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Growth reference charts for children with hypochondroplasia

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Abstract

Hypochondroplasia (HCH) is a rare skeletal dysplasia causing mild short stature. There is a paucity of growth reference charts for this population. Anthropometric data were collected to generate height, weight, and head circumference (HC) growth reference charts for children with a diagnosis of HCH. Mixed longitudinal anthropometric data and genetic analysis results were collected from 14 European specialized skeletal dysplasia centers. Growth charts were generated using Generalized Additive Models for Location, Scale, and Shape. Measurements for height (983), weight (896), and HC (389) were collected from 188 (79 female)

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children with a diagnosis of HCH aged 0–18 years. Of the 84 children who underwent genetic testing, a pathogenic variant in *FGFR3* was identified in 92% (77). The data were used to generate growth references for height, weight, and HC, plotted as charts with seven centiles from 2nd to 98th, for ages 0–4 and 0–16 years. HCH-specific growth charts are important in the clinical care of these children. They help to identify if other comorbidities are present that affect growth and development and serve as an important benchmark for any prospective interventional research studies and trials.

KEYWORDS
anthropometry, growth, head circumference, height, hypochondroplasia, weight

1 | INTRODUCTION

Hypochondroplasia (HCH) (OMIM #146000) is a rare condition characterized by disproportionate short stature. The incidence is stated to be 1 in 100,000, though this is likely to be an underestimate given the variability with which it presents (Almeida et al., 2009; Grigelioniené et al., 2000; Prinster et al., 1998; Riepe et al., 2005; Rousseau et al., 1996; Saunders et al., 2006; Shin et al., 2005; Song et al., 2012). HCH is diagnosed clinically through short stature that is more pronounced in the limbs, mild rhizomelia, relative macrocephaly, and occasionally tibial bowing. Radiographic features are subtle, often not appearing until after the age of 2 years, when failure of the interpedicular distances of the lumbar vertebral pedicles to widen and mild prominence on the deltoid muscle insertion become evident (Prinster et al., 1998; Riepe et al., 2005; Rousseau et al., 1996; Shin et al., 2005; Song et al., 2012). However, these findings are not unique to HCH, and molecular testing is an important diagnostic adjunct when clinically suspected. Heterozygous pathogenic variants in *FGFR3*, encoding fibroblast growth factor receptor type 3, underlie HCH (Bellus et al., 1995), with the recurrent 1620C>A and 1620C>G (p.Asn540Lys) variants affecting the proximal tyrosine kinase domain (TK1) accounting for about 70% of cases (Bellus et al., 1995; Prinster et al., 1998; Ramaswami et al., 1998; Rousseau et al., 1996); other rarer pathogenic variants have also been described (Heuertz et al., 2006). For the remaining individuals with a clinical and radiographic diagnosis of HCH, the underlying molecular cause is undefined. HCH may be dominantly transmitted or represent a new mutation in seemingly sporadic cases. Rarely gonadal mosaicism resulting in unexpected recurrence has also been observed (Ramaswami et al., 1998).

Since *FGFR3* is expressed in the proliferative chondrocytes of the growth plate cartilage, functional disruption of this protein alters endochondral ossification (Davidson et al., 2005). Indeed, HCH is allelic with achondroplasia and thanatophoric dysplasia, also the consequence of FGFR3-signaling activation forming a spectrum of severity with HCH being the mildest and thanatophoric dysplasia which is characterized by neonatal lethality (Naski et al., 1996).

A number of studies have sought to describe the impact on growth conferred through HCH (Appan et al., 1990; Bridges et al., 1991; Çetin et al., 2018; Del Pino et al., 2017; Meyer et al., 2003; Pinto et al., 2014; Rothenbuhler et al., 2012; Saunders et al., 2006). Others have demonstrated a differential effect on growth depending upon the underlying *FGFR3* variant (Friez & Wilson, 2008; Heuertz et al., 2006; Rothenbuhler et al., 2012). As a rule, HCH does not present clinically until late infancy, when growth velocity falls away from the norm, though there is evidence that it can be detected prenatally (Sabir et al., 2021). The growth pattern is different from that seen in children with achondroplasia though, necessitating the need for HCH-specific growth charts to monitor growth and to estimate final height. Therefore, we sought to generate such charts using growth data from specialized bone centers looking after children with HCH.

2 | MATERIALS AND METHODS

2.1 | Study design, inclusion, and exclusion criteria

Anthropometry data from 188 (163 HCH from the United Kingdom, 79/188 female) healthy children <18 years diagnosed with HCH were obtained from 18 specialist skeletal dysplasia centers, 14 from the United Kingdom, and 1 each from France, Germany, Ireland, and Sweden.

The diagnosis of HCH was based on established radiological and clinical criteria (Ramaswami et al., 1998). Centers were asked for the genetic diagnosis and in particular, stipulate if this was negative or not known. Centers put a variety of responses to the request for the genetic diagnosis and due to the long period of data collection and changes in nomenclature, responses varied (Table 1 gives details of the genetic information collected.). A pathogenic variant in *FGFR3* was found in 92% (77) of the 84 children who underwent genetic testing. Forty of the 84 had the classical 1620C>A or 1620C>G (p.Asn540Lys) pathogenic variant, while 35/84 were described as "positive" (without further specific details) or had other pathogenic variants associated with HCH; in 2/84 the variant was not specified.

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TABLE 1 Genetic results as reported by center in 188 individuals.

Variant type	Test outcome	Frequency
Classical variant	N540K	23
	c.1620C>A p.(Asn540Lys)	11
	c.1620C>G p.(Asn540Lys)	5
	C>G p.(Asn540Lys)	1
Other variant	Positive	19
	c.1617C>A p.(Ile539Met)	2
	c.1659C>A p.(Pro550His)	2
	c.817T>C p.(Phe273Val)	2
	c.914A>G p.(Tyr305Cys)	2
	c.1619A>G p.(Asn540Lys)	1
	c.172G>A p.(Glu58Lys)	1
	c.833A>G p.(Tyr278Cys)	1
	1620C	1
	K650N	1
	Lys650Gln	1
	N540S	1
	Y278C	1
	Substitution in exon 13 of FGFR3	1
	Substitution of Asn540Thr of FGFR3	1
–	Negative	7
–	Not tested	104

2.2 | Exclusions

1. Children with a chronic medical condition or comorbidity affecting growth.
2. Measurements in children after treatment with growth-enhancing medication including somatotrophin (measurements before treatment were included).
3. Measurements taken after leg lengthening operations (measurements before treatment were included).
4. Measurements from infants who were born preterm (before 37 weeks gestation).

2.3 | Data

Mixed longitudinal data on height (or length before standing), weight, and head circumference (HC) were collected for ages from birth to 18 years. Infant data were obtained from parent-held records. After excluding duplicates and outliers, there were 983, 896, and 389 measurements for height, weight, and HC, respectively (Table 2). The number of height measurements per patient (median: 2, interquartile range: 1–6) varied widely from 1 (for 85 children) to 20 or more for 14 children, and 1 individual had 46 measurements; the 23 most frequently measured children contributed half of all measurements. Data were included from historical records of affected adults and over 80% of the children were from the United Kingdom. Figure 1 shows plots of height, weight, and HC versus age by sex, where the points indicate the numbers of measurements and the joining lines show repeated measurements in individuals reflecting the number of individuals.

TABLE 2 Numbers of subjects and measurements by age group and sex.

	Males	Females	Total
0–4 years			
Subjects	42	43	85
Height	269	203	472
Weight	270	201	471
Head circumference	180	111	291
0–18 years			
Subjects	109	79	188
Height	574	409	983
Weight	523	373	896
Head circumference	248	141	389
0–4 years (restricted to children with typical HCH FGFR3 variant)			
Subjects	17	18	35
Height	151	120	271
Weight	151	122	273
Head circumference	98	88	186

2.4 | Statistical analysis

The LMS method was used to summarize height, weight, and HC data as growth centile curves (Cole & Green, 1992). This method creates reference centiles by treating all the data as cross-sectional, including data for individuals with multiple measurements. It estimates the median (M), coefficient of variation (S), and skewness (L) of the data as smooth curves plotted against age, from which selected reference centile curves can be calculated and plotted. Data can also be converted to SDS scores. Fitting was done using the Generalized Additive Models for Location, Scale, and Shape package in R, where the LMS method corresponds to the BCCGo family (Rigby & Stasinopoulos, 2014). The sexes were modeled separately, with the M curve a penalized spline in age$^{0.25}$ and the S curve a constant. For height and HC, the L curve was constrained to unity, that is, a normal distribution at all ages, while for weight, it was estimated as a constant across age to model skewness. Charts were plotted for age 0–16 years, and also for 0–4 years to focus on the preschool period where the diagnosis is often made. The centiles were truncated at 16 rather than 18 years as the fitted curves, particularly for weight, continued to rise after age 16 rather than plateauing—this was due to the paucity of data at older ages. The selected centiles were spaced two thirds of an SD apart (Cole, 1994) seven centiles from the 2nd through to the 98th centile. They were plotted

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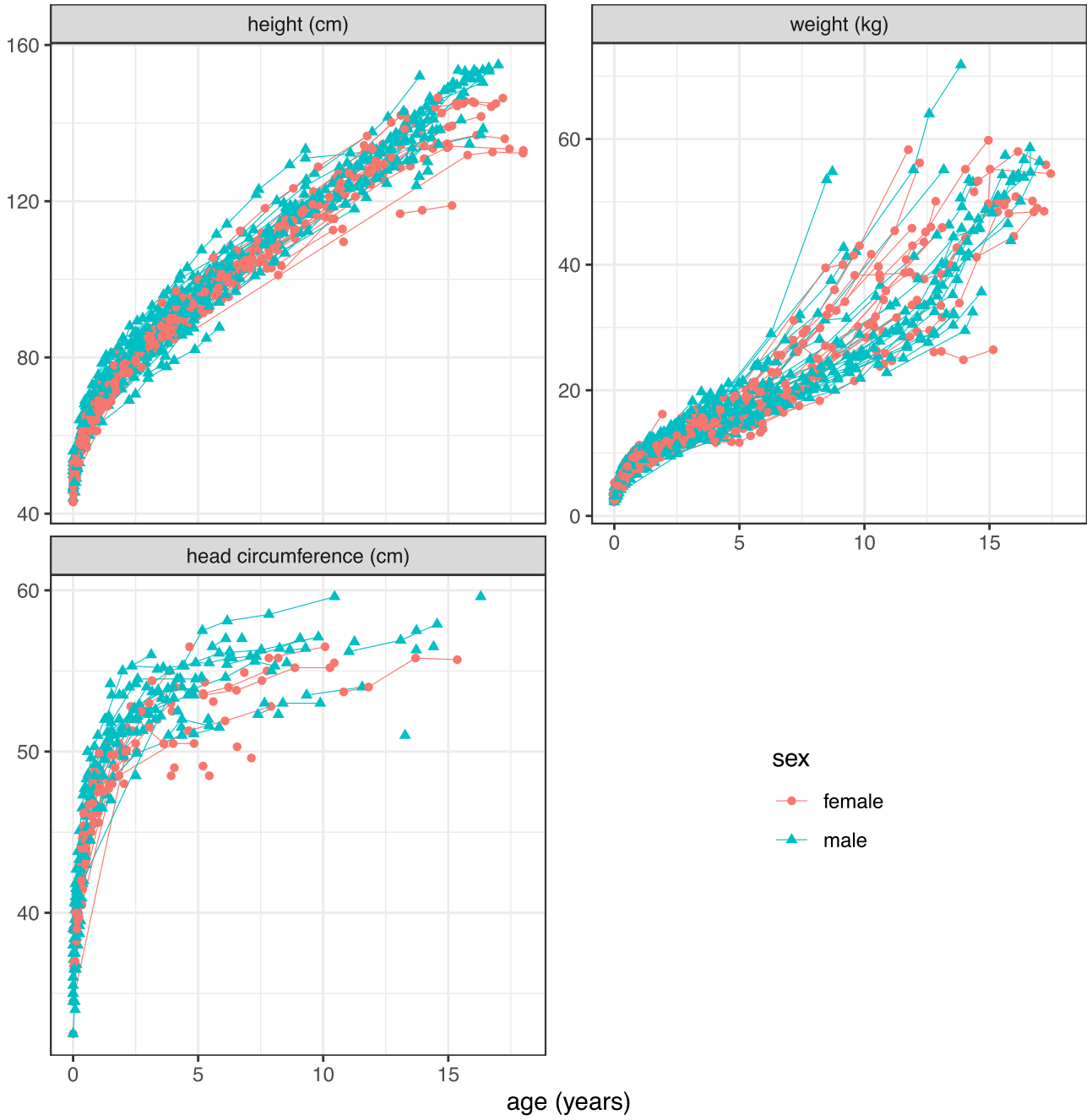


FIGURE 1 Plots of the anthropometry data used to construct the HCH growth charts, by sex. Lines join repeated measurements in individuals. HCH, hypochondroplasia.

superimposed on the corresponding centiles from the British 1990 reference (Cole et al., 1998) to allow comparison with the unaffected population.

2.5 | Consent

Pseudo-anonymized data from contributing centers were collected with written family consent for the use of growth measurements to generate growth charts.

3 | RESULTS

3.1 | Growth from birth to 4 years

Figure 2 shows seven-centile growth charts by sex for height, weight, and HC from birth to age 4 years, with the HCH centiles in color and the British 1990 (UK90) centiles in gray. By 1 year of age, length is already significantly reduced compared to those of the UK90 population, with three quarters of girls and half the boys below the 2nd centile. By 4 years, over 90% and 75% of HCH girls and boys,

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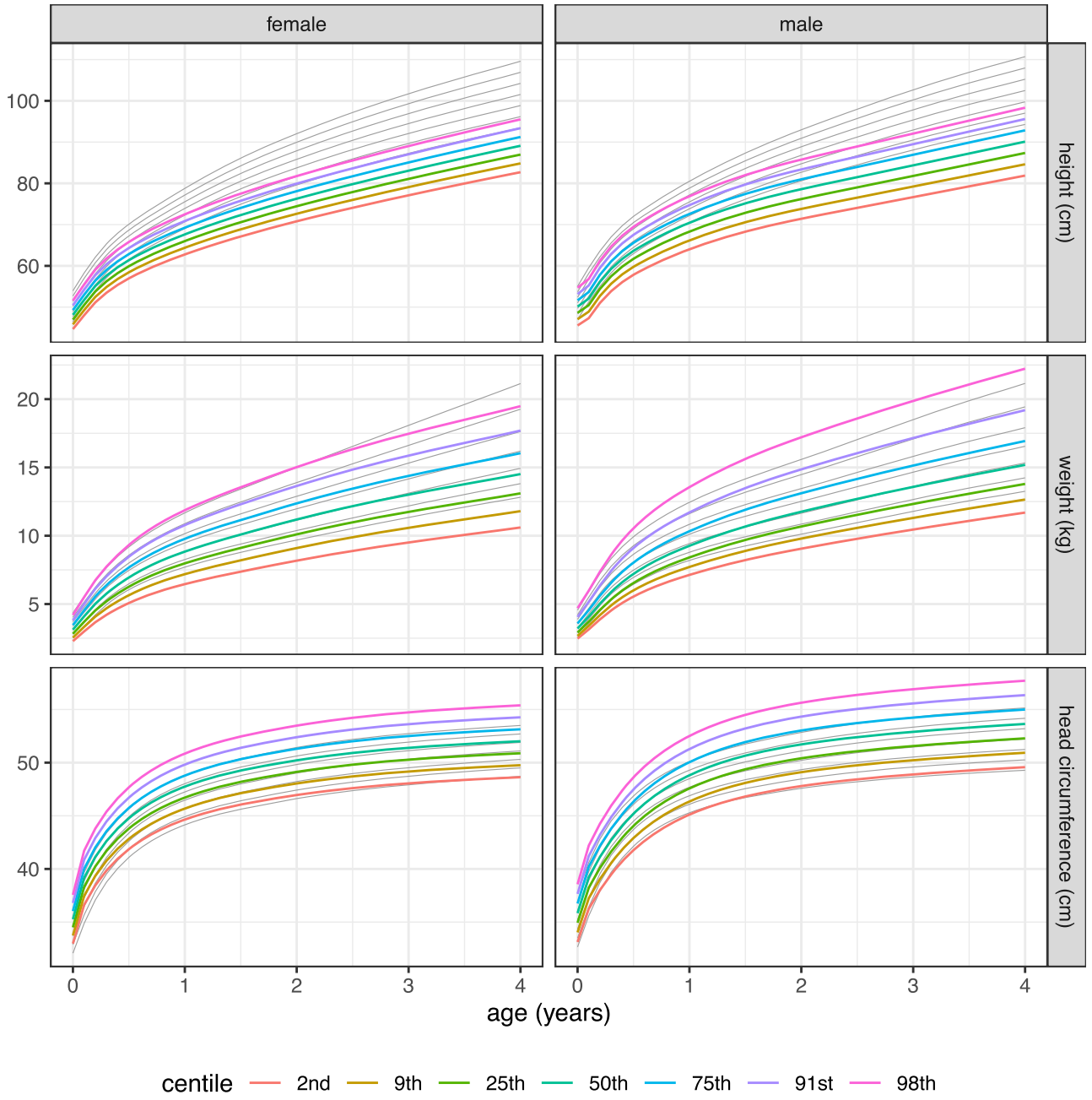


FIGURE 2 Centile charts for height, weight, and head circumference in children with HCH aged 0–4 years, by sex (in color). The gray centiles are the corresponding centiles from the British 1990 reference (Cole et al., 1998). The seven centiles are spaced two thirds of a *Z*-score apart. HCH, hypochondroplasia.

respectively, are below the 2nd on the UK90 centiles with the 50th centile height values corresponding to *Z*-scores of −3.1 and −3.0 in the background population (Table 3). The discrepancy in height is more pronounced at the age of 16 years as demonstrated by the 50th centile for height, having a corresponding *Z*-score of −3.9 and −3.3 in females and males, respectively.

In contrast, median weight is similar for HCH and non-HCH with the 50th centile corresponding to within 1 *Z*-score at all ages. The lack of corresponding compromise in weight suggests that weight is disproportionate to height in this population compared to unaffected individuals.

Like weight, the HC centiles show substantial overlap between affected and unaffected children, with 50th centile measurement compared to UK90 corresponding to within 1 *Z*-score. In addition, among affected children, the variability is much greater for boys than girls at all ages. Contrary to the literature stating macrocephaly in HCH, this lack of distinction from the background population means that a large HC is not a strong distinguishing feature for clinical diagnostic purposes. However, the HC may be deemed macrocephalic relative to height.

Figure 4 shows the same charts for ages 0–4 in the subset of children with a typical HCH *FGFR3* variant (c.1620C>A, c.1620C>G,

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TABLE 3 50th centile value and corresponding *Z*-scores for height, weight, and head circumferences of HCH individuals at age 4, 10, and 16 years.

Age (years)	Sex	Height		Weight (kg)		Head circumference	
		HCH 50th centile value (cm)	UK90 *Z*-score	HCH 50th centile value (kg)	UK90 *Z*-score	HCH 50th centile value (cm)	UK90 *Z*-score
4	Female	89.1	−3.1	14.5	−0.9	52.0	0.8
	Male	90.1	−3.0	15.2	−0.8	53.6	1.0
10	Female	120	−2.9	31.7	−0.1	54.7	0.8
	Male	121	−2.8	27.1	−1.0	55.7	0.8
16	Female	139	−3.9	48.8	−0.9	56.1	0.5
	Male	148	−3.3	52.0	−1.0	57.2	0.4

Abbreviation: HCH, hypochondroplasia.

and/or p.Asn540Lys)—see Table 1 for the numbers of individuals and measurements. The gray background centiles are the HCH centiles from Figure 2, and they confirm that the classic variant centiles are similar to those for the whole cohort. The one exception is for weight in girls, where those with the classic variant are much heavier at all ages—and given that they contribute to both sets of centiles, the contrast would be even greater compared to those without the classic variant. The same does not apply to boys, where the two sets of weight centiles are very similar.

3.2 | Growth from birth to 16 years

Figure 3 shows the corresponding growth charts for ages 0–16 years. Past age 4, the height centiles continue to be much lower than for unaffected individuals. At age 16 years, the height and weight centiles continue to rise rather than starting to plateau, and this is probably due to there being few data past age 16 (Figure 1). For this reason, the centiles are truncated at age 16. In contrast, the HC centiles, despite being based on minimal data past age 10, reflect the UK90 centiles.

4 | DISCUSSION

This study presents growth data for children with a diagnosis of HCH. This is the largest anthropometric database for HCH currently reported and draws from a European background population. The growth data are similar to a South American (Arenas et al., 2018) cohort of 57 children with HCH which demonstrates that the growth of most of the children was below the third centile in comparison to the background population. The European background population is taller than the South American population, where the mean final adult height was 130.8 and 143.6 cm in females and males compared to 139.0 and 148.0 cm at the age of 16 years in females and males in these growth charts. This highlights the importance of using an appropriate chart with as similar a background population as possible when plotting growth data. Similar to our cohort, the South American group also had a paucity of growth data in children greater than 15 years of age, rendering the charts beyond this age inaccurate (Arenas et al., 2018).

Condition-specific growth charts are particularly important when the diagnosis is based primarily on clinical and radiological grounds. A comparison to the unaffected population is helpful both in the clinical setting when speaking to families and when looking at growth patterns.

As expected, the greatest deviation from the growth charts of unaffected individuals is found during infancy, when height velocity should be greatest. This pattern is seen in achondroplasia and other skeletal dysplasia conditions (Hoover-Fong, Schulze, et al., 2021). The second period where there is greater discrepancy with non-HCH children is in puberty, with a notable absence of the pubertal growth spurt. The lack of growth acceleration during puberty is a feature in many skeletal dysplasias, but the mechanism behind the lack of responsiveness to sex hormones remains poorly defined. Like achondroplasia, there is a disproportionate increase in weight compared to height but unlike achondroplasia, the HC is not significantly increased compared to the non-HCH population; however, there still exists a relative macrocephaly if a HC/height ratio for age was compared (Hoover-Fong, Alade, et al., 2021). Obesity is an important morbidity in conditions of short stature as it impacts joints, spine, mobility, and quality of life. The pattern of a high weight relative to height with a wide variation of measurements was also noted in achondroplasia (Hoover-Fong, Alade, et al., 2021). It remains unclear how genetic factors in FGFR3-related conditions play a role in weight gain; nevertheless, a focus on healthy living should be particularly emphasized from diagnosis and reinforced throughout childhood.

There were several challenges when collating data for this study. Generating growth charts for healthy children with rare disorders means that there is a paucity of growth data available, and so to overcome this, a multicenter collaboration was established and data were obtained retrospectively from medical centers and parent-held records. Data were also sourced from some old hospital records and databases when genetic confirmation was not available, so it is possible that some

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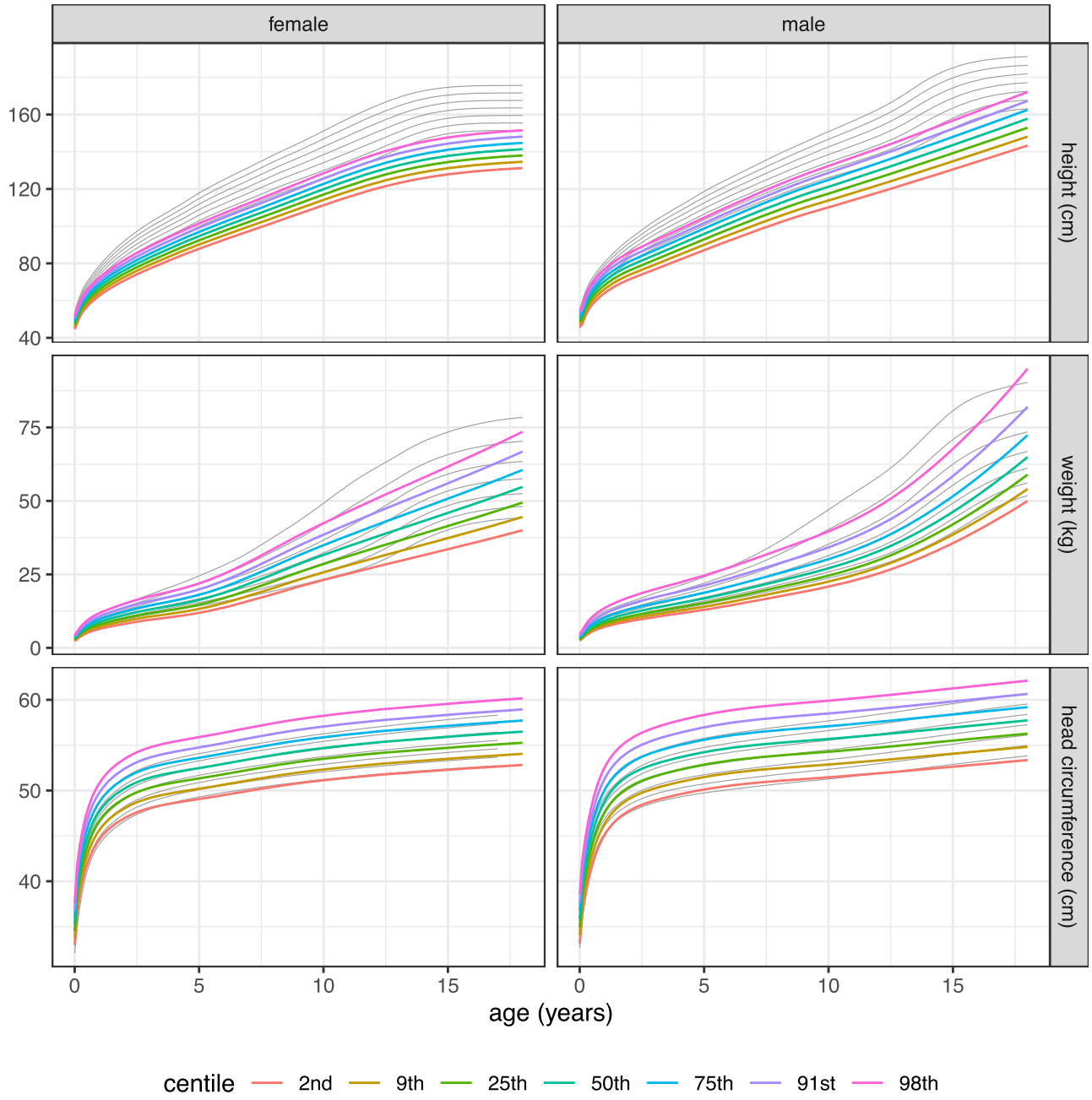


FIGURE 3 Centile charts for height, weight, and head circumference in HCH children aged 0–16 years, by sex (in color). The gray centiles are the corresponding centiles from the British 1990 reference (Cole et al., 1998). The seven centiles are spaced two thirds of a Z-score apart. HCH, hypochondroplasia.

of these individuals may have been affected by other growth-compromising conditions. Centers shared genetic data in different ways and using different nomenclature and as these data were collected over a number of years, and to protect pseudonymization, it was not possible to clarify this data. To assess if these charts would have been significantly confounded by measurements from conditions misdiagnosed as HCH, growth charts using only those children with genetic confirmation were generated and compared to those using data from the whole cohort (Figure 4). As there was a paucity of data from older children, accurate charts for only children under 4 years, with genetic confirmation, could be generated. Reassuringly, these charts are very similar to those generated using the whole database. The genetics of HCH is more heterogeneous than that of achondroplasia (Xue et al., 2014) and more detailed in-depth phenotype–genotype studies have not been performed. Although having a heterogeneous genetic background alongside the challenges of data collection, has made generating accurate charts more challenging, using data from a mixed genetic background and including those who have not had genetic testing, is more reflective of what is seen in clinical practice where genetic testing is not always readily available or confirmed.

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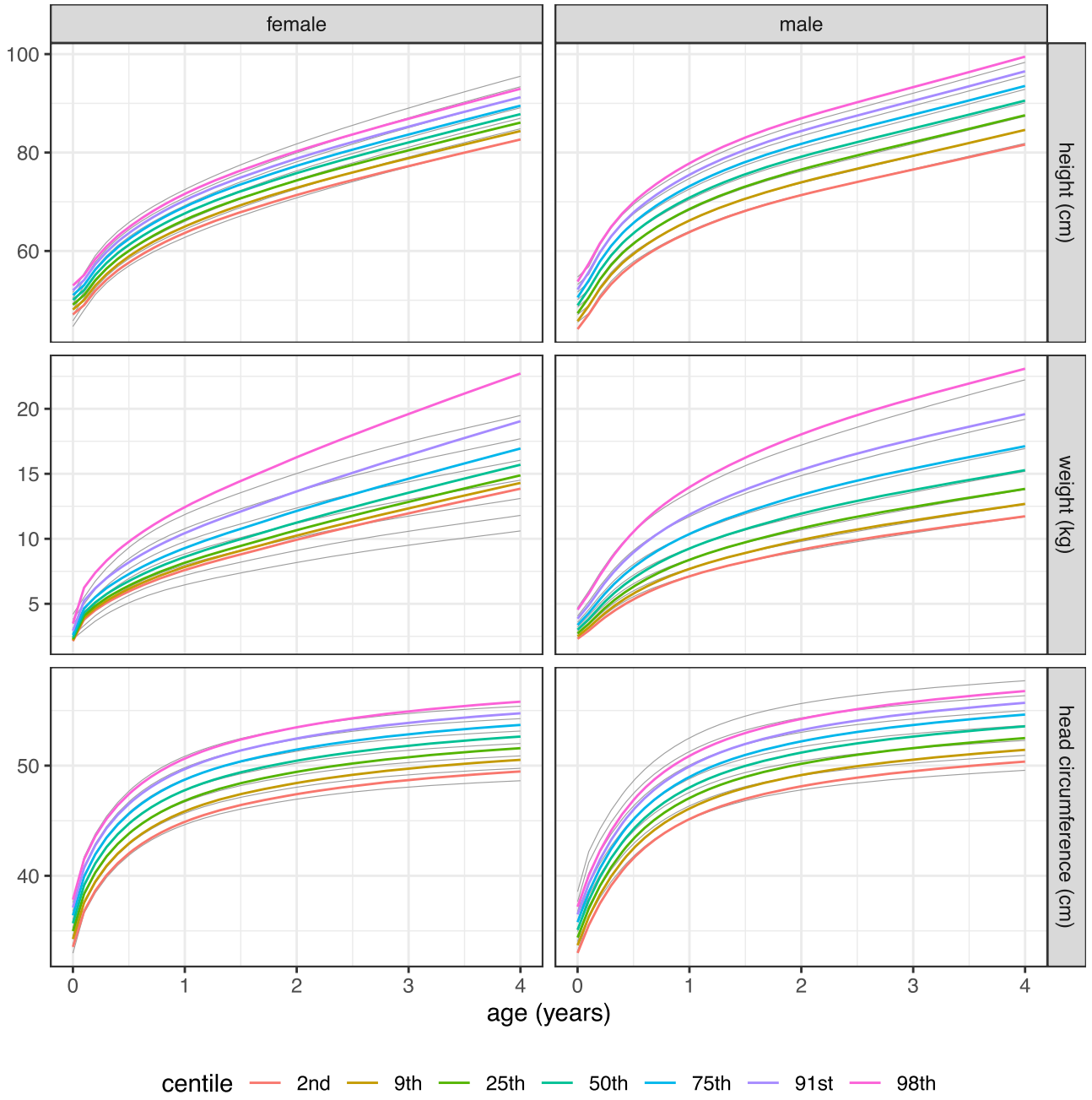


FIGURE 4 Centile charts for height, weight, and head circumference in children with HCH harboring the classical HCH variant aged 0–4 years, by sex (in color). The gray centiles are the colored centiles from Figure 2 based on the HCH cohort. The seven centiles are spaced two thirds of a *Z*-score apart. HCH, hypochondroplasia.

Background population height varies across countries and in this study anthropometrical data was contributed from five northern European countries, with the majority of individuals being from the United Kingdom. Much of the data collected were from historical charts and unfortunately, data on ethnicity were not collected. When selecting a background population, the UK90 was deemed the most appropriate. The UK90 charts are the official growth reference for older children in the United Kingdom, as well as being well-known and highly cited. The limitations of background population heights should be taken into consideration and the most appropriate chart should be chosen. However, the greatest limitation of these growth charts was the paucity of adolescent and final height data. Children with HCH were often discharged after early childhood and so there is a lack of measurements in the medical records. In an effort to increase the data capture for late adolescence and final height, several calls were made to patient support groups. Despite some responses, the additional data collected were insufficient to generate accurate charts, so they were not included in this study. It would be important to collect the final height data of the young people and affected parents to generate more accurate charts in the future.

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5 | CONCLUSIONS

In summary, the growth charts generated from this international, multicenter database will be useful both in clinical practice and research. They show the ages when height falls away compared to the background population. They give an idea of the final height in girls, although the data are not sufficient to address this in boys. Questions about age-specific growth and final height are frequently asked by affected families and these charts with background data will be a valuable visual aid in the clinical setting. Importantly, these charts provide a guide to the expected growth of children with HCH enabling early detection of additional medical conditions that may lead to compromised HC, weight, or height. These charts also enable a greater understanding of the natural history of growth in children with HCH in anticipation of potential clinical trials and ascertaining the effectiveness of potential interventions.

AUTHOR CONTRIBUTIONS

Moira Cheung: Conceptualization; data methodology; data curation; data analysis; writing—original draft; writing—review and editing. **Tim Cole**: Conceptualization; data methodology; statistical analysis; writing—review and editing. **Melita Irving**: Conceptualization; writing—original draft; writing—review and editing. All other authors were involved in data curation, reviewing, and editing the final manuscript.

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CONFLICT OF INTEREST STATEMENT

Christine Burren: Principal Investigator in Pfizer and QED trials in children with achondroplasia. Moira Cheung has participated in advisory boards and worked as a consultant for BioMarin, Ascendis, and QED trials in children with FGFR3 conditions. Wolfgang Högler has worked as a consultant for, and received travel support from, BioMarin. Principal investigator in Ascendis trial in children with achondroplasia. Ciara McDonnell: Principal Investigator in Ascendis clinical trials for children with achondroplasia, advisory board participation for BioMarin. Other authors: no conflicts declared.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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