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Original Research

A Mathematical Model to Predict Pediatric Macrocephaly

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ABSTRACT

Objective: Macrocephaly is defined as a head circumference (HC) above +2 standard deviations (SD) for age and sex, and a value above +3 SD is generally regarded as clinically relevant. Both thresholds are published only as discrete, month-by-month reference tables. This study aimed to reduce the World Health Organization (WHO) upper reference limits of HC to continuous, closed-form functions of age, and to assess how closely such functions reproduce the tabulated values.

Methods: The WHO HC-for-age values corresponding to +2 SD and +3 SD for girls and boys (1–60 months) were used. Six regression models were applied separately to each sex and each threshold. The model with the highest coefficient of determination (R^2) was selected as the best fit.

Results: Logarithmic regression gave the highest R^2 in all four datasets (R^2 = 0.996 throughout). For +2 SD, the models were HC = 38.685 + 3.509 × ln (t) for girls and HC = 39.574 + 3.533 × ln (t) for boys. For +3 SD, they were HC = 39.906 + 3.562 × ln (t) for girls and HC = 40.653 + 3.628 × ln (t) for boys, where t is age in months (all $p < 0.001$). Deviation from the reference was largest in the first three months (up to 0.57 cm) and did not exceed 0.35 cm beyond the first year.

Conclusion: The upper limits of HC follow a logarithmic function of age. Expressing them in closed form allows the thresholds to be embedded in radiological reporting software, evaluated at any age without interpolation, and differentiated to obtain the slope of the threshold curve. A lookup table permits none of these directly. Because the largest deviation from the reference, up to 0.57 cm, occurs within the first three months, a borderline value measured on cross-sectional imaging at that age should be confirmed against the table.

Keywords: cephalometry, growth charts, infant, megalencephaly, reference values, regression analysis

INTRODUCTION

Macrocephaly is defined as a head circumference (HC) more than two standard deviations (+2 SD) above the mean for age and sex [1,2], a limit that corresponds approximately to the 97.7th centile. Megalencephaly is conventionally identified by the same +2 SD limit, but the two terms are related rather than interchangeable: macrocephaly refers to the head as a whole, whereas megalencephaly refers to overgrowth of the brain itself, which can involve only one hemisphere or a limited region and then leaves the head circumference largely unchanged [1,2]. This distinction cannot be drawn from the measurement alone. Whether a large head reflects an enlarged brain or an expansion of some other intracranial compartment is settled by imaging, and that question is addressed before anything else in the radiological workup [1]. Because roughly 2–3% of healthy children have an HC between +2 and +3 SD, a value above +3 SD is often regarded as clinically relevant macrocephaly [1]. The differential diagnosis spans benign familial macrocephaly and benign enlargement of the subarachnoid spaces at one end, and hydrocephalus, subdural collections, storage and metabolic disease, and overgrowth syndromes at the other [1]. When an infant is scanned because the head is large or growing too fast and no structural or developmental abnormality is found, the usual diagnosis is benign enlargement of the subarachnoid spaces, the most common cause of macrocephaly in infancy [1,3]. Less often, a subdural collection or hemorrhage complicates it, or large bilateral collections are themselves the cause, and abusive head trauma then enters the differential [3]. However, the first step is always the same: to establish whether the head is in fact larger than expected.

Main Points

- The upper limits of head circumference in the WHO Child Growth Standards rise logarithmically with age through the first five years, in both girls and boys.
- Two-parameter logarithmic formulas reproduce both the +2 SD threshold that defines macrocephaly and the +3 SD threshold above which it is regarded as clinically relevant, with $R^2 = 0.996$ in every dataset.
- Unlike a reference table, a closed-form threshold can be embedded in radiological reporting software, evaluated at any age without interpolation between months, and differentiated to give the slope of the threshold curve.
- The formulas cannot be used at birth, because ln(0) is undefined, and they deviate most from the reference during the first three months of life (up to 0.57 cm), so borderline results in early infancy should be checked against the table.

The measurement itself, however, is not always at hand. Routine well-child visits carry it only to the age of 2 years, and past that age, no guideline requires it, so in older children, the head is frequently never measured at all [1]. When the referring clinician has supplied no value, the radiologist is the one left to settle the question from the images. This step is more fragile in radiological practice than it appears. Radiologists commonly judge head size by visual impression alone, which is a subjective assessment. When judgments made by eye were checked against the tape, they proved right in barely half to three-quarters of children (52.3–72.7%; kappa 0.27–0.55). Measuring the head on the images and reading the value off the WHO curves did far better: ≥ 95.5% on computed tomography (CT) and ≥ 93.1% on magnetic resonance imaging (MRI), with kappa ≥ 0.92 and ≥ 0.88 [4]. Measuring the head, rather than eyeballing it, is therefore what makes the assessment reliable, and HC can be measured reproducibly on cross-sectional imaging [5].

The measured value must then be compared against an age- and sex-specific threshold. That threshold is published as a discrete table: one value per completed month. A table is adequate for a human reader with a chart in hand, but it is a poor object to compute with. It has no value between two months, it cannot be differentiated, and it must be carried as a lookup array wherever the comparison is to be automated.

A previous study reduced the lower limit of HC to a closed-form function in order to predict microcephaly [6]. The present study addresses the upper limits. The aim was to determine the mathematical rule governing the upper boundary of head growth and to express both the +2 SD and the +3 SD thresholds as continuous functions of age.

MATERIALS AND METHODS

This study was approved by the Gaziantep University Clinical Research Ethics Committee (Date: September 15, 2021, Decision no. 2021/165). It used publicly available reference data and did not involve patients or any identifiable individual data. Permission to use the WHO material was obtained (WHO permission ID: 202609696).

The WHO Child Growth Standards were generated from a multicenter growth reference study of healthy infants and young children from several countries and ethnic backgrounds [7]. The simplified field tables of head-circumference-for-age (birth to 5 years, z-scores) were used [8]. Four datasets were extracted: the +2 SD and +3 SD values for girls and for boys, for each completed month from 1 to 60. The value at birth (month 0) was excluded because the logarithmic term is undefined at zero.

Statistical Analysis

Six regression models were applied to each of the four datasets, with HC denoting head circumference in centimeters and t age in completed months: linear, $HC = b_0 + b_1t$; quadratic, $HC = b_0 + b_1t + b_2t^2$; cubic, $HC = b_0 + b_1t + b_2t^2 + b_3t^3$; logarithmic, $HC = b_0 + b_1\ln(t)$; exponential, $HC = b_0 \times \exp(b_1t)$; and growth, $HC = \exp(b_0 + b_1t)$. The exponential and growth models are alternative parameterizations of the same curve and therefore produce identical fitted values, so their fit statistics coincide. The model with the highest coefficient of determination (R^2) was selected as the best fit. For the selected model, the constant and the regression coefficient were tested, and the residuals between the tabulated values and the model estimates were examined. The coefficients, R^2, root mean square error, and maximum absolute residual of all six models are given in Supplementary Table S1. Analyses were performed with SPSS Statistics 22.0 (IBM Corp., Armonk, NY, USA). A value of $p < 0.05$ was accepted as statistically significant.

RESULTS

Logarithmic regression produced the highest R^2 in all four datasets and was identified as the best model throughout (Table 1).

The four logarithmic models, all of the form $HC = a + b \times \ln(t)$ with t denoting age in completed months, were:

Girls, +2 SD: $HC = 38.685 + 3.509 \times \ln(t)$

Girls, +3 SD: $HC = 39.906 + 3.562 \times \ln(t)$

Boys, +2 SD: $HC = 39.574 + 3.533 \times \ln(t)$

Boys, +3 SD: $HC = 40.653 + 3.628 \times \ln(t)$

All four models were statistically significant ($p < 0.001$), and in each, the constant and the regression coefficient were significant ($p < 0.001$). The residuals between the tabulated values and the model estimates are summarized in Table 2. Figures 1 and 2 show the agreement between the observed data and the logarithmic estimates for girls and boys, respectively.

In all four datasets, the largest deviation occurred within the first three months of life, reaching 0.57 cm. It then decreased, and although it rose again slightly toward the fifth year, it did not exceed 0.35 cm at any age beyond the first year.

DISCUSSION

Both upper limits of HC, namely the +2 SD boundary that defines macrocephaly and the +3 SD boundary above which it is usually considered clinically relevant, increase logarithmically with age through the first five years, in both sexes, and each is reproduced by a two-parameter expression with $R^2 = 0.996$. Two thresholds are given deliberately: +2 SD is the definition. It serves as the screening boundary, while +3 SD separates the 2–3% of healthy children who sit between the two limits from those in whom a large head is more likely to matter [1]. A single pair of formulas per sex, therefore, covers both decisions.

Table 1. Coefficient of determination (R^2) for the six regression models, by sex and threshold.

Regression model	Girls +2 SD	Girls +3 SD	Boys +2 SD	Boys +3 SD
Logarithmic	0.996	0.996	0.996	0.996
Cubic	0.981	0.981	0.979	0.979
Quadratic	0.940	0.939	0.935	0.936
Linear	0.783	0.782	0.775	0.780
Exponential	0.763	0.762	0.755	0.761
Growth	0.763	0.762	0.755	0.761

R^2, coefficient of determination; SD, standard deviation. R^2 for the exponential and growth models was calculated from how closely the fitted values reproduce the tabulated HC, as for the other four models, so that all six are compared on the same basis. Software that fits these two models by first taking the logarithm of HC reports R^2 for those log-transformed values instead, which gives slightly lower figures.

Table 2. Model coefficients, R^2, and residuals (cm) for the four logarithmic models.

Dataset	Constant (*a*)	Coefficient (*b*)	R^2	*e* min	*e* max	SD res
Girls +2 SD	38.685	3.509	0.996	−0.54	+0.25	0.19
Girls +3 SD	39.906	3.562	0.996	−0.52	+0.26	0.20
Boys +2 SD	39.574	3.533	0.996	−0.56	+0.30	0.21
Boys +3 SD	40.653	3.628	0.996	−0.57	+0.29	0.20

e min, minimum residual; *e* max, maximum residual; R^2, coefficient of determination; SD, standard deviation; SD res, standard deviation of the residuals.

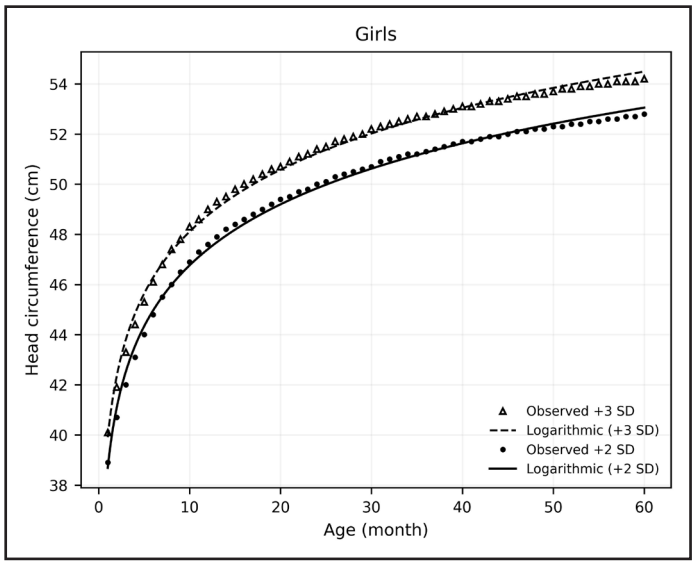

Figure 1. Girls. Observed WHO values at +2 SD (dots) and +3 SD (triangles) with the corresponding logarithmic estimates (solid and dashed lines).

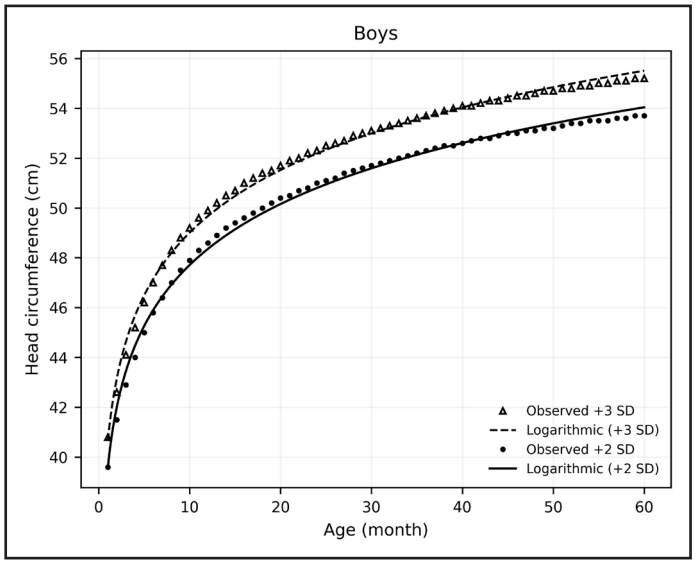

Figure 2. Boys. Observed WHO values at +2 SD (dots) and +3 SD (triangles) with the corresponding logarithmic estimates (solid and dashed lines).

The practical value of a closed-form model does not lie in replacing the table for a reader who has the table open. It lies in what a function can do that a list of numbers cannot. First, the expression can be embedded directly in reporting or picture archiving and communication system software: a system that measures HC on cross-sectional images can compare it against a threshold computed on the fly, without shipping and maintaining a 60-row lookup array for each sex and each limit. Given that visual impression alone misclassifies head size in a substantial proportion of children [4], such automated flagging addresses a real weakness in routine reporting. Second, the function is continuous in age: a child of 7 months and 18 days is evaluated at $t = 7.6$ with no interpolation between table rows. Because the models were fitted to values tabulated at completed months, a threshold returned at a fractional age is a model-based estimate rather than a tabulated reference value. Third, the expression is differentiable: its derivative, $dHC/dt = b/t$, gives the slope of the threshold curve at any age, which a table can supply only as a difference between adjacent rows.

The logarithmic form is also interpretable in itself. It states that HC increases in proportion to the logarithm of age, which is to say that equal increments of head circumference correspond to equal multiples of age rather than equal amounts of time. This is why head growth is rapid in early infancy and slows progressively thereafter, and it is consistent with the shape of the WHO curves at the lower limit as well [6].

Country-specific references may differ from the WHO standard, and the difference is not trivial. When 12 population references from 11 countries were compared with the WHO standard, head circumference lay above the WHO reference distribution in nearly every group, so that at 12 and 24 months about 8–9% of children would have been classified as macrocephalic rather than the 3% the definition implies [9]. A national head-circumference reference has also been published for Turkish children [10].

Which reference a center should adopt is a separate question from whether that reference can be reduced to a formula. The constants reported here belong to the WHO standard; the same regression can be applied to any national reference to obtain the corresponding local expression.

Limitations

The models are undefined at birth, since ln (0) does not exist, and should be applied from the first completed month onward. The fit, although close, is not exact: the deviation from the reference is greatest in the first three months, reaching 0.57 cm; within this period the model slightly underestimates the limit at the first month and overestimates it at the second and third, so a borderline result in early infancy should be confirmed against the table. The constants are not memorable, which is a further reason to regard the models as objects to be implemented rather than recited. Finally, the models describe the WHO reference; they do not validate it, and any error in the underlying standard is inherited.

CONCLUSION

The upper limits of the human head circumference follow a logarithmic rule with age. Reducing the +2 SD and +3 SD thresholds to closed-form functions makes them computable at any age, embeddable in reporting software, and differentiable into the slope of the threshold curve, and thereby supports the recognition of macrocephaly on cross-sectional imaging. The deviation from the reference is greatest within the first three months, reaching 0.57 cm, so a borderline value at that age should be confirmed against the reference table. The same approach can be extended to country-specific references.

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Conflict of Interest: The authors declare no conflict of interest.

Informed Consent: Not applicable. The study did not involve human participants; it used only publicly available, aggregate reference values published by the World Health Organization, and no identifiable individual data were accessed.

Data Availability Statement: Not applicable in the sense of restricted data: this study generated no private data. The analysis is based entirely on the WHO Child Growth Standards simplified field tables for head-circumference-for-age (birth to 5 years, z-scores), which are publicly available at https://www.who.int/tools/child-growth-standards/standards/head-circumference-for-age. Permission to use this material was granted by the World Health Organization (permission ID 202609696). The +2 SD and +3 SD values for months 1 to 60, together with the fitted models and residuals, are reported in full in the manuscript and its tables, so that any reader can reproduce the regressions from the cited source.

Ethical Approval: Gaziantep University Clinical Research Ethics Committee; approval date September 15, 2021; Approval number 2021/165. A copy of the approval report is submitted with this manuscript.

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