

New Argentine head circumference references for people with achondroplasia from 0 to 21 years of age

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ABSTRACT

Introduction. Macrocephaly is a phenotypic feature of achondroplasia (ACH), the most common form of disproportionate short stature. In 2011, we published head circumference (HC) references for this population, but due to the scarcity of data about older ages, the centiles were estimated only up to 6 years of age.

Objective. To estimated centiles of the HC between birth and 21 years of age for ACH.

Population and methods. Data from children with ACH assisted between 1992 and 2024 at a third-level hospital in Argentina were used for its estimation. The growth curves were adjusted using the LMS method. To evaluate the magnitude of the differences between the Argentine references of ACH and those of the general population, the 3, 50, and 97 centiles at different ages were plotted comparatively.

Results. The HC of ACH was more significant at all ages than the general population's references. During the first year of life, males and females reach 84% and 86% of adult size, respectively, completing growth after 20 years of age.

Conclusions. Due to the difference in cephalic size between the general population and ACH, it is essential to have specific references for this population. This will allow us to detect growth trajectories not attributed to ACH and to suspect deviations that require a rapid interdisciplinary approach.

Keywords: achondroplasia; cephalometry; growth charts; reference values.

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INTRODUCTION

Achondroplasia (*FGFR3*- ACH, MIM #100800) (ACH) is the most common form of short stature with short limbs, with an incidence of 0.47/10 000 in Argentina.¹

It is an autosomal dominant condition, with complete penetrance and fixed expressivity, caused by a gain-of-function mutation of the fibroblast growth factor receptor type 3 (*FGFR3*) gene, located on chromosome 4p16.3.²

This mutation primarily causes inhibition of endochondral bone growth, manifesting a distinctive clinical, auxological, and radiological phenotype.^{3,4} Affected individuals have severe growth retardation and consequently disproportionate short stature with short limbs, narrow thorax, trident configuration of the hands, ligament hyperlaxity, and macrocephaly with frontal bossing.³⁻⁶

The compromise of endochondral ossification produces an alteration in the base of the skull and, as a consequence, a decrease in the size and alteration of the shape of the foramen magnum, short vertebral pedicles, a narrow spinal canal, and a decrease in the diameter of other communication orifices of vascular and neural structures.⁷ This generates compression of the protruding cranial nerves that pass through these orifices at the base of the skull and an increase in venous pressure, generating persistence of the emissary's veins and procidence of the jugular gulf in the middle ear.^{7,8}

With time, this compromise of the cranial venous outflow determines communicating hydrocephalus at the expense of the slowed venous outflow. On the other hand, this leads to a slight increase in pressure in the cranial venous sinuses, presumably the cause of megalencephaly, i.e., an increase in the encephalic mass that may or may not be accompanied by slightly enlarged ventricles.⁸⁻¹⁰

The persistence of prominent emissary and meningeal veins supports the role of collateral vessel formation in offsetting intracranial venous hypertension and increased cerebrospinal fluid pressure.^{8,9}

Although non-communicating hydrocephalus due to aqueduct stenosis has been described, this is rare.^{11,12}

Because of these anatomical features and the functional consequences of children with ACH, it is necessary to follow up on the head circumference growth with specific references.

The rapid rate of cephalic growth, together with other clinical signs or symptoms of hydrocephalus or cervical-spinal compression, could indicate the urgent need for studies and consultation with a neurosurgeon with experience in the follow-up and treatment of this population.¹³

In 2011, we published references for weight, height, and HC for the clinical follow-up of children with ACH. However, due to the scarcity of HC data at older ages, we did not achieve a good fit of the data in that age range and published references from birth to 6 years of age.⁵

In this work, we report head circumference references of the Argentine population with ACH from birth to 21 years of age, and the selected percentiles are estimated using the LMS method.^{14,15}

POPULATION AND METHODS

This is an observational, descriptive, cross-sectional study. The data from 519 individuals with a confirmed diagnosis of ACH, aged between birth and 21 years (262 males and 257 women) assisted by the multidisciplinary study of skeletal dysplasias between 1992 and May 2024, at a third-level public hospital constituted the eligible sample for estimating HC-for-age centiles. Some HC data were previously used to estimate the centiles of the Argentine references of HC from 0 to 6 years of age and the head circumference/height index.^{5,6}

The diagnosis was made based on clinical and radiological signs.⁴ The G380R variant of fibroblast growth factor 3 (*FGFR3*) in peripheral blood lymphocytes was studied in 327/519 patients.

HC data were excluded for patients born preterm up to 2 years of corrected age and for those patients with surgical requirements due to progressive hydrocephalus.

Methods

All measurements were taken at variable periods in each patient under follow-up, using standardized anthropometric techniques recommended by the Sociedad Argentina de Pediatría¹⁶ in the Anthropometry Laboratory of the Growth Service and Development. The PC was measured with non-stretchable plasticized tape. The technical error for intraobserver measurement was 0.10 cm.

The data on PC at birth were obtained from the information recorded in the families' health booklets.

Data analysis and processing

Scatter and box plots were constructed to remove outliers. PC data between the mean $\pm$ 4 standard deviations (SD) scores were included for estimating centiles.

The HC centiles for age were estimated using the LMS method. This method allows adjustment for skewness using the Box-Cox transformation (L), which normalizes the distribution of the data at each age,^{14,15} considering the median (M) and the coefficient of variation of the distribution (S). The proposed LMS model has the property that when fitted with data, the estimated values of L, M, and S will change smoothly with the abscissa t (age) so that they can be representative of the population with smoothed curves plotted as a function of the ordinate y (HC). At each age, the HC distribution is summarized by three coefficients: L, M, and S. L indicates the skewness; M is the median; and S is the coefficient of variation for each age and sex. These parameters were calculated according to the penalized maximum likelihood procedure.^{15,17} The centiles were calculated using the formula:^{14,17}

$$C_{100\alpha(t)} = M(t) (1 + L(t) S(t) Z\alpha)^{1/L(t)}, \text{ where:}$$

$C_{100\alpha(t)}$ is the HC centile corresponding to $Z\alpha$.

$Z\alpha$ is the quantile (centile) 100α of the normal standard distribution.

t is the age in years

L(t): skewness, M(t): median, S(t): coefficient of variation, and $C_{100\alpha(t)}$ indicate the corresponding values of each curve at age t .

The normality of the residuals was assessed using Q-Q plot tests, and the Q test was applied to evaluate the goodness-of-fit.^{17,18}

For statistical processing, the LMSChartMakerPro program was used.¹⁹

To evaluate the magnitude of the differences between the Argentinean references of the general population²⁰ and those of ACH at different ages, the 3, 50, and 97 centiles of both references were plotted.

The Ethics and Research Committee of the Hospital Garrahan approved research project N.º 492.

RESULTS

The final sample included 259 boys and 259 girls. All data from 9 patients were excluded due to progressive hydrocephalus requiring surgery. *Table 1* shows the number of HC measurements included according to sex and age group. *Tables 2a* and *b* show the L, M, and S values together with the centiles 3, 10, 25, 50, 75, 90, and 97 for both sexes.

The reference curve's adjustment degree is expressed as "equivalents of degrees of freedom" (edf). In males, the parameters of the fitted curve were L4, M9, S5 R edf; in females, they were L 3.1, M 7.7, and S 4.8 R edf. The Q-test plots for males and females, where it is observed that L,

TABLE 1. Number of head circumference measurements included according to sex and age group

Age group (years)	Men	Women
0 to <1	502	455
1 to <2	290	322
2 to <3	205	208
3 to <4	176	174
4 to <5	153	139
5 to <6	120	134
6 to <7	126	127
7 to <8	104	107
8 to <9	91	83
9 to <10	85	85
10 to <11	74	67
11 to <12	94	82
12 to <13	74	61
13 to <14	60	64
>14 to 15	38	53
>15 to 16	46	33
>16 to 17	33	27
>17	43	41
Total	2314	2316

M, and S are within the range ± 2 , indicating a good fit of the selected model, are presented in the supplementary material.

Figures 1a and b illustrate the HC reference curves from 0 to 21 years in males and females, respectively, in the seven-centile format (3, 10, 25, 50, 75, 90, and 97). During the first year of life, males reach 84% of the adult size of the head circumference and, at 5 years of age, 93%. From this age until puberty, it grows by 2% more and it is completed after age 20. In females, the size reached, expressed as a percentage of adult size, is 86% at one year and 93% at five years of age. It increases by 4% between age 5 and puberty and reaches 100% after age 20.

The raw data on LMS-adjusted centiles for males and females are presented in the supplementary material.

Figures 2a and b show the Argentine achondroplasia 3, 50, and 97 centile values and those corresponding to the Argentine references of the general population.²⁰ In both

sexes, the values of the 3 and 97 centiles of the Argentine ACH references were higher than those of the general population at all ages. However, regarding percentile 3, in adulthood, both references overlapped.

A comparison of the median curve between the populations of both males and females among those accurately diagnosed with the detection of the variant in the gene *FGFR3* and those with only clinical radiological diagnosis showed no differences.

DISCUSSION

In this paper, we present the ACH HC references, constructed with updated data, for the Argentine population from birth to 21 years of age in the 7-centile format.

As in the general population, the most rapid growth of HC occurs during the first year of life, reaching more than 80% of adult size in both sexes. After 5 years of age, changes in cephalic size are of less magnitude and constant until

TABLE 2a. 3, 10, 25, 75, 90, and 97 centiles, and L, M (50 centile), and S values corresponding to the head circumference of Argentine men with achondroplasia aged 0 to 21 years

Age (years)	L	S	Centile 3	Centile 10	Centile 25	Centile 50	Centile 75	Centile 90	Centile 97
0.00	0.01	0.05	33.51	34.53	35.60	36.83	38.11	39.29	40.49
0.08	0.53	0.05	35.47	36.55	37.65	38.90	40.17	41.32	42.48
0.25	1.27	0.04	39.07	40.19	41.32	42.57	43.81	44.92	46.00
0.50	1.10	0.04	42.94	44.00	45.08	46.27	47.45	48.52	49.57
0.75	-0.23	0.04	45.34	46.30	47.29	48.42	49.59	50.67	51.77
1.00	-1.69	0.03	46.83	47.71	48.65	49.75	50.93	52.05	53.23
1.50	-3.30	0.03	48.77	49.61	50.53	51.64	52.86	54.08	55.41
2.00	-3.63	0.03	49.81	50.67	51.61	52.76	54.05	55.33	56.76
3.00	-3.62	0.04	51.03	51.93	52.93	54.15	55.51	56.88	58.41
4.00	-3.59	0.04	51.65	52.58	53.60	54.84	56.24	57.64	59.20
5.00	-3.57	0.04	52.00	52.93	53.96	55.22	56.63	58.05	59.62
6.00	-3.55	0.04	52.32	53.26	54.30	55.57	56.99	58.42	60.01
7.00	-3.54	0.04	52.66	53.61	54.65	55.94	57.37	58.81	60.41
8.00	-3.53	0.04	52.89	53.84	54.90	56.19	57.63	59.08	60.69
9.00	-3.52	0.04	53.01	53.97	55.02	56.32	57.76	59.22	60.84
10.00	-3.51	0.04	53.15	54.12	55.18	56.48	57.93	59.39	61.02
11.00	-3.51	0.04	53.43	54.40	55.48	56.79	58.26	59.73	61.38
12.00	-3.50	0.04	53.74	54.73	55.81	57.14	58.63	60.13	61.79
13.00	-3.50	0.04	54.04	55.04	56.14	57.49	58.99	60.52	62.21
14.00	-3.50	0.04	54.33	55.34	56.46	57.82	59.35	60.90	62.62
15.00	-3.51	0.04	54.61	55.63	56.76	58.15	59.70	61.28	63.03
16.00	-3.52	0.04	54.85	55.88	57.03	58.43	60.01	61.61	63.39
17.00	-3.53	0.04	54.99	56.03	57.19	58.60	60.19	61.81	63.61
18.00	-3.53	0.04	55.10	56.15	57.30	58.73	60.33	61.96	63.78
19.00	-3.54	0.04	55.22	56.28	57.44	58.88	60.49	62.13	63.97
20.00	-3.54	0.04	55.36	56.42	57.59	59.04	60.66	62.32	64.18
21.00	-3.55	0.04	55.48	56.54	57.72	59.18	60.81	62.48	64.36

TABLE 2b. 3, 10, 25, 75, 90, and 97 centiles, and L, M (50 centile), and S values corresponding to the head circumference of Argentine women with achondroplasia aged 0 to 21 years

Age	L	S	Centile 3	Centile 10	Centile 25	Centile 50	Centile 75	Centile 90	Centile 97
0.00	2.84	0.04	33.16	34.17	35.15	36.18	37.16	38.00	38.80
0.08	2.38	0.04	34.98	35.97	36.93	37.96	38.95	39.82	40.64
0.25	1.48	0.04	38.34	39.27	40.21	41.23	42.24	43.14	44.02
0.50	0.25	0.03	42.03	42.91	43.81	44.83	45.87	46.82	47.77
0.75	-0.74	0.03	44.11	44.97	45.88	46.93	48.03	49.05	50.09
1.00	-1.46	0.04	45.33	46.22	47.16	48.27	49.45	50.56	51.73
1.50	-2.16	0.04	46.72	47.67	48.69	49.91	51.23	52.52	53.90
2.00	-2.18	0.04	47.67	48.65	49.72	51.00	52.39	53.74	55.20
3.00	-1.62	0.04	49.04	50.11	51.25	52.61	54.06	55.46	56.94
4.00	-1.21	0.04	49.74	50.86	52.05	53.44	54.92	56.33	57.80
5.00	-1.00	0.04	50.07	51.21	52.42	53.82	55.31	56.72	58.19
6.00	-0.84	0.04	50.30	51.46	52.68	54.10	55.59	57.00	58.46
7.00	-0.68	0.04	50.52	51.69	52.92	54.35	55.85	57.26	58.71
8.00	-0.50	0.04	50.75	51.94	53.19	54.63	56.13	57.53	58.97
9.00	-0.25	0.04	51.04	52.26	53.53	54.98	56.49	57.89	59.32
10.00	0.07	0.04	51.38	52.63	53.93	55.40	56.91	58.31	59.72
11.00	0.43	0.04	51.73	53.02	54.35	55.84	57.36	58.75	60.14
12.00	0.75	0.04	52.03	53.36	54.71	56.23	57.76	59.14	60.51
13.00	1.00	0.04	52.25	53.61	54.99	56.52	58.05	59.42	60.78
14.00	1.19	0.04	52.41	53.80	55.19	56.73	58.26	59.64	60.99
15.00	1.36	0.04	52.56	53.96	55.37	56.92	58.45	59.82	61.16
16.00	1.52	0.04	52.70	54.12	55.54	57.10	58.64	60.00	61.34
17.00	1.67	0.04	52.82	54.27	55.70	57.27	58.81	60.17	61.49
18.00	1.82	0.04	52.95	54.41	55.86	57.43	58.97	60.33	61.65
19.00	1.96	0.04	53.06	54.54	56.00	57.58	59.13	60.48	61.79
20.00	2.09	0.04	53.17	54.67	56.15	57.73	59.28	60.63	61.93
21.00	2.23	0.04	53.29	54.81	56.30	57.89	59.44	60.79	62.08

puberty, and the slight increase seen in the general population at those ages is not observed. Sex differences were observed in the “tempo” of growth, with females being more advanced than males.

Macrocephaly is a common and easily recognizable phenotypic feature of ACH,²¹ which makes it imperative to make specific references for the clinical follow-up of this population to detect any deviation not attributed to their baseline condition and to suspect complications that require a rapid interdisciplinary approach.

Centile scores can also indirectly infer the growth velocity of HC. The accelerated growth velocity and other clinical signs and symptoms may indicate the need for urgent evaluation by a neurosurgeon experienced in the follow-up and treatment of children with ACH and the performance of more complex studies. This situation is of particular concern in children under 2 years of age with delayed motor development.⁹

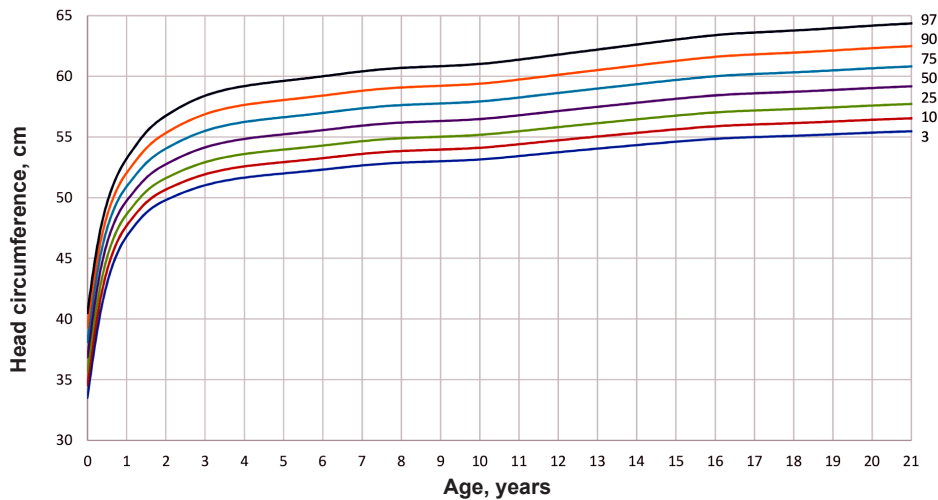
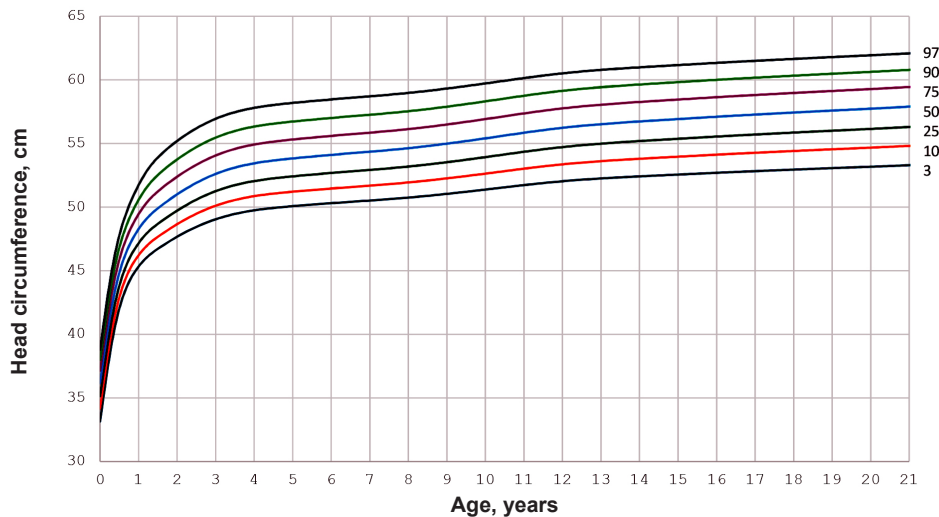
Comparing these references with those

published by Hoover-Fong et al. (2021) and Merker et al. (2108), we found they have similar trajectories with accelerated growth during the early years of age, showing that there is a common basis in the impact of the *FGFR3* mutation on cephalic growth.^{22,23}

However, the cephalic size of the Argentine references is 1.3 cm smaller at 12 and 24 months, as is observed if we compare the cephalic size of the general population between these regions, which could reflect local environmental or genetic factors. Comparison graphs are presented in the *Supplementary material*.

On the other hand, this tool completes the data for the auxological evaluation of this population, which is essential for assessing the efficacy and possible changes with treatments under development.²⁴

One of the strengths of these references is that they are constructed with data from a population of children with ACH, followed by a single center, where trained personnel perform standardized

FIGURE 1a. Centiles of head circumference in men with achondroplasia**FIGURE 1b. Centiles of head circumference in women with achondroplasia**

measurements. On the other hand, the LMS method was applied for their construction. It allows the estimation and summarization of the HC curves to convert measurements to Z scores, facilitating comparisons with other populations and their inclusion in Excel add-ins for data analysis in large populations.²⁵

CONCLUSIONS

The availability of references from birth to 21 years of age will allow us to follow up the cephalic growth of this population throughout

childhood and into adulthood. It is a valuable tool for diagnosing deviations that require a rapid interdisciplinary approach. ■

The supplementary material provided with this article is presented as submitted by the authors. It is available at: https://www.sap.org.ar/docs/publicaciones/archivosarg/2025/10565_AO_DelPino_Anexo.pdf

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FIGURE 2a. Comparison between head circumference (centiles 3, 50, and 97) of the general population and achondroplasia in men

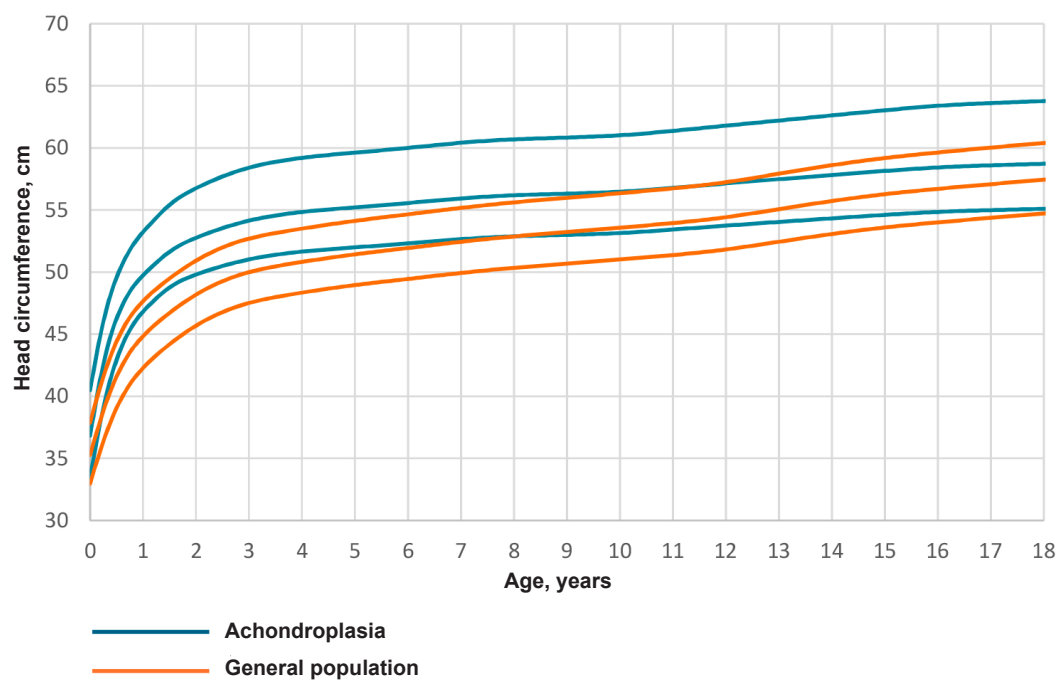
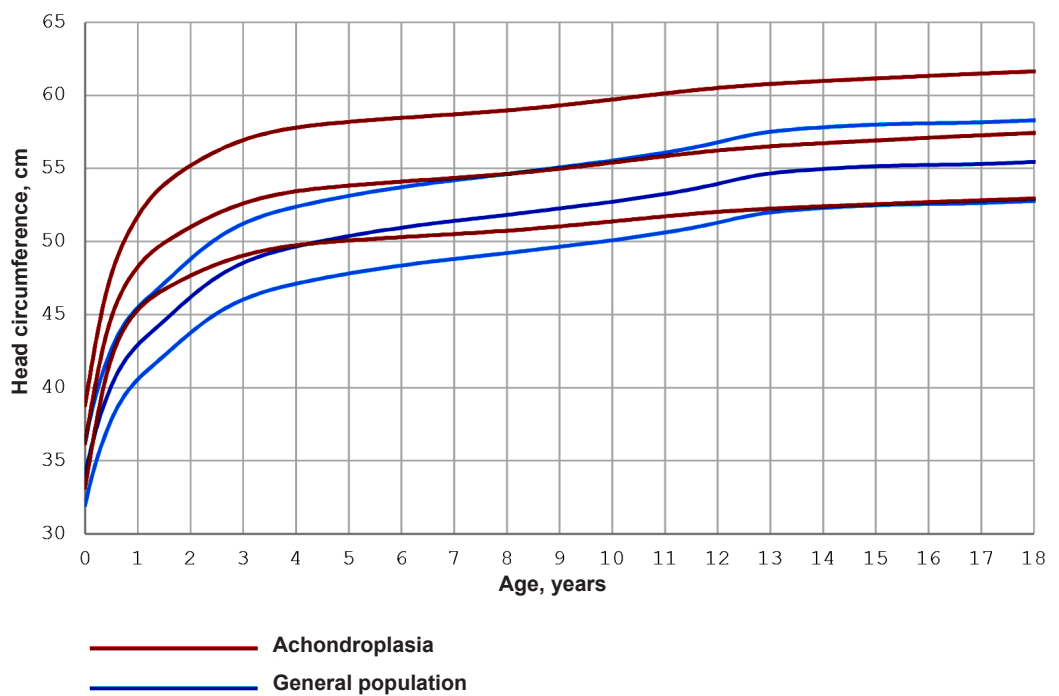


FIGURE 2b. Comparison between head circumference (centiles 3, 50, and 97) of the general population and achondroplasia in women



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