

## ORIGINAL ARTICLE

# Growth in achondroplasia: Development of height, weight, head circumference, and body mass index in a European cohort

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As growth references for achondroplasia are limited to reports from United States, Japan, Argentina, and Australia, the aim of this study was to construct growth references for height, weight, head circumference, and body mass index (BMI) from a European cohort of children with achondroplasia and to discuss the development of these anthropometric variables. A mix of cross-sectional and longitudinal, retrospective, and prospective data from 466 children with achondroplasia and 4,375 measuring occasions were modeled with generalized additive model for location, scale and shape (GAMLSS) to sex-specific references for ages 0 to 20 years. Loss in height position, that is, reduction in height standard deviation scores, occurred mainly during first 2 years of life while pubertal growth seemed normal if related to adult height. Adult height was 132 cm in boys and 124 cm in girls with a variability comparable to that of the general population and seems to be remarkably similar in most studies of children with achondroplasia. BMI had a syndrome-specific development that was not comparable to BMI development in the general population. Weight and BMI might be misleading when evaluating, for example, metabolic health in achondroplasia. Head circumference reached adult head size earlier than in the general population. Increased tempo of head circumference growth necessitates thus close clinical follow-up during first postnatal years.

## KEYWORDS

achondroplasia, BMI, GAMLSS, growth, head circumference, height, weight

## 1 | INTRODUCTION

An activating mutation of the FGFR3 (fibroblast growth factor receptor 3) causes major growth inhibition of the extremities and thus extreme short stature in achondroplasia. Growth in achondroplasia has been described by several authors (Murdoch et al., 1970; Nehme, Riseborough, & Tredwell, 1976; Wynne-Davies, Walsh, & Gormley, 1981) and growth curves have been published from the United States (Hoover-Fong, McGready, Schulze, Alade, & Scott, 2017; Hoover-Fong,

McGready, Schulze, Barnes, & Scott, 2007; Hoover-Fong, Schulze, McGready, Barnes, & Scott, 2008; Horton, Rotter, Rimo, Scott, & Hall, 1978), Japan (Tachibana, Suwa, Nishiyama, & Matsuda, 1997), Argentina (Del Pino, Fano, & Lejarraga, 2011), and Australia (Tofts, Das, Collins, & Burton, 2017). However, there are no recent European growth curves. The aim of this study was to construct growth references for height, weight, head circumference, and body mass index (BMI) from a European cohort of children with achondroplasia and to discuss the development of these anthropometric variables.

## 2 | MATERIALS AND METHODS

### 2.1 | Data collection

The dataset was a mix of cross-sectional and longitudinal data of children of European origin. The majority of measurements were prospectively conducted by the same observer (LN) mainly through 1998 to 2014 during routine clinical visits at the skeletal dysplasia clinic at the Department of Pediatrics at Karolinska University Hospital in Stockholm, Sweden and at annual meetings of German Association for People of Short Stature and their Families (Bundesverband Kleinwüchsige Menschen und ihre Familien e. V., BKMf). For children up to about 2 years of age, length was measured in supine position with legs extended and heels against a moveable board. Older children were measured in stretched standing position, with back and heels against the wall while looking straight ahead, using a stadiometer (Hyssna Measuring Equipment AB, Sweden). A calibrated digital scale was used for weight measurements with the child in light clothing and without shoes. A nondistensible tape was used for measuring head at its maximum circumference. Further measurements were collected retrospectively from birth records, child health, and school records. Data were also collected from colleagues in Denmark, Finland, Norway, and Sweden and in collaboration of Sweden's Association of Short stature (Föreningen för kortvuxna, DHR). Additional measurements from the same observer (LN) were available from another previous study (Hertel et al., 2005).

Diagnosis was made by genetic and/or clinical/radiological investigations.

### 2.2 | Data analysis

All measurements from adults, aged 20 to 40 years, were regarded as measurements at age 20 years. Related BMI measurements, that is, for ages beyond 20 years ( $n = 33$ ), were not higher than BMI at 20 years, and were therefore not excluded from the BMI reference. The growth pattern of each individual with several measurements was plotted to identify possible measurement errors, which were then excluded from the final dataset. Measurements during the first 12 months of life were excluded for those born prematurely, that is, before gestational week 37 (6 boys). Additional exclusion criteria were growth-promoting therapy such as growth hormone (10 boys/20 girls) or leg lengthening (7 boys/4 girls) and other conditions or diseases affecting growth (1 boy/3 girls). Measurements from individuals ( $n = 28$ ) with eight-plates (Zajonz et al., 2017) applied for correction or prevention of varus or valgus deformity of legs were not excluded. All head circumference measurements from children with shunts were excluded (6 boys/3 girls). Finally the dataset was trimmed for each participant only contributing one measurement to each predefined age group. A summary of exclusions can be found in Supporting Information Table 1.

Sex-specific growth references were modeled using generalized additive model for location, scale and shape (GAMLSS) (Rigby & Stasinopoulos, 2005) in R Version 3.2.3. The distribution of each anthropometric variable for age was summarized by three curves: Box-Cox power transformation (L), the median (M), and the coefficient of

TABLE 1 Mean/median and normal ranges for height, weight, head circumference, and BMI at selected ages

| Age<br>(years) | Height |              |       | Weight |              |        | Body mass index |        |              | Head circumference |              |       |              |      |      |      |      |      |      |      |      |      |      |      |
|----------------|--------|--------------|-------|--------|--------------|--------|-----------------|--------|--------------|--------------------|--------------|-------|--------------|------|------|------|------|------|------|------|------|------|------|------|
|                | Boys   |              | Girls | Boys   |              | Girls  | Boys            |        | Girls        | Boys               |              | Girls |              |      |      |      |      |      |      |      |      |      |      |      |
|                | Mean   | Normal range | Mean  | Median | Normal range | Median | Normal range    | Median | Normal range | Mean               | Normal range | Mean  | Normal range |      |      |      |      |      |      |      |      |      |      |      |
| 0              | 47.7   | 43.9         | 51.5  | 47.3   | 43.2         | 51.5   | 3.3             | 2.5    | 4.1          | 3.3                | 2.5          | 4.3   | 15.2         | 12.2 | 17.9 | 15.0 | 12.0 | 17.9 | 36.7 | 33.8 | 39.6 | 36.6 | 33.8 | 39.4 |
| 1              | 65.9   | 61.5         | 70.4  | 64.6   | 59.8         | 69.5   | 8.0             | 6.4    | 9.7          | 7.7                | 6.0          | 9.8   | 18.7         | 15.8 | 21.7 | 18.4 | 15.4 | 21.8 | 50.2 | 47.0 | 53.4 | 49.6 | 46.0 | 53.1 |
| 2              | 72.9   | 68.0         | 77.7  | 71.5   | 66.2         | 76.8   | 10.5            | 8.6    | 12.6         | 9.8                | 7.8          | 12.6  | 19.8         | 16.9 | 22.8 | 19.3 | 16.4 | 22.9 | 53.8 | 50.2 | 57.4 | 52.8 | 49.0 | 56.7 |
| 6              | 91.6   | 84.8         | 98.5  | 90.2   | 81.6         | 98.7   | 17.2            | 13.9   | 21.6         | 16.1               | 12.8         | 21.5  | 20.5         | 17.4 | 24.9 | 20.1 | 17.0 | 24.6 | 56.6 | 52.5 | 60.6 | 55.6 | 51.5 | 59.7 |
| 9              | 103.1  | 94.4         | 111.7 | 102.0  | 92.3         | 111.7  | 22.7            | 17.2   | 32.0         | 21.7               | 16.6         | 30.5  | 21.1         | 17.2 | 27.9 | 20.9 | 17.3 | 26.8 | 57.1 | 53.1 | 61.1 | 56.6 | 52.5 | 60.6 |
| 18             | 131.7  | 121.4        | 141.9 | 124.4  | 114.9        | 133.9  | 50.5            | 35.9   | 74.5         | 45.9               | 31.7         | 64.1  | 29.8         | 21.9 | 44.0 | 29.7 | 23.0 | 41.0 | 59.4 | 55.5 | 63.3 | 58.1 | 54.2 | 62.1 |
| 20             | 132.3  | 122.5        | 142.2 | 124.4  | 115.1        | 133.7  | 54.5            | 39.2   | 77.4         | 48.4               | 32.9         | 66.8  | 31.1         | 22.6 | 45.3 | 31.1 | 23.7 | 43.3 | 59.8 | 55.9 | 63.7 | 58.2 | 54.3 | 62.2 |

This table gives an overview of the values given in Supporting Information Tables 2–5. Normal ranges are defined as  $\pm 2$  SD.

variation (S) (Cole & Green, 1992). Final model choice was based on model fit, evaluated by QQ-plot, as well as appearance. For comparison to the general population, the WHO height reference (de Onis et al., 2007; WHO Multicenter Growth Reference Study Group, 2006) was used as well as the national British UK90 head circumference reference (Cole, Freeman, & Preece, 1998).

This study was approved by the Regional Ethical Review Board at Karolinska Institutet, Stockholm, Sweden.

### 3 | RESULTS

Growth data from 4,375 measuring occasions were collected for 210 boys and 256 girls. The total number of data points included in the data analysis was for length and height 1,767/2,051 (from 202 boys/252 girls), for weight 1,706/1,987 (from 190 boys/237 girls), for head circumference 1,203/1,413 (from 181 boys/229 girls), and for BMI 1,645/1,881 (from 186 boys/234 girls). Descriptive statistics and fitted values of L, M, and S for age are summarized for all variables in Supporting Information Tables 2–5. Normal ranges, defined as  $\pm 2$  SD, for height, weight, head circumference, and BMI at selected ages are summarized in Table 1.

Familial cases comprised 17% in the clinics and 7% in the support group participants (data were available for only 46% ( $n = 191$ ) of the total sample). Parental height was  $179.2 \pm 7.9$  cm (paternal) and  $166.7 \pm 7.0$  cm (maternal) for the sporadic cases.

#### 3.1 | Height development

Scatter plots of height with mean and normal ranges are shown per sex in Figure 1. Mean birth length was 47.7 cm for boys and 47.3 cm for girls. Also postnatal growth was relatively normal during the first months of life (data not shown) but thereafter growth velocity abruptly slowed down causing a major decrease in height position on the general population growth curve approaching  $-4.0$  standard deviation score (SDS) before 1 year of age and  $-5.0$  SDS at 2 years of age (Figure 2). This position was then maintained during childhood growth. Relative to the general population about 15 cm of height position was “lost” during the first 2 years of life and almost 23 cm during the first 5 years. This means that for boys about 33% of total height deficit at adulthood occurred during the first 2 years of life and about 51% before 5 years. Deficit for girls was about 37% and 59%, respectively.

During infancy and childhood, boys were approximately 1.5 cm taller than girls, but no sex difference was seen during 10 to 14 years of age. Thus, girls never became taller than boys during these pubertal ages like in the general population.

Almost one additional SDS in height position is lost during pubertal ages. No pubertal growth spurt was visible from annual height increments of the total data cohort; that is, the differences between mean values (data not shown). However, inspection of individual growth patterns often revealed a clear acceleration during early pubertal ages; that is, around 12 years for boys and 10 years for girls. Total height gain between these early pubertal ages and

final height was 18.5 cm in boys and 17.8 cm in girls (data available for 17 boys and 24 girls) or 14.2/14.5% of adult height. Pubertal growth ranged from 14 to 25 cm in boys and 12 to 27 cm in girls, which was 10% to 19% and 9% to 20% of adult height, respectively. Using smoothed mean height values of the entire cohort, corresponding height gain was 18.7 cm for both sexes or 14.2/15.1% of respective adult height.

There were no signs of deviating maturational tempo in late adolescence (data for evaluating age at which adult height was attained was available for 13 boys and 20 girls). Adult height was  $132.3 \pm 4.9$  cm in males and  $124.4 \pm 4.6$  cm in females, resulting in a sex difference of 7.9 cm. Total average height deficit compared to the general population was thus 45 cm for males and 40 cm for females, resulting in an adult height of roughly  $-6.0$  SDS for both sexes.

A positive association between parental height and final adult height was found (Figure 3).

#### 3.2 | Weight and BMI

Scatter plots of weight and BMI with median and normal ranges are shown in Figures 4 and 5. Median birth weight was 3.324 g for boys and 3.302 g for girls with normal ranges covering about 1.6 kg (from 2.476 g to 4.109 g) and 1.9 kg (from 2.456 g to 4.311 g), respectively. Weight at birth is normal,  $-0.1$  SDS for boys and  $+0.2$  SDS for girls, but weight position falls to  $-1.5$  SDS during the first year of life. Although, median weight was lower in girls during both childhood and prepubertal ages, variability was more pronounced for girls. For instance at 2 and 6 years of age, normal ranges covered 4.0 and 7.7 kg for boys but 4.8 and 8.8 kg for girls. Weight dramatically increased in a small group of boys ( $n = 5$ ) from early school ages, which was evaluated as unhealthy. Related measurements were therefore not included in the weight and BMI reference. Median adult weight at 20 years was 54.5 kg for males and 48.4 kg for females with normal ranges covering 38.1 and 33.9 kg, respectively.

The growth deficit in height cannot easily be translated or compared to weight due to the greatly distorted ratio between trunk and legs, which also changes with age, and possibly also increased head size. BMI for age is likewise misleading in its absolute value. The absolute BMI value becomes considerably larger in achondroplasia compared to the general population due to pronounced body disproportion with short legs. At birth, BMI was  $15.2/15.0$  kg/m<sup>2</sup> with a normal range of 12.2 to 17.9 kg/m<sup>2</sup> in boys and 12.0 to 17.9 kg/m<sup>2</sup> in girls. BMI increased gradually until the age of 3 years and stayed thereafter constant during prepubertal ages at about  $20.5/20.1$  kg/m<sup>2</sup>. The infancy peak and adiposity rebound, as typical for the general population (Faenza, Wang, Fruhbeck, Garruti, & Portincasa, 2016; Rolland-Cachera & Peneau, 2013), was thus not present. Adult BMI at 20 years of age was  $31.1$  kg/m<sup>2</sup> in both sexes with normal ranges of 22.6 to 45.3 kg/m<sup>2</sup> in males and 23.7 to 43.3 kg/m<sup>2</sup> in females.

Sex differences in median BMI development were thus only minor but variability was somewhat higher in girls during the first years of life with more girls at lower end of distribution than boys.

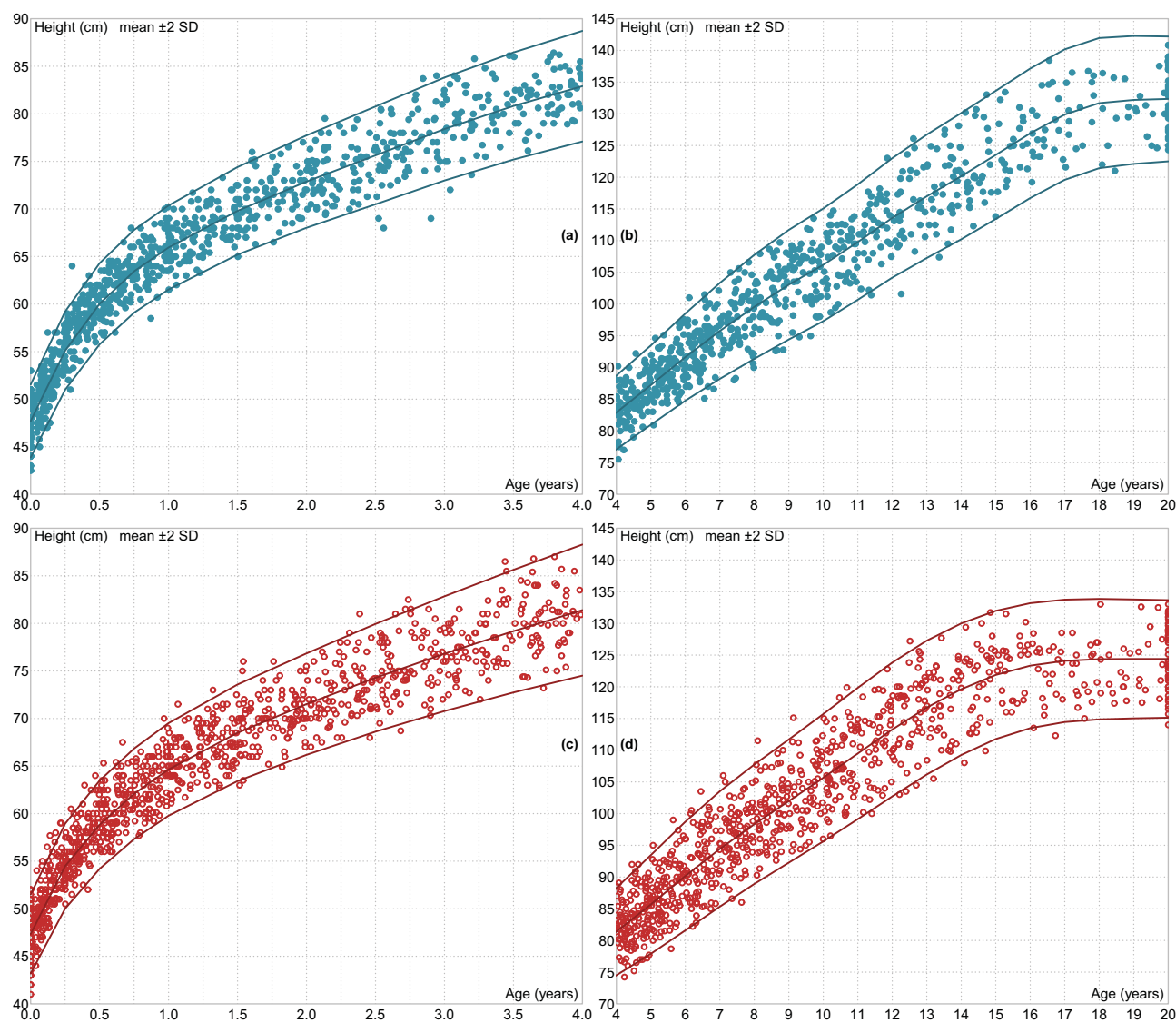


**FIGURE 1** Height for age in achondroplasia: Scatter plot and normal ranges, defined as mean  $\pm$  2 SD, for height of 1,767 male measurements (202 boys), (a) 0–4 years and (b) 4–20 years, and of 2,051 female measurements (252 girls), (c) 0–4 years and (d) 4–20 years [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

### 3.3 | Head circumference development

Scatter plot of head circumference with mean and normal ranges are shown per sex in Figure 6 and comparison to the general population at selected ages in Table 2. Macrocephaly is typical for achondroplasia but at birth head circumference was only marginally increased at 36.7 cm for boys and 36.6 cm for girls. During the first year head circumference increased by 13.5/13.0 cm boys/girls and at 2 years of age head circumference was 53.8/52.8 cm. Adult head circumference was  $59.8 \pm 1.9$  cm for males and  $58.2 \pm 2.0$  cm for females.

Compared to the general population, head circumference in achondroplasia accelerated postnatally faster to a maximal position at 2 years; in boys from  $+1.2$  to  $+2.7$  SDS and in girls  $+1.7$  to  $+3.2$  SDS (Figure 7a). About 90% of adult head circumference was achieved for males and females by 2 years of age, almost 1 year earlier than in the general population. This also means that there were fewer adults than infants and children with extreme head sizes. As shown in Figure 7b,

the proportion of cases with head circumference above normal range, that is, above  $+2$  SDS, decreased from 70% at 2 years of age to less than 45% at adult ages. Similarly, the number of cases above  $+3$  SDS decreased from 45% to less than 25% (data not shown).

Evaluating a longitudinal subset (data available for 195 cases, note all without shunt) for pattern in tempo of adaption to final head circumference showed 7% of cases with an early acceleration with secondary adaptation (downwards), 26% showed early acceleration without any adaptation, 23% showed neither acceleration or adaptation and 13% showed no acceleration but secondary adaptation while 32% followed the median. There seemed thus to be four different head growth patterns.

## 4 | DISCUSSION

Compared to other common skeletal dysplasias, for example, many clinical entities in the type I and type II collagen spectra, the auxological

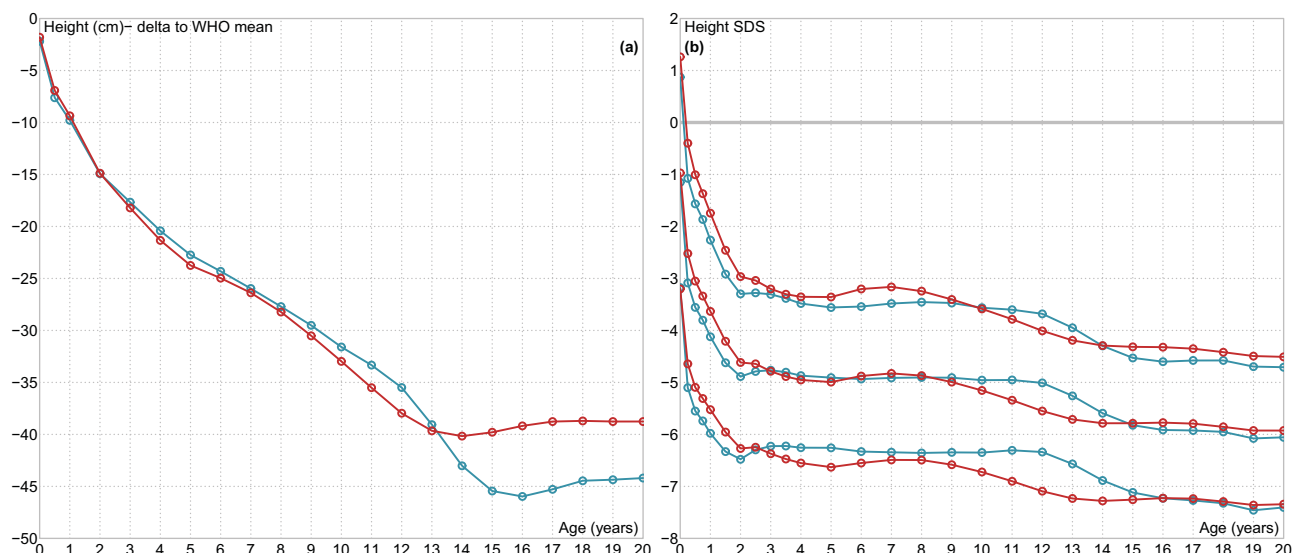


**FIGURE 2** Height development in achondroplasia compared to the general population (WHO reference): expressed as (a) loss of height in cm and (b) as height SDS, mean  $\pm 2$  SD [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

phenotype in achondroplasia is homogenous with low variability in height and body proportion both within and between families. Variability for height and head circumference, expressed as coefficient of variation, fluctuates around 3% to 5% at all ages, which is comparable to that in the general population. It could be argued that this homogeneity is due to the fact that the constitutively activating but ligand dependent mutation in *FGFR3* is almost universally

uniform and likely to confer near maximal negative influence on growth of the extremities (for review see Foldynova-Trantirkova, Wilcox, & Krejci, 2012; Qi et al., 2014). This will then leave for only marginal modulating effect from parental or background population stature. The negative influence on growth of the trunk, in contrast, is minimal. While leg length corresponds to  $-8$  to  $-9$  SDS in adulthood, trunk length, measured by sitting height, is only to  $-1$  SDS (Merker et al., 2018; Nehme et al., 1976). It seems therefore obvious that NPR2 and BMPR signaling in the growth plates is not counteracted nearly to the same extent by the increased *FGFR3* activity in the vertebra. The decrease in adult total height is 40–45 cm from this activating mutation (Figure 5). A major loss of *FGFR3* activity as in human CATSHL syndrome may, on the contrary, give an extra 15–20 cm gain over population mean (Makrythanasis et al., 2014; Toydemir et al., 2006).

This study describes the growth pattern in achondroplasia, covering also timing and magnitude of deviation from the general population, which seems to be similar to previous studies from other geographical regions. For comparison of height with other achondroplasia references see Supporting Information Table 6.

#### 4.1 | Near-normal intrauterine growth

Birth length is only slightly reduced as reported previously (Horton et al., 1978; Tachibana et al., 1997) demonstrating that intrauterine growth is only marginally affected. Taking into consideration that slightly early delivery should be overrepresented due to elective cesarean section when the condition is detected by prenatal ultrasound, this would reinforce the notion of normal intrauterine growth. Normally fetal growth amounts to 0.8 cm/week at the end of gestation (Sankilampi, Hannila, Saari, Gissler, & Dunkel, 2013). Increased skull circumference in achondroplasia could, however, contribute slightly to length.

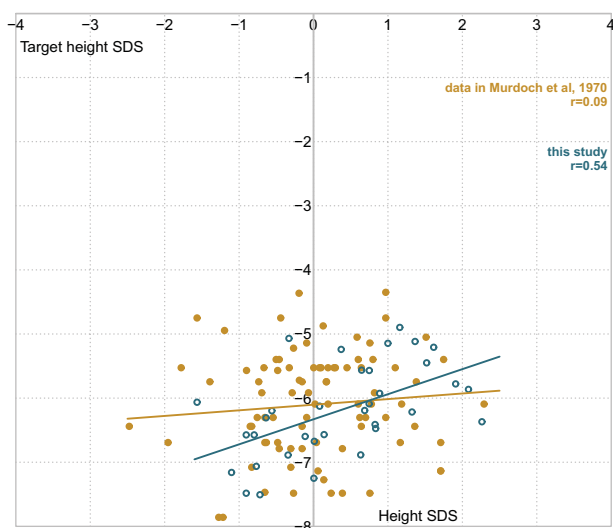


**FIGURE 3** Mid-parental (target) height versus adult height for sporadic cases in this cohort (circles,  $n = 34$ ,  $r = .54$ ,  $p$ -value  $< .001$ , final adult height =  $-6.2$  SDS, parental height =  $+0.4$  SDS) and in data obtained from a U.S. sample (Murdoch et al., 1970) (dots,  $n = 86$ ,  $r = .09$ ,  $p$ -value = .4, final adult height =  $-6.1$  SDS, parental height =  $0.0$  SDS). Data from both cohorts were converted to SDS relative to WHO reference (de Onis et al., 2007). An association between target and adult height was reported from Argentina ( $r = .4$ ,  $p$ -value  $n/a$ ,  $n = 19$ , adult height measurements from ages 16.0 to 19.1 years in boys and 14.1 to 19.2 years in girls) (Del Pino & Fano, 2013) [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

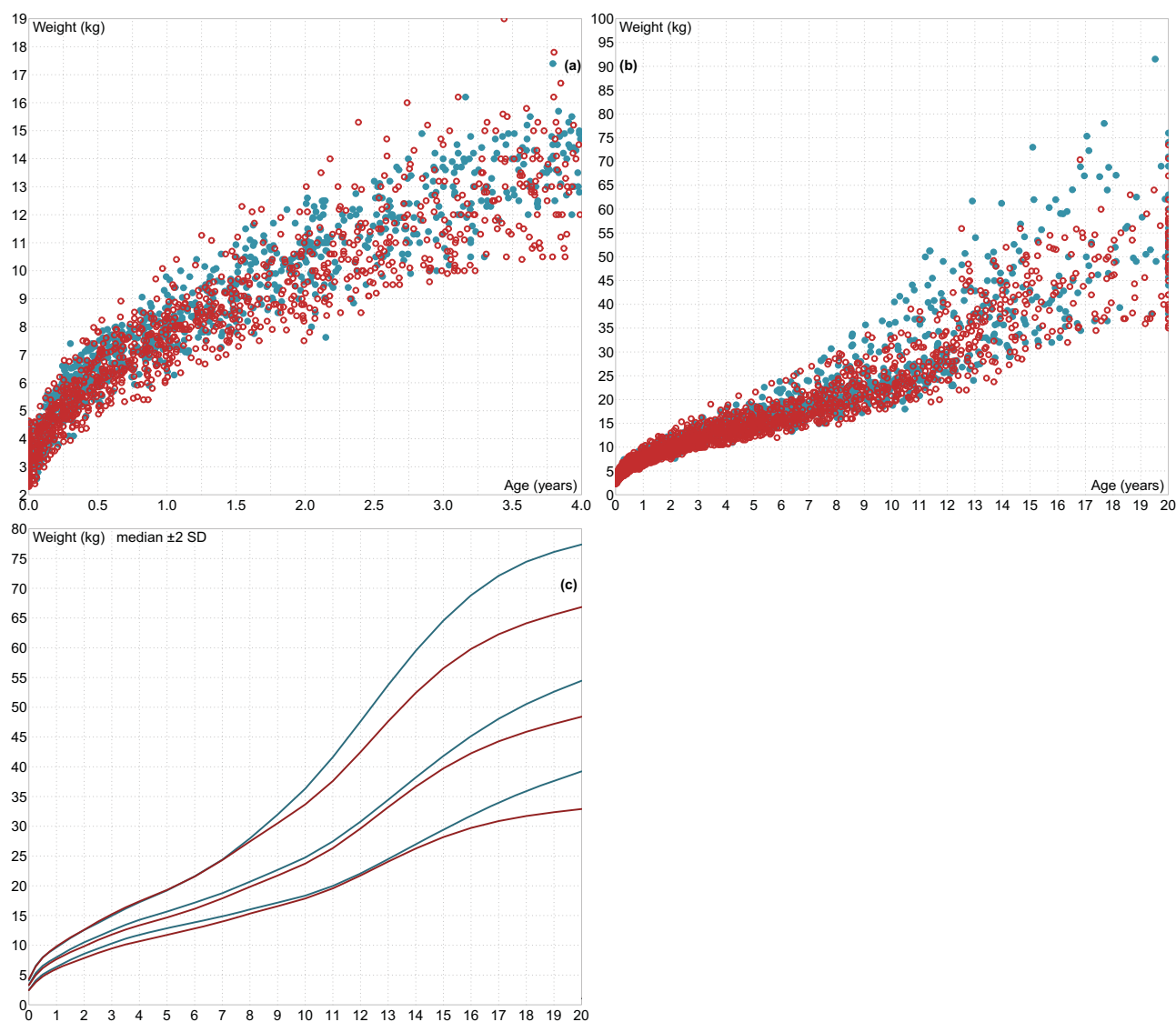


**FIGURE 4** Weight for age in achondroplasia: Scatter plot for weight of 1,706 male measurements (190 boys) and 1,987 female measurements (237 girls) in (a) 0–4 years and (b) 0–20 years of age as well as (c) median and  $\pm 2$  SD curve for boys (blue) and girls (red) [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

## 4.2 | Extensive loss in height position during the first years of life

In contrast to other forms of skeletal dysplasia, for example, pseudoachondroplasia, where height position is gradually lost over the whole growth period (Horton, Hall, Scott, Pyeritz, & Rimoin, 1982), growth inhibition in achondroplasia seems to occur more abruptly during the first years of life. The reason for this remains unclear. FGFR3 signaling might be more dominant during this period (infancy) or might play a different role than in later growth periods. Further studies are therefore needed to investigate the role of FGFR3 during all stages of the growth process.

## 4.3 | Normal pubertal growth when related to adult height

Total pubertal growth in centimeters is, for the general population, statistically similar between individuals of average height and those that

are short, at least within ranges between  $-2$  and  $-3$  SDS (Mulligan, Bailey, Voss, & Betts, 1999). This also implies that height position in SDS at pubertal start will also be the position of final adult height for those that have average ages for puberty. Clinical experience speaks for normal timing of pubertal start in achondroplasia but height SDS development indicates that the pubertal growth component is subnormal resulting in height position on the growth curve being further compromised over pubertal ages into adulthood.

Since height develops at an extreme in achondroplasia, that is, 5 to 7 SD below normal mean, a possible height spurt might be difficult to distinguish from inspecting the individual's measurements plotted on standard growth chart. Also other authors found no evidence of pubertal spurt in achondroplasia (Hoover-Fong et al., 2017). Yet, total height increase from early pubertal ages, that is, 12 years for boys and 10 years for girls, to adult height seems to be comparable to that in the general population when related to adult height (males/females: 14.2/

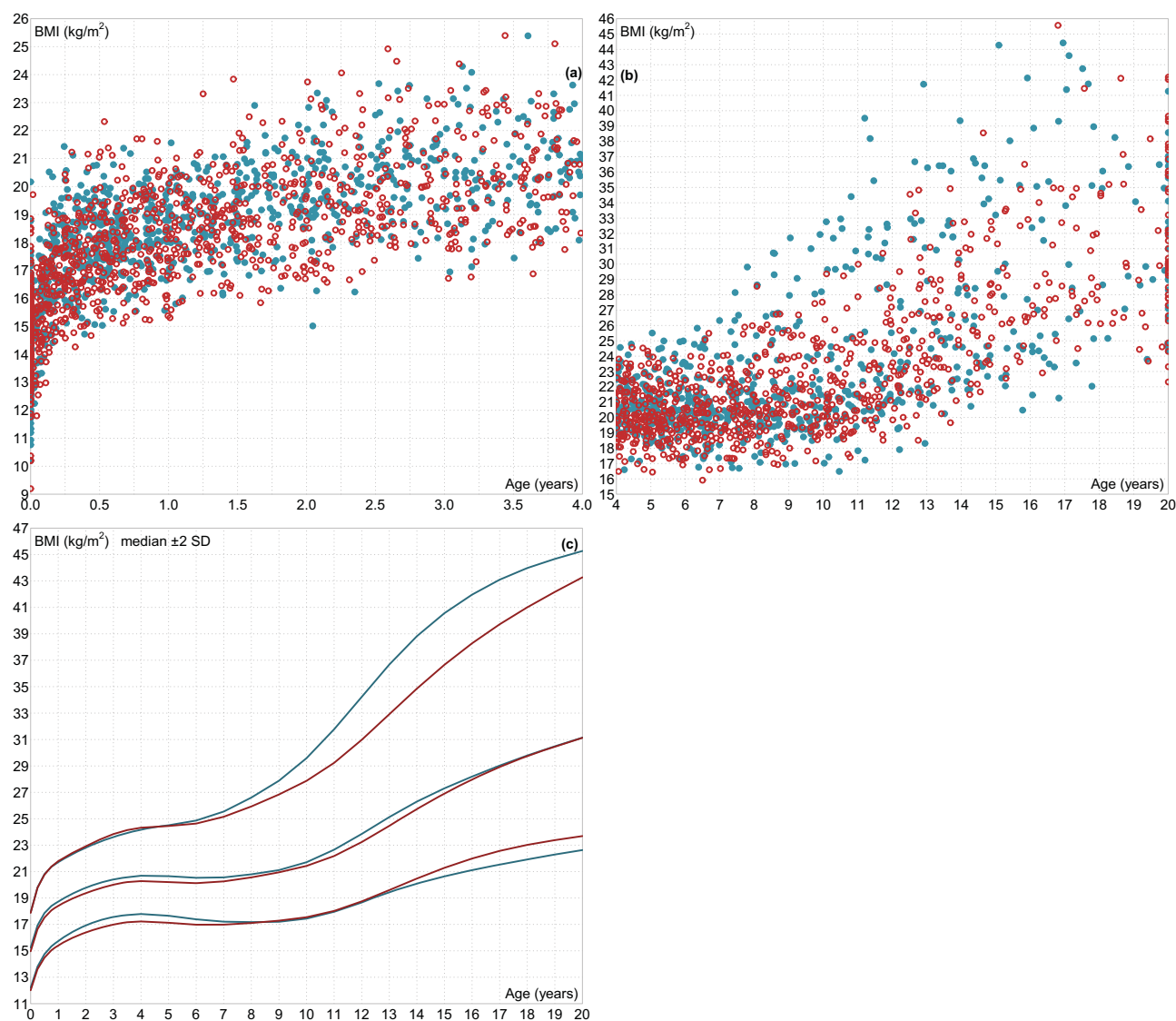


**FIGURE 5** Body mass index for age in achondroplasia: Scatter plot for BMI of 1,645 male measurements (186 boys) and 1,881 female measurements (234 girls) in (a) 0–4 years and (b) 0–20 years of age as well as (c) median and  $\pm 2$  SD curve for boys (blue) and girls (red) [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

15.1% in achondroplasia compared to 15.6/15.0% in the general population). Also evaluation of individual longitudinal measurements in this material confirms the presence of a pubertal growth spurt. Normal pubertal timing and presence of growth spurt has also been observed in American (Horton et al., 1978) and in Argentinian adolescents with achondroplasia (Mariana del Pino, personal communication 2017).

It is thus questionable how pubertal growth component should be evaluated in achondroplasia and other extreme short stature conditions. Note that a pubertal spurt in achondroplasia might mainly be seen in sitting height as sex steroids influence the growth of spine more than long bones.

#### 4.4 | Homogenous adult height

Despite differences in height of background populations, ages for reporting adult height and data collection periods, adult height is remarkably similar between achondroplasia growth studies (Table 3).

Exceptions might be recent U.S. (Hoover-Fong et al., 2017) and Argentinian references (Del Pino et al., 2011), although, it is not clear whether final adult height was captured in these studies. Adult height in a recently published U.S. report (Hoover-Fong et al., 2017) is clearly lower than in previous U.S. studies (Horton et al., 1978; Murdoch et al., 1970). Secular trends in height or the influence of background population, which is primarily dependent on changes in leg length (Bogin & Varela-Silva, 2010; Tanner, Hayashi, Preece, & Cameron, 1982), is not or is only marginally detectable in achondroplasia with its maximal growth inhibition of extremities.

#### 4.5 | Normal target height but unclear association to achondroplasia height

Parental height of sporadic achondroplasia cases is normal, both in earlier reports (Murdoch et al., 1970; Nehme et al., 1976) and in this European cohort. Target height in this study is, however, higher than in the U.S.

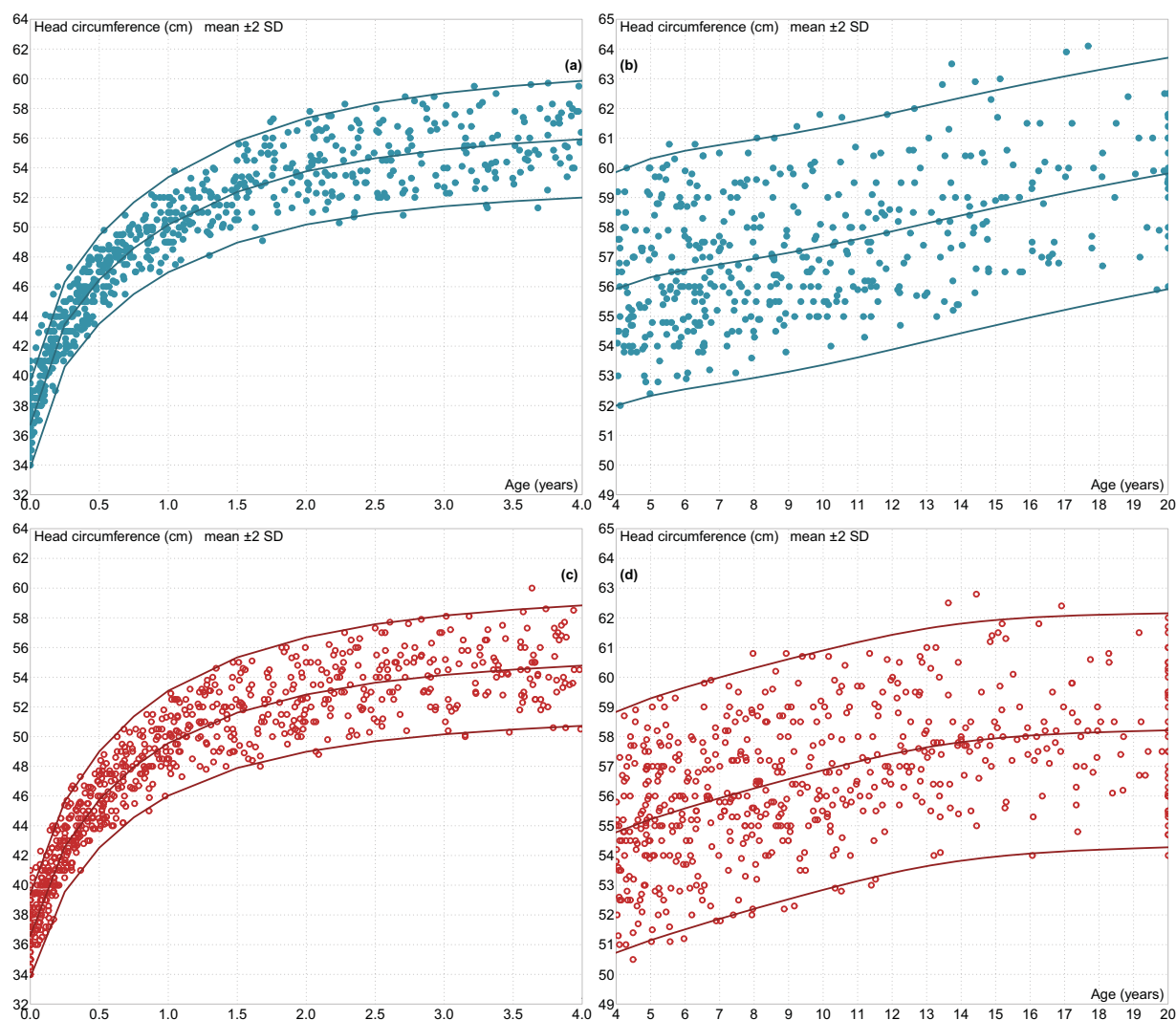


**FIGURE 6** Head circumference for age in achondroplasia: Scatter plot and normal ranges, defined as mean  $\pm$  2 SD, for head circumference of 1,203 male measurements (181 boys), (a) 0–4 years and (b) 4–20 years, and of 1,413 female measurements (229 girls), (c) 0–4 years and (d) 4–20 years [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

**TABLE 2** Head circumference in achondroplasia and in the general population at selected ages

| Age (years) | Achondroplasia |       |                | UK90 |       |                |
|-------------|----------------|-------|----------------|------|-------|----------------|
|             | Boys           | Girls | Sex difference | Boys | Girls | Sex difference |
| 0           | 36.7           | 36.6  | 0.1            | 35.2 | 34.5  | 0.7            |
| 1           | 50.2           | 49.6  | 0.6            | 47.7 | 46.5  | 1.2            |
| 2           | 53.8           | 52.8  | 1.0            | 50.2 | 49.0  | 1.2            |
| 6           | 56.6           | 55.6  | 1.0            | 53.2 | 52.2  | 1.0            |
| 9           | 57.1           | 56.6  | 0.5            | 54.2 | 53.4  | 0.8            |
| 18          | 59.4           | 58.1  | 1.3            | 57.3 | 55.5  | 1.8            |
| 20          | 59.8           | 58.2  | 1.6            |      |       |                |

Head circumference in achondroplasia shows less sex differences than found in the background/general population.

report from 1970 (Murdoch et al., 1970), which also found no or only minor association between parental and final adult height. From Argentina an association between target and achondroplasia height was reported, although, ages at adult height measurements contributing ranged from 16.0 to 19.1 years in boys and 14.1 to 19.2 years in girls (Del Pino & Fano, 2013). Results on association between target height and achondroplasia height are thus contradictory, but seemingly lower than in the general population or what is reported for in sex chromosome disorders. Mid-parental height-offspring correlation is about 0.6 in both normal males and females as well as in Klinefelter's and Turner's syndrome (Brook, Gasser, Werder, Prader, & Vanderschueren-Lodewyck, 1977).

#### 4.6 | Weight and increased BMI might be misleading in achondroplasia

Compared to other short stature skeletal dysplasias, such as for instance collagen type II diseases, individuals with achondroplasia seem

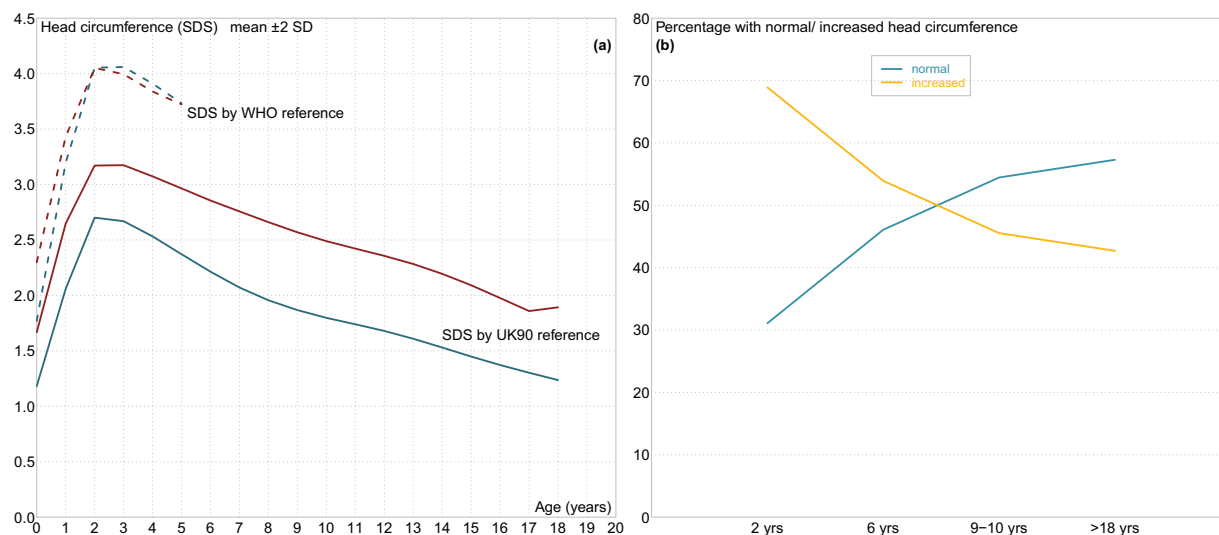


**FIGURE 7** Head circumference development in achondroplasia compared to the general population: (a) expressed as SDS relative to WHO reference (WHO Multicenter Growth Reference Study Group, 2006) (dashed) and national UK90 reference (Cole et al., 1998) (line) in boys (blue) and girls (red) Data in the WHO reference only cover ages 0–4 years. (b) Percentage of individuals within/beyond  $\pm 2$  SD at 2 years ( $n = 119$ ), at 6 years ( $n = 102$ ), at 9–10 years ( $n = 101$ ), >18 years ( $n = 89$ ). Head circumference SDS expressed relative to UK90 reference (Cole et al., 1998). [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

to have greater predisposition to accumulate fat tissue. In this cohort, there are children, especially boys, who developed gross overweight (data not shown). Previous studies emphasize that there is a risk of excessive weight gain and that obesity is more common in achondroplasia (Hecht et al., 1988). Yet, it is questionable how obesity should be defined in a population with extreme short stature and explicit body disproportions. Various indicators of body fat; for example, mean weight-for-age, weight-for-height, weight/height<sup>2</sup> (BMI), and triceps skinfold thickness (Hecht et al., 1988) or correlation between

abdominal, scapular, and triceps skinfold thickness and height or weight (Hunter, Hecht, & Scott, 1996) as well as BMI, various skinfold thicknesses and body circumferences (Owen et al., 1990) were investigated without any clear, decisive conclusion regarding risk limits for overweight and obesity.

Evaluating weight-for-height might also be misleading without taking the effect of age into account; since the metabolic situation of an adult with height of 130 cm would be wrongly compared to that of a prepubertal child of average stature.

**TABLE 3** Adult height, in cm and SDS relative to WHO reference, in various achondroplasia cohorts

| Region/study                       | Age (years) | Adult height cm (mean $\pm$ SD) |                  |                | Adult height SDS |       | Sample size (male/female) |
|------------------------------------|-------------|---------------------------------|------------------|----------------|------------------|-------|---------------------------|
|                                    |             | Boys                            | Girls            | Sex difference | Boys             | Girls |                           |
| Northern Europe (this study)       | 20+         | 132.3 $\pm$ 4.9                 | 124.4 $\pm$ 4.6  | 8 cm           | −6.1             | −5.9  | 91 (36/55)                |
| USA (Murdoch et al., 1970)         | 16+         | 131.6 $\pm$ 5.6                 | 123.5 $\pm$ 6.0  | 8 cm           | −6.2             | −6.1  | 108 (52/56)               |
| USA (Horton et al., 1978)          | 18          | 130.7 $\pm$ 6.5                 | 125.2 $\pm$ 6.0  | 6 cm           | −6.1             | −5.7  | n/a                       |
| USA (Hoover-Fong et al., 2017)     | 15.8+       | 126.7 $\pm$ 10.1                | 119.9 $\pm$ 10.4 | 7 cm           | −5.8             | −6.2  | 16 (7/9)                  |
| USA and Canada (Owen et al., 1990) | 19+         | 135.2 $\pm$ 5.6                 | 125.9 $\pm$ 3.9  | 9 cm           | −5.7             | −5.7  | 27 (16/11)                |
| UK (Wynne-Davies et al., 1981)     | n/a         | 132.2 $\pm$ 1.6                 | 123.9 $\pm$ 1.1  | 8 cm           | −6.1             | −6.0  | n/a <sup>a</sup>          |
| Japan (Tachibana et al., 1997)     | 17.8        | 130.4 $\pm$ 5.9                 | 124.0 $\pm$ 5.3  | 6 cm           | −6.1             | −5.9  | n/a                       |
| Argentina (Del Pino et al., 2011)  | 15+         | 128.3 $\pm$ 7.7                 | 119.9 $\pm$ 7.2  | 8 cm           | −6.4             | −6.5  | 54 (21/33)                |
| Australia (Tofts et al., 2017)     | 18          | 134 $\pm$ n/a                   | 125 $\pm$ n/a    | 9 cm           | −5.6             | −5.8  | 6 (2/4)                   |

Adult height in males and females in cm and SDS relative to WHO reference (de Onis et al., 2007). If data were not published in text or tabled format, values were read from illustrations in the respective publication. Missing information is indicated as n/a. The age column indicates how final height was defined (ages contributing to adult height). Adult height is remarkably similar in most achondroplasia cohorts despite differences in height of background populations and data collection period. Note that adult height calculations in some studies are based on small samples.

<sup>a</sup>Visually read from figure  $n = 17$  (3 male/14 female >17.5 years).

In addition, reduced ability to physical activities due to the short legs and genu varum together with aberrant hip joint anatomy and claudication due to spinal stenosis can easily influence accumulation of excess weight causing additional disability.

#### 4.7 | Significance of obesity regarding metabolic health

Since trunk size is nearly normal in achondroplasia, waist circumference would be a more realistic measure when following weight status from a metabolic perspective. Definition of obesity in achondroplasia should thus take into consideration location of fat tissue where abdominal distribution of fat as measured by waist circumference would have different metabolic impact than fat accumulation in thigh and buttocks. Different distribution of fat tissue thus complicates how BMI values should be interpreted if health issues are in focus. Reports have been showing that metabolic variables like blood glucose, triglyceride, free fatty acid, insulin and thyroid hormone are normal in achondroplasia despite many individuals having waist/hip ratio comparable with abdominal obesity (Owen et al., 1990). Also, resting metabolic rate is increased per unit body weight or for an identical fat-free mass compared to normal sized individuals (Owen et al., 1990). This would hypothetically be in line with increased insulin sensitivity and resistance toward development of metabolic disease despite increased prevalence of truncal obesity. Clinical experiences and patient surveys also show decreased occurrence of diabetes type 2 in achondroplasia (Julie Hoover-Fong, personal communication 2017). The possible link to increased FGFR3 signaling remains to be investigated. Weight and BMI need to be used with caution and with other information when evaluating metabolic health in achondroplasia.

Mortality related to metabolic and cardiovascular morbidity has been reported for achondroplasia. While overall mortality is increased at all ages (Hecht, Francomano, Horton, & Annegers, 1987; Wynn, King, Gambello, Waller, & Hecht, 2007), deaths due to cardiovascular causes is increased between ages 25 and 54 years, also coinciding with marked spinal stenosis (Hecht et al., 1987). Heart disease was stated to count for 32% of all deaths in achondroplasia population (Wynn et al., 2007). Yet, no precedent medical consultations that could be related to increased risk for early death was generally recorded for these cases and thus mortality cause seems not to be supported by precedent clinical illness data. Rather than metabolic disease-related cardiovascular causes, these could hypothetically be "sudden death" incidents due to chronic sleep hypoventilation and apnea, at times with resulting secondary pulmonary hypertension. Contributing to nighttime hypoventilation with hypoxia and hypercapnia should, to varying degree, be small upper airway dimensions including a narrow throat, compression of brainstem at craniocervical junction as well as dysregulation of breathing mechanics due to narrowness of foramina in the skull base through which cranial nerves regulating respiration (Nn. vagus, glossopharyngeus and hypoglossus) pass.

#### 4.8 | Increased tempo in head growth

Tempo in head growth is obviously increased in achondroplasia approaching adult size earlier. Data from the United States (Horton et al., 1978) are

generally similar ( $\pm 0.5$  cm) to our study but suggest that already 94% of head circumference in females is achieved at 2 years of age.

Interesting to observe is a smaller sex difference in achondroplasia than found in the general population, resulting in girls with higher SDS position. Head circumference development seems thus to be more homogenous with less pronounced biologic differences between sexes. These findings represent most probably FGFR3 influence on CNS growth while differentiation and growth of the skull bone would be a secondary adaptation. Microcephaly is, for instance, reported for cases of decreased or abolished FGFR3 signaling as in human CATSHL syndrome (Toydemir et al., 2006); see also (Makrythanasis et al., 2014). In achondroplasia, increased liquor pressure caused by communicating hydrocephalus may contribute to the increased skull size and varying adaption to increased intracranial pressure could, theoretically, explain part of different tempo in head growth. As suggested by Baujat, Legeai-Mallet, Finidori, Cormier-Daire, and Le Merrer (2008), an internal hydrocephalus might develop due to increased venous pressure caused by narrow foramina in the skull base.

Activating mutations in FGF receptors may, rather than increased skull growth, give reduced growth of skull base and/or craniosynostosis; for example, FGFR1 (osteoglophonic and Pfeiffer syndromes), FGFR2 (Crouzon syndrome), and FGFR3 (thanatophoric dysplasia type 2). Morphometric studies of CNS via MR imaging confirmed increased brain tissue volume (Thompson et al., 1999). Extreme values for head circumference are probably often avoided by closer follow-up and evaluation for shunting (Baujat et al., 2008). An example of the effect from shunting is shown in Figure 8.

#### 4.9 | Different head growth patterns

Interesting to note is the clinical impression of Judith Hall (in Horton et al., 1978) who suggests that there are three different growth patterns for head circumference in achondroplasia; one in which the head is large at birth and grows parallel to the mean at a high position, a second in which the head is normal or slightly large at birth but grows dramatically crossing centiles before leveling off, and a third with gradually increasing head size during the first year (Horton et al., 1978). Similar observations could be made in our sample.

#### 4.10 | Sporadic versus familial cases and overlapping phenotype to hypochondroplasia

The prevalence of achondroplasia ranges from 0.13 to 0.64 per 10,000, depending on study design and setting (Waller et al., 2008). The pathogenic variant in sporadic cases is regarded to be uniformly paternal (Risch, Reich, Wishnick, & McCarthy, 1987). Its high occurrence, in relative measures, might be caused by a mutational sensitive position in the gene together with a survival advantage for germ cell clones carrying an activating FGFR mutation (Goriely et al., 2005, 2009; Juul et al., 2007). Percentage of familial and sporadic cases was calculated from a subcohort only, that is, is based on those for which data were available for both parents. The rate of sporadic cases might therefore not be representative but is expected to be lower.

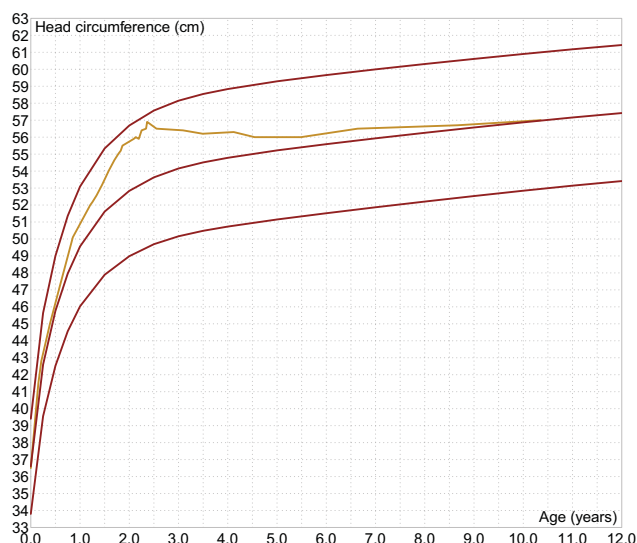


**FIGURE 8** Head circumference development in a girl illustrating effect of shunting at 2.5 years of age [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

Diagnosis was made by genetic and/or clinical/radiological investigation. Although the features of achondroplasia are distinctive (Baujat et al., 2008), it cannot be excluded that the present cohort contains a few cases of individuals with hypochondroplasia and a severe phenotype (Heuertz et al., 2006; Wynne-Davies et al., 1981; Xue et al., 2014). Achondroplasia and hypochondroplasia are overlapping in auxological and radiological phenotype and severe hypochondroplasia cases can also exhibit significant craniocervical narrowings (Hagenäs, personal observation).

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## CONFLICT OF INTEREST

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## SUPPORTING INFORMATION

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