch population, the final height of RSTS males was -2.99 SDS and RSTS females was -3.02 SDS [Schönbeck et al., 2013]. Growth charts for RSTS males and females are presented in Figures 1 and 2, and comparisons with the standard Dutch growth charts for height are shown in Figures 3 and 4.

The EDF parameters for weight were L1 M6 S3 for both boys and girls. The mean weight at 21 years of age was 60.67 ± 13.63 kg for RSTS males and 61.43 ± 14.89 kg for RSTS females. This corresponds with -1.78 SDS (males) and -0.21 SDS (females) of the general Dutch population [Fredriks et al., 2000]. Weight-for-age charts are shown in Figures 5 and 6.

BMI Charts

The BMI EDF parameters were L2.1 M6.0 S2.1 for both men and women. The mean BMI at 21 years of age was 21.90 ± 3.45 kg/m² for men and 26.64 ± 5.5 kg/m² for women. This corresponds with

-0.06 SDS (males) and 1.40 SDS (females) in the general Dutch population [Fredriks, 2000]. The BMI charts are shown in Figures 7 and 8.

Growth Charts for Head Circumference

The HC parameters were L1.4 M5.6 S2.0 for males and L1.4 M5.6 S1.6 for females. The mean HC at 21 years of age was 54.40 ± 1.4 cm males and 50.70 ± 1.38 cm for females. This corresponds with -1.89 SDS (males) and -2.71 SDS (females) in the general Dutch population [Fredriks et al., 2000]. The charts for HC for age are depicted in Figures 9 and 10.

DISCUSSION

In the present study, height, weight, BMI, and HC for age and sex charts were constructed using a sample of 92 RSTS individuals in whom the clinical diagnosis has been confirmed cytogenetically or molecularly. The results indicate that prenatal growth retardation in length, weight, or HC does not occur in RSTS. Compared to the 1990 RSTS growth curves, there is no statistical significant difference in average length, weight, and HC at birth [Stevens et al., 1990]. The outcome of length of birth was 49.7 and 48.6 for males and females respectively, for weight at birth was 3.30 and 2.97 kg and for HC 34.2 and 32.2 cm.

We show postnatal growth retardation occurs in the first year of life during which the 0 SDS line of RSTS drops to -2.0 SDS of the general Dutch population and thereafter follow this till 10 years

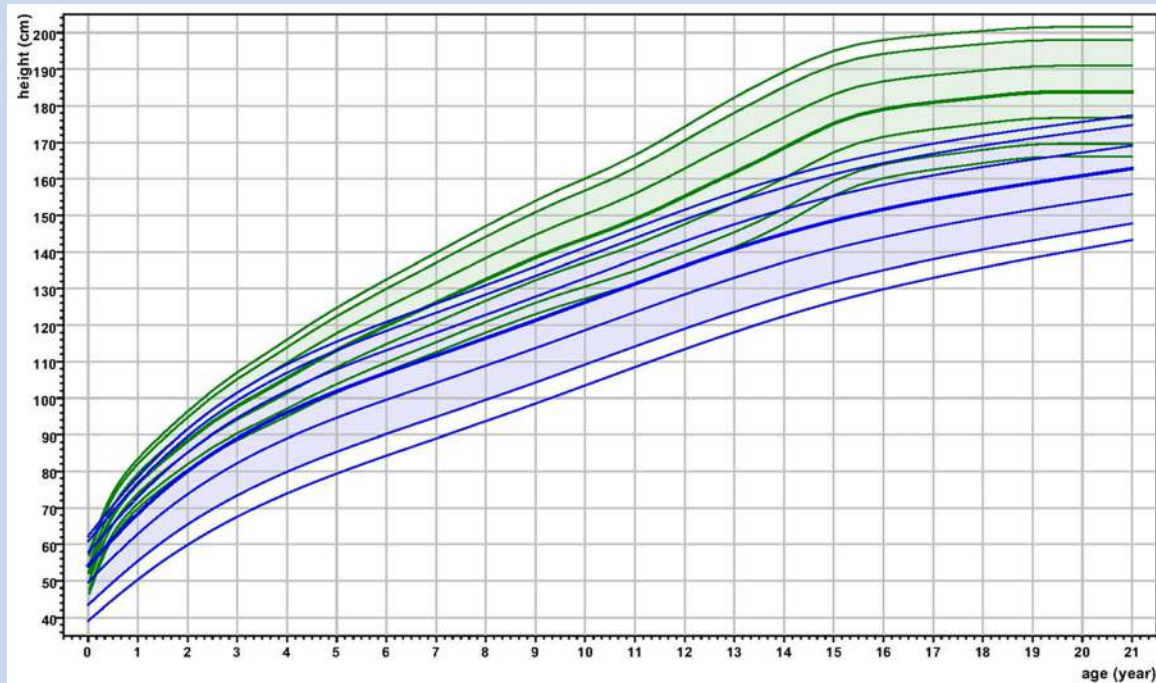


FIG. 3. Comparison of constructed growth chart for RSTS for boys (blue), with Dutch reference Chart 2009 height for age (green).

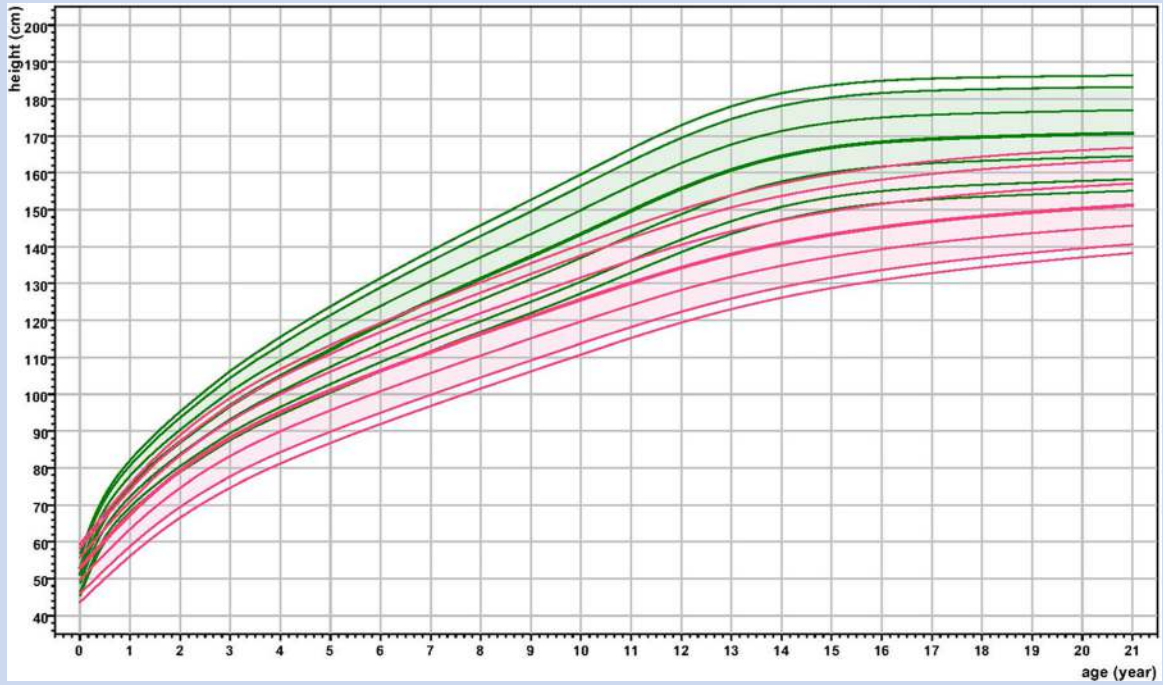


FIG. 4. Comparison of constructed growth chart for RSTS for girls (pink), with Dutch reference Chart 2009 height for age (green).

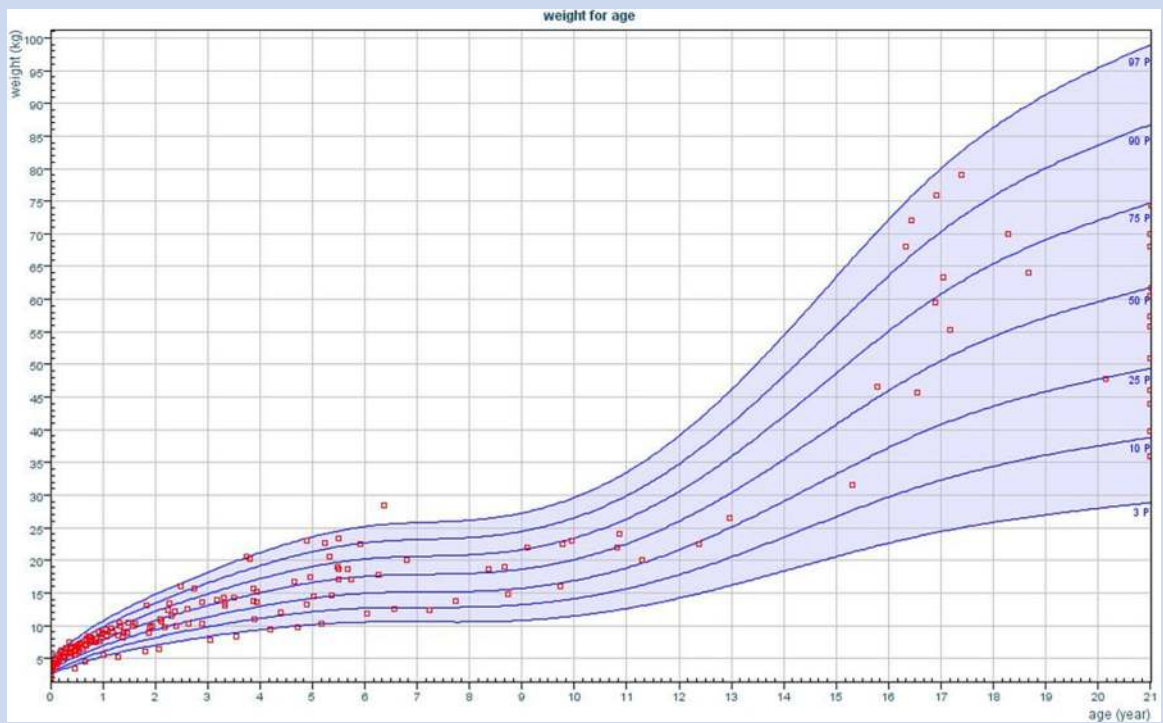


FIG. 5. Weight in males with RSTS, ages 0–21, showing individual data points.

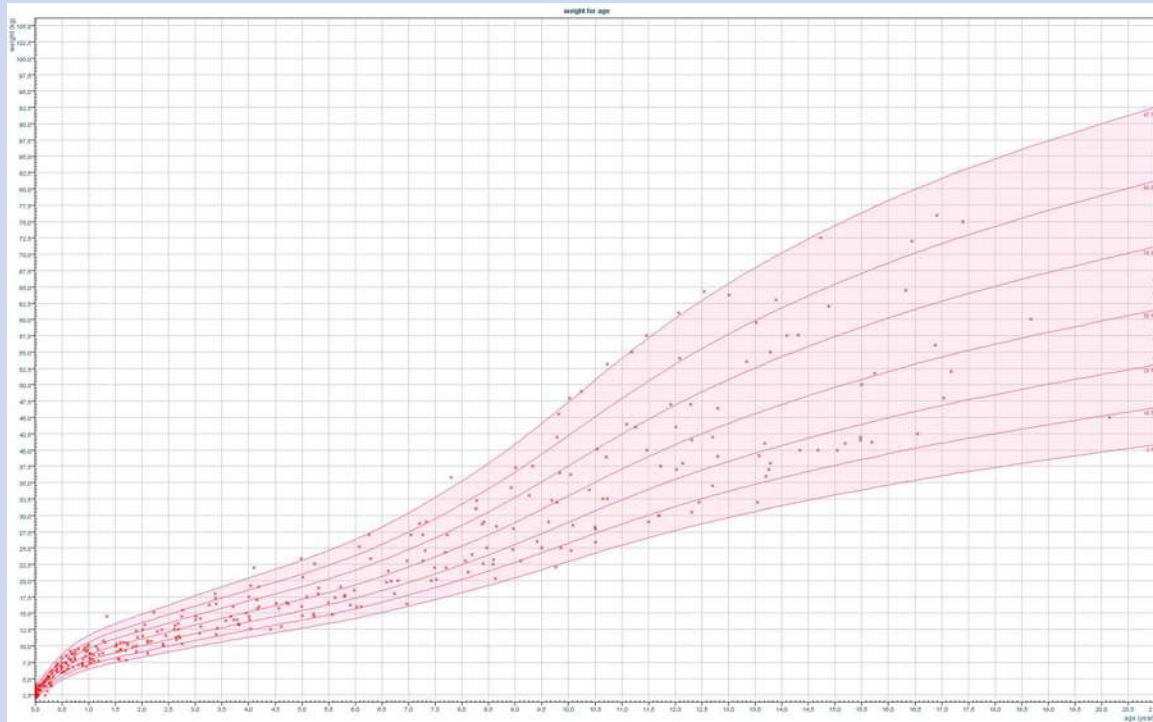


FIG. 6. Weight in females with RSTS, ages 0–21, showing individual data points.

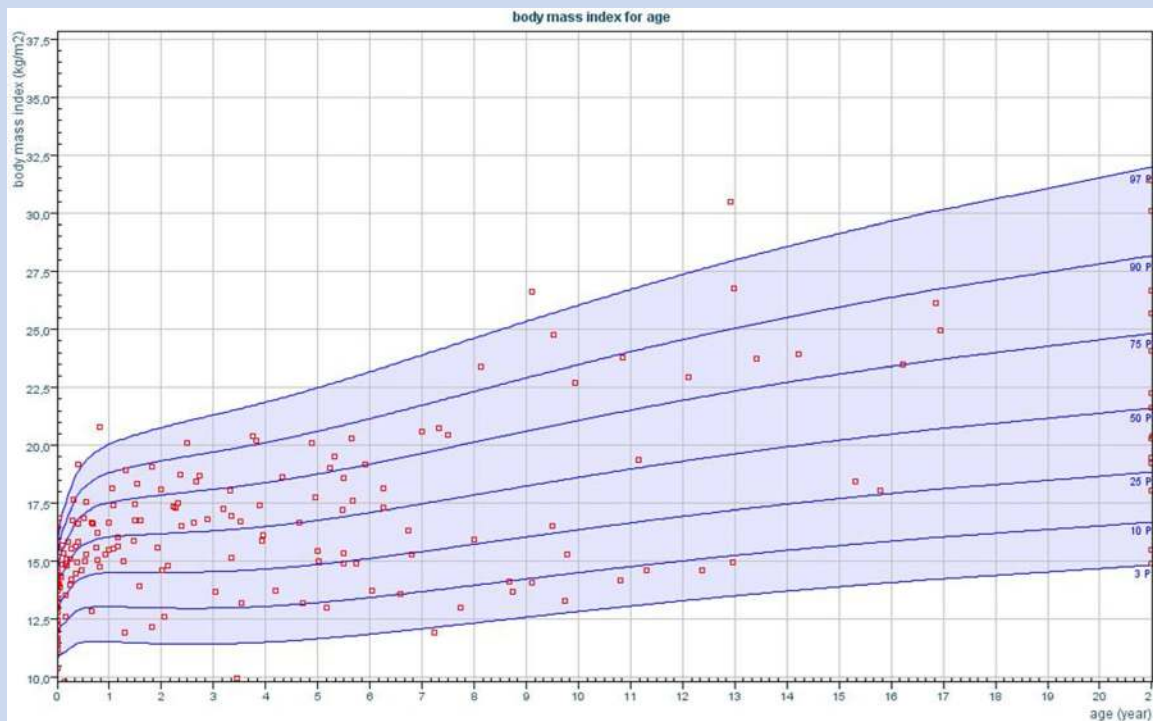


FIG. 7. BMI in males with RSTS, ages 0–21, showing individual data points.

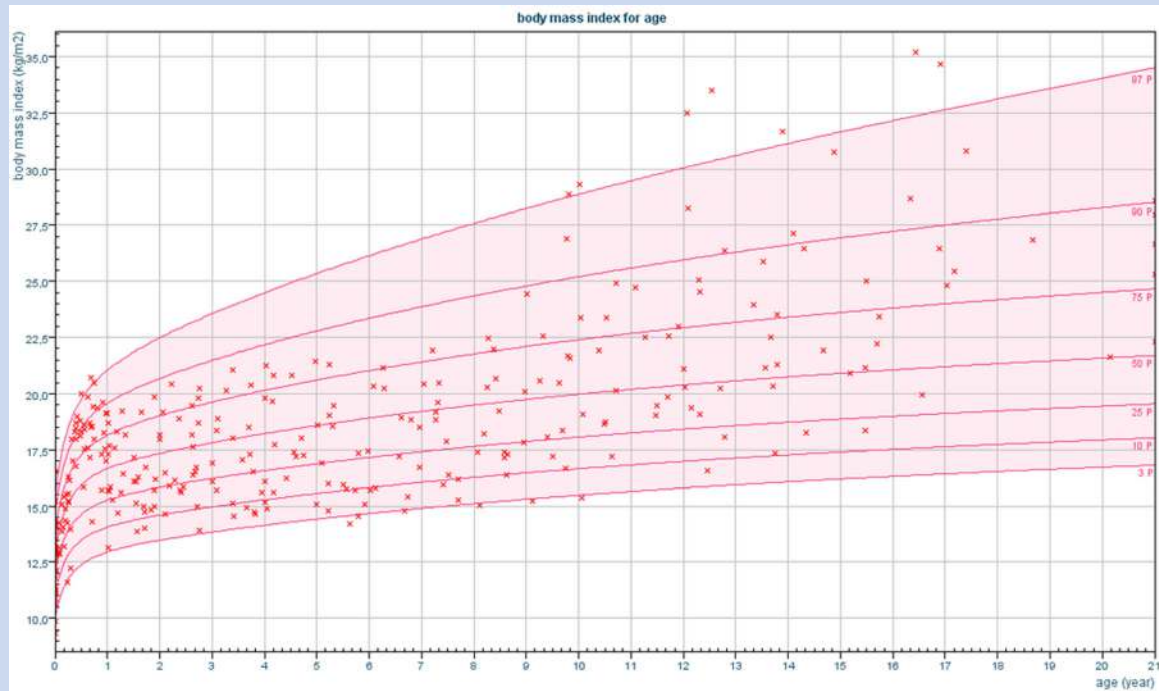


FIG. 8. BMI in females with RSTS, ages 0–21, showing individual data points.

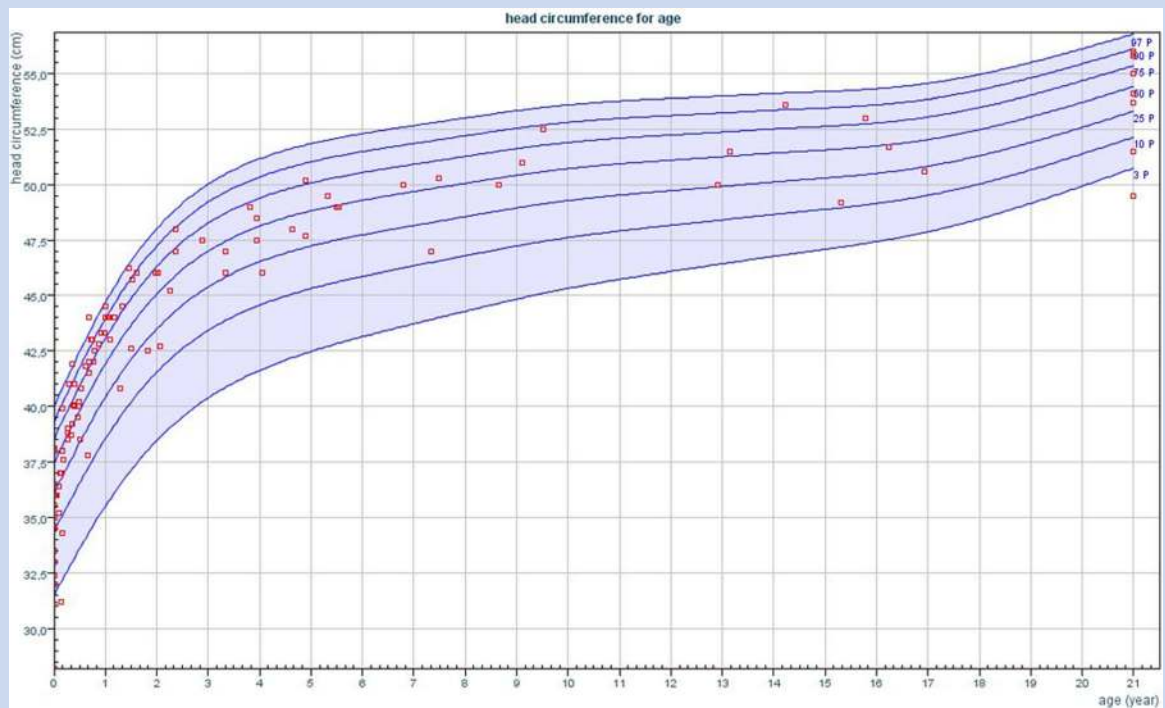


FIG. 9. Head circumference in males with RSTS, ages 0–21, showing individual data points.

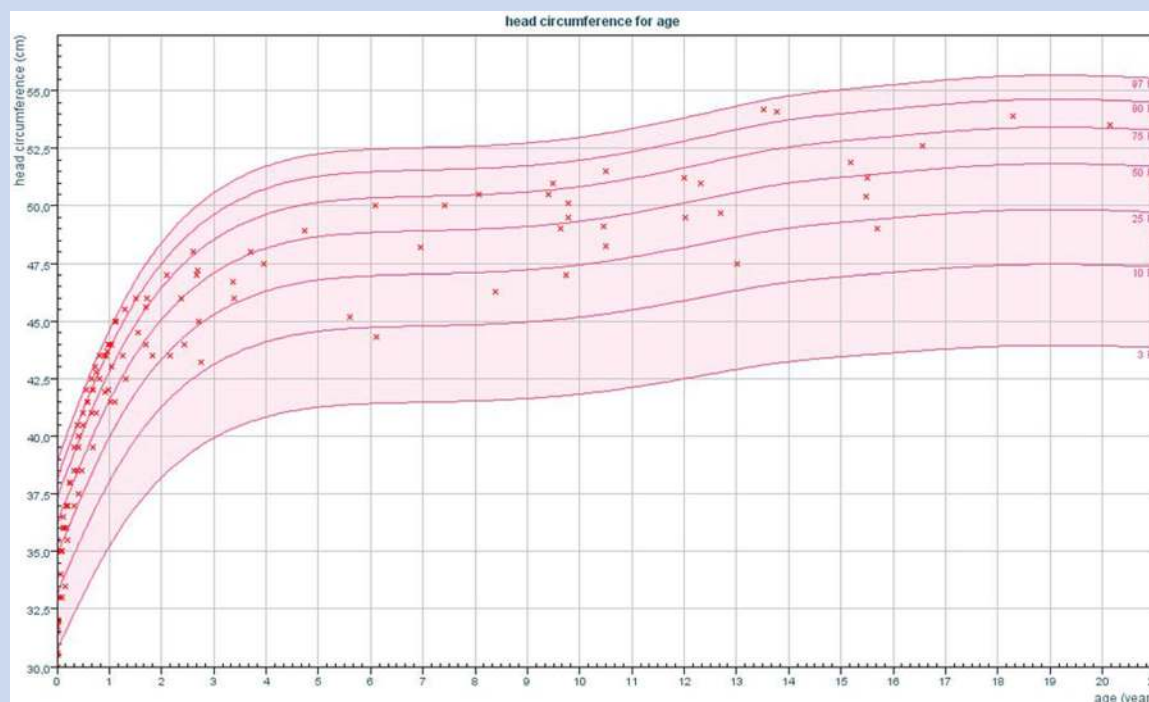


FIG. 10. Head circumference in females with RSTS, ages 0–21, showing individual data points.

(females) and 13 years (males) when it drops below -2.5 SDS of the general population (Figs. 3 and 4). We also show the absence of the growth spurt during adolescence, which adds to the reduced final height of male and female RSTS individuals. There is no clear final plateau in early adulthood which seems to indicate growth may continue after 18 years for a limited number of years. One of us (RCMH) has followed a male RSTS patient with an exceptional growth pattern, who was still growing at 35 years of age (bone age was 12 years at that time) for which no cause was found.

Compared to the 1990 RSTS growth curves, the present average final height in RSTS males (162.6 cm) is significantly higher ($P < 0.05$) than the 153.1 cm found in 1990. Possibly, the secular trend [Schönbeck et al., 2013] and misdiagnoses [Lowry, 1990] explain this difference. However, there is no significant difference in average final height for females; 146.7 (1990) versus 151.0 cm (± 7.0 cm) (present study) while the secular trend and misdiagnoses will have been present in females as well. We have no explanation for this difference. There is no statistical difference between adult weight in females and HC in males or females compared to the 1990 study population. The adult weight in males did increase significantly however (48.14 kg vs. 60.67 kg; $P = 0.019$). The present study is the first to evaluate BMI in RSTS patients. Males had a normal mean BMI of 21.90 ± 3.45 kg/m² at 21 years of age. Females had a high mean BMI at 21 years of age (21; 26.64 ± 5.5 kg/m²). The large difference in BMI between female RSTS individuals is mirrored in the large Standard Deviation (5.5 kg/m²).

A limitation of the present study remains the limited number of participants which is comparable to the number in the earlier

publication [Stevens et al., 1990]. The various corrections that were used to correct for secular trends and variation in country of origin, and the prerequisite that only molecularly confirmed individuals with RSTS were allowed to enter the study, allow the statement that although numbers are still small, all data that were used are reliable.

The present growth charts can be used to compare the growth of RSTS individuals for height, weight, BMI, and HC to growth in the general population. For RSTS individuals, the syndrome-specific growth charts can be used in managing problems related to growth. The present growth charts can be used worldwide but should be used with caution when studying RSTS individuals with other ethnic backgrounds. In such circumstances, it is usually advisable to change measurement into SDS scores which allow more meaningful use.

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