




ORIGINAL ARTICLE 

The Head Circumference Height Index (HCH-I) to Quantify Relative Macrocephaly and Aid Identification of Hypochondroplasia in Children

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ABSTRACT

Hypochondroplasia (HCH) is a rare skeletal dysplasia caused by pathogenic variants in the *FGFR3* gene. We hypothesized that the relative disproportion between head circumference and height in HCH might be diagnostically informative and generated a simple index of head-stature disproportion to help pediatricians diagnose HCH. The Head Circumference Height Index (HCH-I), based on formal statistical principles, is defined as $\text{height Z-score} - 1/2 \text{ head circumference Z-score}$, with the Z-scores based here on the UK90 growth reference. An HCH-I below the cut-off of -2 indicates substantial head-height disproportion. We validated the index by comparing children diagnosed with HCH ($n=364$), using data from the recent European HCH growth charts, to children from the Cambridge Infant Growth Study (CIGS) ($n=4620$). The mean (SD) HCH-I was -3.0 (1.2) in the HCH cohort, compared to -0.2 (0.9) in the CIGS cohort. An HCH-I below -2 correctly identified 78% of children with HCH, while only 2.4% of CIGS children fell below the cut-off. An HCH-I below -2 identifies children with head-height disproportion who may have HCH or another genetic disorder. The index is deliberately simple to calculate and should prove useful in clinical practice.

1 | Introduction

Hypochondroplasia (HCH, OMIM #146000) is a rare genetic disorder characterized by short stature and caused by pathogenic variants in the *FGFR3* gene (Kim et al. 2023). Unlike its allelic counterpart, achondroplasia, HCH exhibits a broad spectrum of phenotypic variability, which can result in challenges with clinical identification. The estimated prevalence of HCH ranges from 1 in 15,000 to 1 in 40,000 live births (Kim et al. 2023); however, the true prevalence is likely underestimated due to underdiagnosis and misdiagnosis.

The two main diagnostic opportunities during childhood are presentation with short stature and neurological/neurocognitive complications. Infants may exhibit neurological symptoms such as temporal lobe seizures, ranging from subtle apneic episodes to generalized tonic-clonic seizures (Ahmadi et al. 2022; Bernardo et al. 2021; Kim et al. 2023; Okazaki et al. 2017; Romeo et al. 2014). In addition, affected individuals may present with specific learning difficulties, which warrant early identification and intervention (Bernardo et al. 2021; Kim et al. 2023). More commonly, HCH presents with disproportionate short stature, prompting endocrine evaluation. Clinical hallmarks include

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disproportionate rhizomelic short stature and relative macrocephaly. There may be no or very subtle radiographic findings, but if present, may include posterior scalloping of the vertebral bodies and absence of normal interpedicular widening in the lumbar spine (Sargar et al. 2017). Although final height is often below the genetic potential (i.e., mid-parental height), it may remain within the lower percentiles of the general population, especially through to mid-childhood. The lack of a pubertal growth spurt often results in an increasingly evident height deficit during adolescence (Cheung et al. 2024).

The natural history of HCH remains poorly characterized; however, emerging data suggest that the condition is associated with significant lifelong morbidity. Historically, the mild phenotype and absence of targeted treatments contributed to limited medical surveillance and follow-up. This trend was evident during the development of updated HCH-specific growth charts, where growth data for older individuals were notably scarce (Cheung et al. 2024). Recent advances, including clinical trials targeting *FGFR3*-related conditions, provide a critical opportunity to better understand the natural history and to identify unmet clinical needs in this population. Early diagnosis and careful monitoring are essential to optimize emerging therapeutic interventions (Savarirayan et al. 2024).

The diagnosis of HCH can be challenging and is frequently delayed, particularly in cases with a milder phenotype. In this context, we aimed to produce a practical tool using measurements available in the pediatric setting which could facilitate the early identification of HCH in children presenting with short stature. Affected individuals often demonstrate macrocephaly relative to height; however, unlike in achondroplasia, head circumference typically overlaps with that of nonsyndromic children (Cheung et al. 2024), making it an unreliable standalone clinical marker. We hypothesized that the relative difference between head circumference and height could be exploited as an index to help differentiate patients with HCH from the nonsyndromic population. We named it the *Head Circumference Height Index* (HCH-I), a name intended to act as a reminder to general pediatricians and endocrinologists to prompt consideration of HCH in the differential diagnosis of short stature.

2 | Methods

2.1 | Subjects

The index was developed using data from an unaffected cohort of children enrolled in the Cambridge Infant Growth Study (CIGS), which comprised 255 infants born in Cambridge, UK, between 1984 and 1987, and followed longitudinally. Anthropometric measurements, including weight and head circumference, were recorded at up to 21 prespecified time points between 2 weeks and 6 years of age (Cole et al. 2016; Paul et al. 1998). Ethical approval for the study was obtained from the ethics committees of the Medical Research Council Dunn Nutrition Centre, Cambridge, and the Cambridge Area Regional Health Authority.

To validate the index, it was applied to data collected from a cohort of patients with HCH who contributed to the recently

published HCH growth reference for height and head circumference (Cheung et al. 2024). The genetic characteristics of the cohort are described there.

2.2 | Data

Paired measurements of height and head circumference were converted to age- and sex-adjusted *Z*-scores using the British 1990 (UK90) growth reference (Cole et al. 1998). The UK90 reference was selected over the World Health Organization (WHO) standard for two primary reasons: first, the majority of individuals in the HCH growth dataset were from the UK; and second, the UK90 reference provides a more accurate fit to the comparatively larger head sizes observed in British children (Wright et al. 2011).

2.3 | Statistical Methods

Cole et al. (1998) derived an index of conditional growth velocity based on the *Z*-scores of two paired measurements and the correlation between them (Cole 1998). The relevant formula is:

$$\text{Index} = Z_2 - r \times Z_1$$

where Z_1 and Z_2 are the two *Z*-scores, r is the correlation between them, and the Index is a measure of Z_2 adjusted for Z_1 . The same index can be extended to any pair of *Z*-scores where the correlation is known. In this study, our focus was on identifying disproportion between height and head circumference. Data from the CIGS (Cole et al. 2016; Paul et al. 1998) were used to estimate the correlation between height and head circumference *Z*-scores at various ages, stratified by sex, to determine a representative value for r that could be applied broadly. The index can be constructed in two ways: either as head circumference adjusted for height, or vice versa, and both alternatives were considered. The chosen formulation was then applied to clinical data for patients with HCH, using an appropriate threshold to flag potential cases of disproportion.

A more direct way to estimate r is to use multivariable logistic regression to predict the chance of an individual being from the HCH group (as opposed to the CIGS group) given their height *Z*-score (Htz) and head circumference *Z*-score (HCz):

$$\begin{aligned} \text{Logit}(\text{Probability}(\text{HCH})) &= a + b \times \text{Htz} + c \times \text{HCz} \\ &= a + b \times \left(\text{Htz} + \frac{c}{b} \times \text{HCz} \right) \\ &= a + b \times (\text{Htz} - r \times \text{HCz}) \end{aligned}$$

where a , b and c are regression coefficients. Rearranged as shown, the ratio of regression coefficients $\frac{-c}{b}$ estimates r for the index of height adjusted for head circumference, while for the reverse index of head circumference adjusted for height $\frac{-b}{c}$ estimates r . As a correlation the value of r needs to be less than one, so the index to use has $r < 1$.

Theoretically, when applied to the reference population from which the *Z*-scores were derived—where Z_1 and Z_2 have mean 0 and standard deviation (SD) 1—the resulting index has mean 0

and SD $\sqrt{1-r^2}$. So the SD of the index is less than 1 and decreases as r increases. The index is also highly correlated with Z_2 and uncorrelated with Z_1 . When applied to other populations, the index should have a mean and SD near these theoretical values, permitting the use of a consistent cut-off. A cut off of ± 2 was adopted, depending on the direction of the index, as this identifies 2%–3% of the reference population—a common criterion also used by the World Health Organization (WHO) to define short stature (A Health Professional’s Guide for Using the New WHO Growth Charts 2010). Once a suitable value for r had been established, the index was calculated for both the HCH patient cohort and the CIGS controls, and the resulting distributions were compared.

3 | Results

Summary statistics for age, height Z-score, and head circumference Z-score by sex for both datasets are presented in Table 1. The HCH cohort ($n=364$ measurements from 72 patients) was, on average, older, significantly shorter, and had markedly larger head circumferences compared to the CIGS cohort ($n=4620$ measurements from 255 subjects). Within each cohort, results were consistent across the sexes. The difference in mean age between groups arose from the CIGS study design, which included 14 four-weekly measurements per child during the first year of life; as a result, only 28% of CIGS measurements occurred after 1 year of age.

The logistic regression coefficients and standard errors (SE) based on $364 + 4620 = 4984$ points were as follows:

$$\text{Logit}(\text{Probability}(\text{HCH})) = -4.4 \text{ (SE 0.1)} - 1.17 \text{ (SE 0.05)} \times \text{Htz} + 0.66 \text{ (SE 0.05)} \times \text{HCz}$$

Both height and head circumference were highly significant for predicting HCH ($p < 0.0001$), but in opposite directions. Height had the larger coefficient, so this defined the optimal index as

$$\text{Htz} - \frac{-0.66}{-1.17} \text{HCz} = \text{Htz} - 0.56 \times \text{HCz}$$

With the coefficient for Htz negative, negative values of HCH-I were more associated with HCH cases.

The correlation between height Z-score and head circumference Z-score was 0.42 for females and 0.50 for males in the CIGS cohort, and 0.22 in both sexes in the HCH patients. Taking the regression and correlation evidence together, an index with $r = 0.5$ was chosen for four reasons: (a) 0.5 is close to the optimal value from the logistic regression; (b) it also reflects the correlation observed in the control population; (c) the exact value of r is not critical for clinical discrimination, and (d) $r = \frac{1}{2}$ simplifies the calculation of the index. Based on this, we defined the HCH-I as follows:

$$\text{HCH-I} = \text{height Z-score} - 1/2 \text{ head circumference Z-score}$$

where the name and acronym were chosen (with some poetic license as strictly it should be HtHC-I) to reflect the target condition.

Table 2 presents the proportions of individuals meeting criteria for short stature ($Z < -2$), macrocephaly ($Z > +2$), and disproportion (below the HCH-I cut-off of -2), stratified by group and sex. Among patients with HCH, approximately two-thirds exhibited short stature and one-quarter had macrocephaly, compared to just 2%–3% of the CIGS cohort. The index flagged 78% of children with HCH as being below the cut-off of -2 , but only 2.4% of the CIGS cohort, indicating high specificity.

Figure 1 shows histograms of the HCH-I index with cut-off -2 . Figure 1a shows the CIGS subjects in 22 age groups from birth to 6 years, where around 2.4% are below the cut-off at each age. Figure 1b shows the corresponding histogram for all HCH cases. Figure 1c shows histograms for cases of HCH divided into five genetic diagnostic groups. *FGFR3* positive refers to cases in whom a variant in *FGFR3* has been identified, but its exact

TABLE 1 | Summary statistics for HCH patients and CIGS controls (mean and SD).

	HCH			CIGS		
	Male <i>n</i> = 235	Female <i>n</i> = 129	Total <i>n</i> = 364	Male <i>n</i> = 2461	Female <i>n</i> = 2159	Total <i>n</i> = 4620
Age (years)	2.9 (3.3)	2.6 (3.2)	2.8 (3.2)	1.1 (1.2)	1.1 (1.2)	1.1 (1.2)
Height Z-score	−2.5 (1.2)	−2.5 (1.1)	−2.5 (1.1)	−0.2 (1.0)	−0.2 (1.0)	−0.2 (1.0)
Head circ Z-score	1.2 (0.9)	1.1 (1.1)	1.0 (1.4)	0.0 (1.0)	0.0 (1.0)	0.0 (1.0)

TABLE 2 | Percentages by sex of HCH patients and CIGS controls flagged for disproportion by height and/or head circumference.

Sex	HCH (<i>n</i> = 364)			CIGS (<i>n</i> = 4620)		
	Male (%)	Female (%)	Total (%)	Male (%)	Female (%)	Total (%)
Proportion with height Z-score < −2	66	68	66	3.1	3.6	3.3
Proportion with head circ Z-score > +2	18	33	23	1.7	2.6	2.1
Proportion with HCH-I < −2	73	87	78	2.0	3.0	2.4

nomenclature is unspecified. *FGFR3* negative refers to cases in whom *FGFR3* testing has been undertaken, but no causative variant was identified. Not tested refers to cases in whom genetic testing has not been undertaken.

Overall the true positive rate is 78%, while the false positive rate is 2.4%. Figure 2 shows how the true and false positive rates vary as

the value of r in the index varies, with the rates for $r=0$, $\frac{1}{2}$ and 1 highlighted. The false positive rate needs to be as small as possible to optimize resources, and the y-axis in Figure 2 is on a log scale to emphasize how the rate depends on r . The false positive rate in CIGS is near minimal for $r = 0.5$. The value $r = 0$ corresponds to the index Htz on its own, where the false positive rate is 3.3%, while $r = 1$ is the index Htz–HCz where the false positive rate is

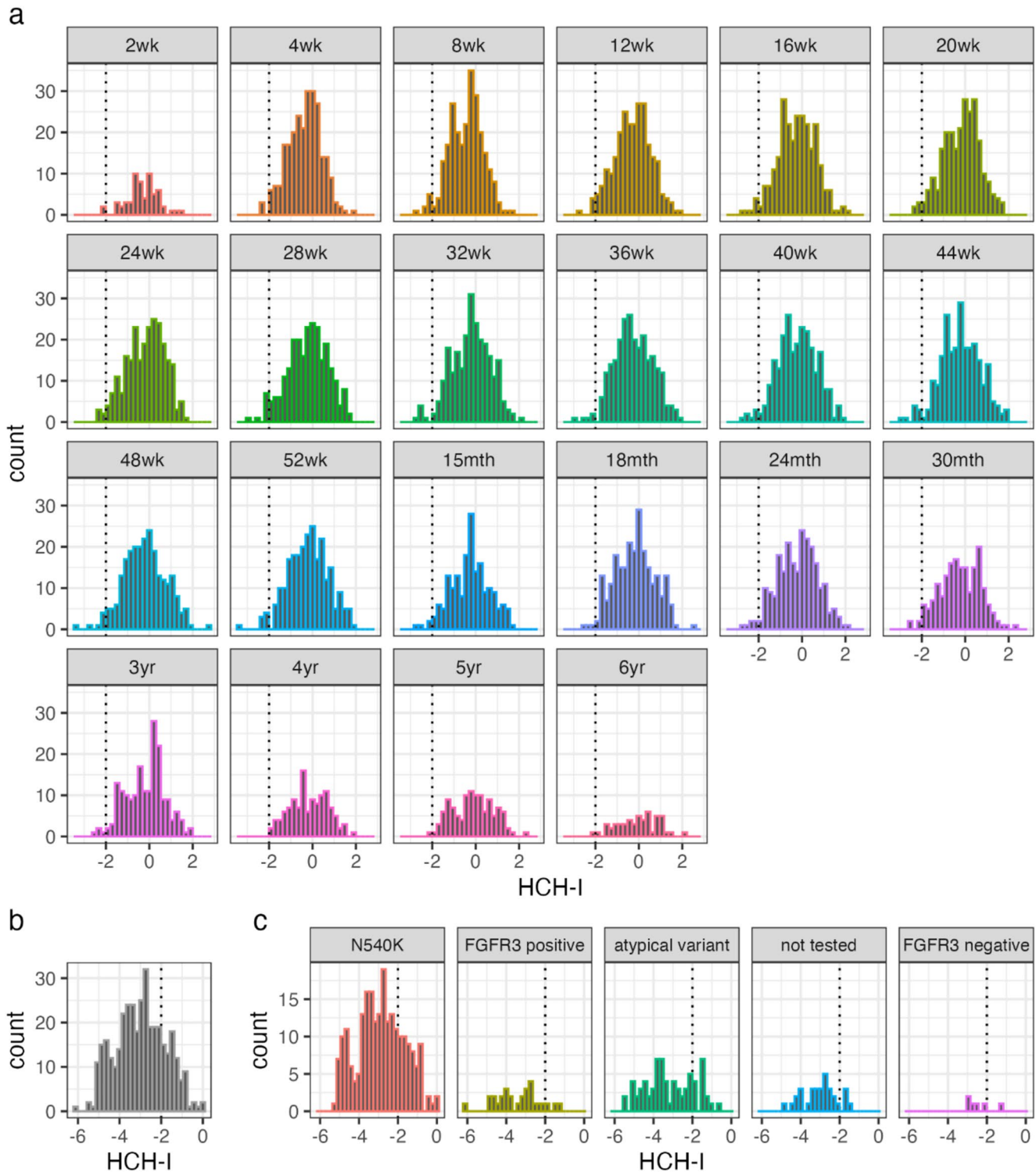


FIGURE 1 | Histograms of the index HCH-I with the cut-off of -2 highlighted: (a) by age group in the Cambridge Infant Growth Study (CIGS), (b) all patients with HCH, and (c) patients with HCH by genetic diagnosis group. For the CIGS subjects, only 2.4% on average have HCH-I below the cut-off, while for the patients 78% are below the cut-off.

3.7%. The true positive rate increases from 66% to 81% across the range of r , i.e., a substantial 12% rise from 0 to $\frac{1}{2}$ but only 3% from $\frac{1}{2}$ to 1, so the true positive rate is close to maximal.

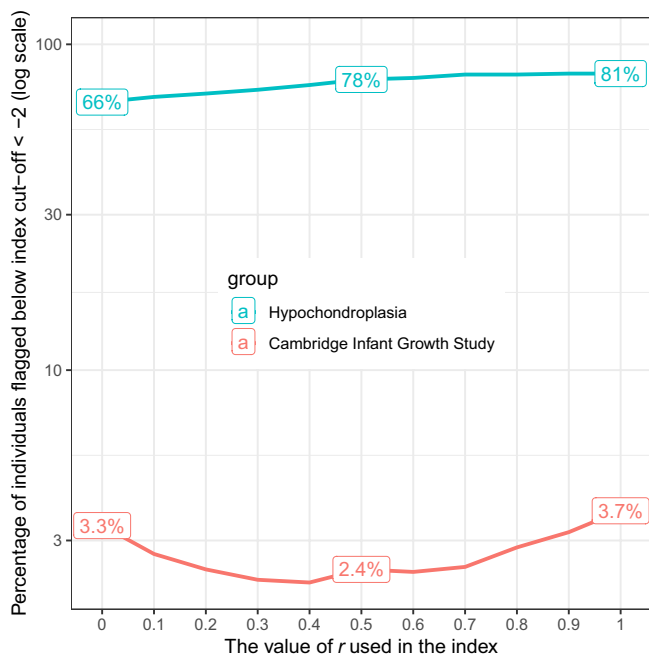


FIGURE 2 | The proportions of HCH patients and CIGS subjects with the index below -2 , when the index is based on different values of r .

Figure 3 shows a scatter plot of HCH-I by age in the two sexes for patients with HCH and CIGS controls, and shows that in patients HCH-I falls after the first year, improving its performance.

To quantify the effect of age on index performance, Table 3 compares results from measurements taken during infancy with those obtained at older ages. The index is more effective in identifying disproportion in older children, correctly classifying 90% of HCH patients over 1 year of age, compared to 63% during infancy. Similarly, the proportion of controls flagged as disproportionate decreases with age, from 2.7% in infancy to 1.9% beyond 1 year.

4 | Discussion

Hypochondroplasia (HCH) is an important yet often under-recognized cause of mild disproportionate short stature, with diagnosis frequently delayed due to subtle clinical features (Bernardo et al. 2021; Kim et al. 2023). With the advent of targeted therapies and advances in genetic testing, early identification has become increasingly important. On the assumption that z -scores for height and head circumference are available in the patient's notes, the HCH-I offers a simple, accessible screening tool that can be calculated by any pediatrician without the need for specialized equipment. An HCH-I value below -2 identifies nearly 80% of individuals with HCH, while flagging only 2.4% of the unaffected population, making it a useful prompt to consider HCH in the differential diagnosis of short stature.

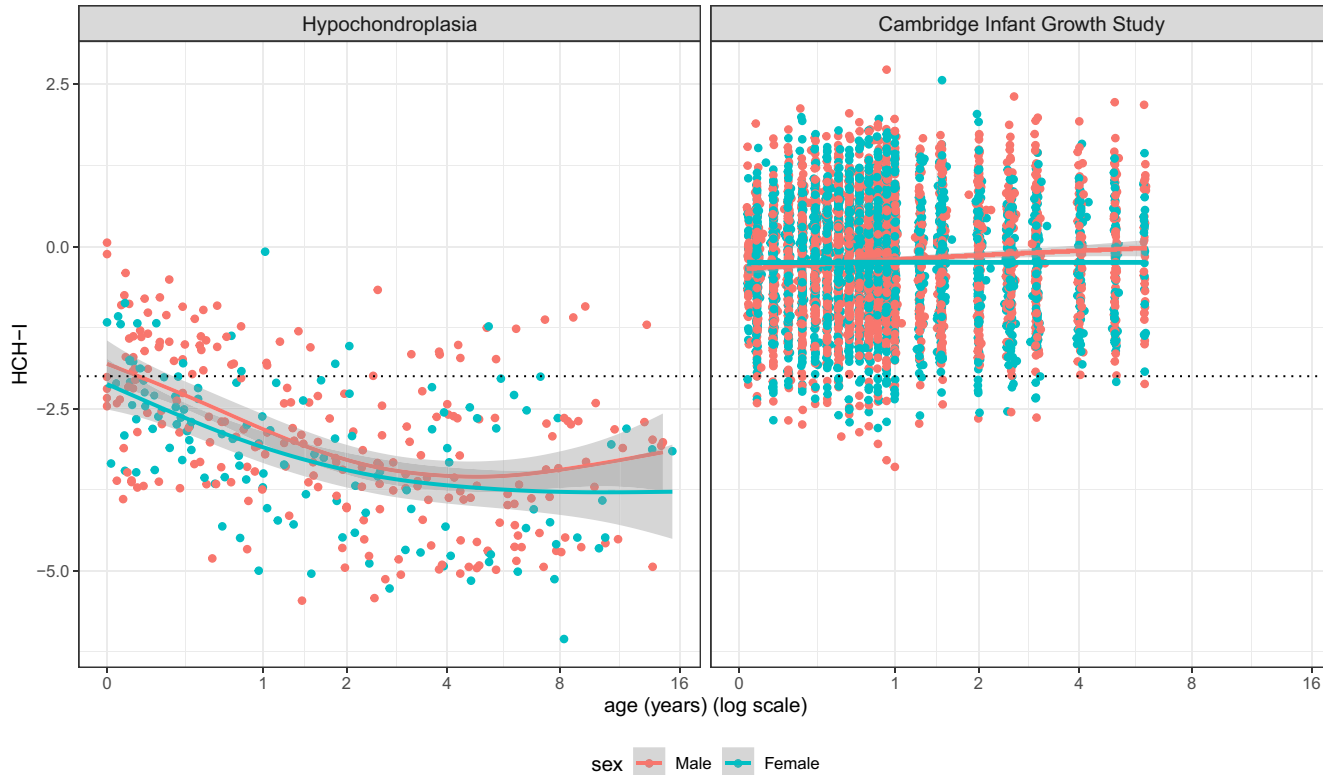


FIGURE 3 | Scatterplots of HCH-I versus age by sex for patients with HCH and controls from the Cambridge Infant Growth Study, with fitted trend lines and 95% confidence intervals.

TABLE 3 | Percentages by age group of HCH patients and CIGS controls flagged for disproportion by height and/or head circumference.

Age group	HCH (n = 364)			CIGS (n = 4620)		
	<1 year n = 162 (%)	>1 year n = 202 (%)	Total (%)	<1 year n = 3307 (%)	>1 year n = 1313 (%)	Total (%)
Proportion with height Z-score < -2	44	84	66	3.4	3.1	3.3
Proportion with head circ Z-score > +2	31	17	23	2.3	1.7	2.1
Proportion with HCH-I < -2	63	90	78	2.7	1.9	2.4

A limitation of the study is that the CIGS control data stopped at 6 years while the HCH data extended to 18 years, so the distribution of the HCH-I in older controls is not well documented. However, Geraedts et al. (2011) studied the correlation between height and head circumference in a large cohort of Dutch children and young people from birth to 18 years, where the correlation by age ranged from 0.32 to 0.52, averaging 0.44 for ages 11–16. So their correlation was not materially different from 0.5 at older ages, and the HCH-I distribution at older ages should be similar to that up to age 6. Geraedts et al. argued that a chart of head circumference for height might be useful for interpreting head circumference in tall or short children, yet the results here suggest the opposite, at least for HCH—that height adjusted for head circumference is a more effective index.

While absolute macrocephaly is common in achondroplasia, an allelic condition, head circumference in HCH typically falls within the normal range (Cheung et al. 2024). Therefore, absolute head size is not a reliable diagnostic indicator. However, studies have demonstrated that the disproportion in *FGFR3*-related conditions arises not only from shortened limb segments but also from a relatively large head relative to height (Del Pino and Fano 2025; Del Pino et al. 2017; Arenas et al. 2018). Del Pino et al. demonstrated that in HCH the correlation between head circumference and height ranged from 0.3 to 0.5 with a median head circumference/height ratio from 0.45 at age 6 years to 0.34–0.33 at age 17 years in both sexes (Del Pino et al. 2017). Arenas from the same group (Arenas et al. 2018) reported the head circumference/height ratio and suggested it could differentiate between genetically proven HCH patients with p.Asn540Lys and unaffected controls. However, this ratio varies by a factor of two between birth and 15 years, so it needs to be age adjusted, and it is not simple to calculate, unlike the HCH-I, which is both independent of age and simple to calculate. It is important to use appropriate population charts to calculate the Z-scores for height and head circumference.

In achondroplasia, the mechanism underlying absolute macrocephaly remains poorly understood, though it is already apparent prenatally and may be related to restriction of venous and CSF flow through skull base foramina. In contrast, HCH has few of the complications of base of skull foramina stenosis seen in achondroplasia. It remains uncertain whether children with HCH exhibit isolated limb shortening, with sparing of the trunk and head, or whether a degree of relative macrocephaly also contributes to the phenotype.

Children are frequently referred for evaluation of short stature, and a wide range of diagnoses—genetic or not—may underlie height measurements that fall just below or well below the normal range (Polidori et al. 2020). Skeletal dysplasias, in particular, are challenging for nonspecialists to diagnose, given their rarity and heterogeneity (Unger et al. 2023). Body disproportion was used by Fredriks et al. (2005) to help with the diagnostic workup of short stature, and they showed that sitting height/height Z-score versus height Z score could be helpful in identifying those with hypochondroplasia. Sitting height, however, is not a routine measurement in most pediatric or even endocrine settings, unlike head circumference. The index HCH-I is a simple tool specifically developed for use in general pediatric settings, designed to encourage consideration of rare genetic conditions such as HCH and to prompt timely referral to specialist services. It does not need access to a specialist chart, and the HCH-I cut-off of -2 is easy to remember. In some countries such as the UK, patients need to meet certain clinical criteria to be considered eligible for genetic testing. At present, the UK Genomic Test Directory (2025) states that a patient must have “clinical features strongly suggestive of hypochondroplasia” to be eligible for genetic testing.

Hypochondroplasia (HCH) presents with a broad phenotypic spectrum and is genetically heterogeneous. The database that provided the HCH data did not have genetic confirmation for all patients, and some non-*FGFR3* HCH patients may have been included, which is a limitation of this study. Furthermore, the database lacked ethnicity; although most of the data came from northern Europe—this is another study limitation. Further investigation using a larger cohort of genetically confirmed HCH patients with ethnicity recorded is warranted to confirm the sensitivity and specificity of this tool and explore if there is any genotype–phenotype relationship.

5 | Conclusion

In summary, the HCH-I is a simple and accessible tool for quantifying relative macrocephaly, i.e., the disproportion between height and head circumference Z-scores. It has potential applications in both clinical practice and research. Clinically, it may aid in distinguishing children with possible HCH from those in the general population, supporting earlier recognition and diagnosis. The index may also prove useful in identifying other genetic conditions associated with relative macrocephaly, although this requires further study. In the context of clinical trials, the HCH-I could serve as an outcome measure for monitoring disproportion

not only between limbs and trunk, as is current practice, but also between head circumference and overall height.

Author Contributions

Moira S. Cheung: conceptualization, project administration, writing – original draft and editing. **Ruggero Lanzafame:** data curation, data methodology, writing – review and editing. **Karen J. Low:** data curation, data methodology, writing – review and editing. **Tim J. Cole:** conceptualization, statistical analysis, data curation, data methodology, writing – original draft and editing.

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Conflicts of Interest

Dr. Cheung is an investigator on clinical trials for BioMarin, Tyra, and Kyowa Kirin. She has received honoraria for speaking and participating on advisory boards from BioMarin, BridgeBio, Tyra Biosciences, and Kyowa Kirin.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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