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Research paper

## Head circumference from birth to five years in France: New national reference charts and comparison to WHO standards

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## ABSTRACT

**Background:** The monitoring of head circumference (HC) is essential to early detect any conditions affecting its growth in early childhood. A positive secular trend and regional specificities in HC suggested the need to provide updated national HC reference growth charts.

**Methods:** We extracted all growth data collected from 42 primary-care physicians from across the French metropolitan territory who used the same electronic medical-records software. We selected HC measurements up to age five years for all children who were born after 1990 with birth weight > 2500 g. We derived new HC growth charts by using Generalized Additive Models for Location, Scale and Shape, then externally validated them until 30 months of age by comparison with the national population-based *Étude Longitudinale Française depuis l'Enfance* (ELFE) birth cohort and compared them to previous French and WHO growth charts.

**Findings:** With 973,869 HC measurements from 157,762 children, new calibrated HC growth charts from birth to age five years were generated. The new HC growth charts showed good external fit by comparison with the ELFE birth cohort. As compared with the new HC growth charts, the previous French and WHO growth charts mean HC z-scores were, respectively, -0.4 and -0.6 SD for girls and -0.2 and -0.6 SD for boys.

**Interpretation:** We produced and validated national calibrated HC growth charts by using a novel big-data approach applied to data routinely collected in clinical practice. Comparison with previous French and WHO growth charts confirmed a positive secular trend since the 1960s and regional specificities.

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Abbreviations: ELFE, *Étude Longitudinale Française depuis l'Enfance*/French longitudinal study of children; HC, head circumference; GAMLSS, Generalized Additive Models for Location, Scale and Shape; SD, standard deviation; WHO, World Health Organization

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## Research in context

### Evidence before this study

The monitoring of head circumference (HC) is essential to early detect any conditions affecting its growth in early childhood. A positive secular trend and regional specificities in HC suggested the need to provide updated national HC reference growth charts.

### Added value of this study

We produced and validated national calibrated HC growth charts by using a novel big-data approach applied to data routinely collected in clinical practice. Comparison with previous national and WHO growth charts confirmed a positive secular trend since the 1960s and regional specificities.

### Implication of all the available evidence

HC growth monitoring may be optimized by using these national calibrated HC growth charts generated from a big-data approach, based on data routinely collected in clinical practice.

update of existing French HC growth charts seems necessary to provide an accurate tool for clinical monitoring with good calibration to the contemporary paediatric population.

The present study aimed at producing French calibrated HC growth charts from birth to age five years, to externally validate them with a national population-based birth cohort and to compare them with previous French and WHO growth charts. We also proposed and validated a big-data approach based on data routinely collected in clinical practice to produce these French calibrated HC growth charts [26].

## 2. Population and methods

### 2.1. Derivation of new HC growth charts

We used a two-step multicentre longitudinal design. First, we automatically extracted data for individual paediatric patients from electronic medical records fulfilled by primary-care physicians; we combined these data in a secured medical observatory dedicated to research and accredited for data health storage. Second, tens of thousands of extracted HC measurements were analysed. This approach has been described in detail elsewhere for the derivation of height and weight growth charts [26]. The study protocol was approved by the ethics committee and institutional review board of the French Institute of Medical Research and Health (Inserm IRB00003888, IOR0003254, FWA00005831), which provided a waiver of consent given the completely anonymous design of data collection.

We included all children up to age five years who were born after 1990 with birth weight > 2500 g and who were measured at least once by their primary-care physician. Participating physicians belong to one of two participating primary-care medical societies (French Association of Ambulatory Pediatrics or French Society of General Medicine) and had to use the last version of the same electronic medical-records software. We recruited 32 randomly sampled primary-care paediatricians after stratification by geographical area and size of urban area (*i.e.*, four participants for each of the eight Research and National Development zones—two in large urban areas and two in small urban areas), and 10 volunteer general practitioners (Supplementary Figure 1).

Participating physicians had routinely entered data including sex, year of birth, HC and age at growth measurement into the electronic medical records between 1990 and 2018, and such data were automatically and anonymously extracted from their computers. Children ( $n=4,883$ ) with an excessive number of growth measurements after age six months were excluded because frequent medical visits after this age were likely to reflect an underlying condition that might affect growth (Supplementary Table 1). A data-cleaning process was applied to growth data to detect and delete measurement or transcription errors. After removing duplicates, we deleted absolute z-scores  $\geq 5$  standard deviations (SDs) based on WHO growth charts and aberrant z-score variations between two successive measurements (Supplementary Figure 2). We randomly selected a limited number of measurements per child to speed computations and to reduce the over-representation of children measured more frequently before age two years by retaining no more than five measurements per child from ages 1–6 months, three from ages 6–12 months, and three from ages 12–24 months.

For each sex, we derived HC growth charts from birth to age five years as a function of age (in days) by using Generalized Additive Models for Location, Scale and Shape (GAMLSS) [28]. Because HC is normally distributed, the modelling of its growth was based on two parameters: the median ( $M$ ) and the coefficient of variation ( $S$ ). Cubic-penalized B-splines were used as smoothing functions. We selected the best final model by a step-by-step process from the simplest to most complicated model by varying the numbers of knots and equivalent degrees of freedom separately for each parameter,

## 1. Introduction

Head circumference (HC) is a major indicator of brain development, especially in early childhood and is correlated with cognitive function in children and adults [1–3]. The monitoring of HC is essential to early detect any conditions affecting its growth in early childhood. Numerous affections can lead to macrocephaly (*e.g.*, hydrocephalus, brain tumours or other expansive conditions) or microcephaly (*e.g.*, genetic or metabolic causes, brain injuries or some craniosynostosis) [4,5]. Post-natal HC growth is also affected by many determinants, including prenatal exposure to toxic agents, antenatal growth restriction, gestational age, birth weight, nutrition or socio-economic status [6–11]. Finally, parents' HC is responsible for half of the variability in HC [12,13]. Consequently, accurate recognition of a departure from normal HC growth is both essential and challenging.

HC growth monitoring relies on growth charts to define what constitutes normal and abnormal growth, based on both clinical expertise and algorithms [14]. In many countries with advanced economies, healthcare practitioners usually use national reference growth charts [15–18]. In 2006, the World Health Organization (WHO) published and recommended the use of international growth standards for HC growth monitoring [19]. However, a recent meta-analysis showed that HC growth in children up to age five years varies widely between countries, notably due to genetic differences, which suggested, that the use of an international HC growth chart was not appropriate [20]. In France, previous HC growth charts were based on a small sample of about 600 children born from 1953 to 1954, with strong and early attrition [21]. We already demonstrated that previous French and WHO height and weight growth charts were poorly calibrated to contemporary French children, with clinically meaningful consequences on the performance of the algorithms aimed at defining abnormal growth [22, 23]. Furthermore, some countries with advanced economies have reported a positive secular trend in HC, with a mean increase of one to three cm between the 1950s and the 1990s in children [17, 18, 24, 25]. The hypothesis of such a secular trend in HC in France is supported by the positive secular trend in height recently described in this country [26] and the well-known correlation between height and HC [24, 27]. Thus, an

and compared models with the Generalized Akaike Information Criterion (Supplementary Box 1). HC growth charts were modelled until age five years because the number of measurements after this age was insufficient to allow a good fit of the model and good accuracy of the growth charts. Furthermore, the clinical interest of HC monitoring after age five years requires additional evidence [5,29].

The internal fit of the final model was checked by inspecting empirical SD values and worm plots [30]. Empirical SD values were calculated by grouping data by 3-month intervals. Worm plots were represented by two-month intervals from birth to six months, three-month intervals from six to 12 months, six-month intervals from 12 to 24 months, and 12-month intervals from 24 to 60 months.

## 2.2. External validation and comparison with previous charts

To externally validate the new HC growth charts, we used data from the *Étude Longitudinale Française depuis l'Enfance* (ELFE) birth cohort (French Longitudinal Study of Children; <https://www.elfe-france.fr/en/>) that included 18,329 children born in 2011 in a random sample of 349 maternity units in France and was previously described in detail [31]. The main inclusion criteria for the ELFE birth cohort were singleton births or twins born after 33 weeks' gestation to mothers aged 18 years or older. For the present analysis, children with a parental withdrawal of consent ( $n=56$ ), birth weight  $< 2500$  g ( $n=921$ ) or no HC measurement ( $n=244$ ) were excluded. We applied the same data-cleaning process described above and restricted the comparison to 30 months because of the paucity of HC measurements after this age in the ELFE birth cohort. Thus, 16,873 children included in the ELFE birth cohort with 70,996 HC measurements from birth to 30 months were analysed.

Data from the ELFE birth cohort, and previous French and WHO growth charts, as summarised in Supplementary Table 2, were compared to new HC growth charts by converting HC values to z-scores based on the new HC growth charts [32]. We assessed and represented graphically the mean HC z-score-for-age from birth to five years. We performed a visual comparison of the median and  $\pm 2$  SD for the new HC growth charts with the ELFE birth cohort data and with previous French and WHO growth charts.

All statistical analysis involved using R v3.4.2 (R foundation for Statistical Computing, Vienna, Austria) and GAMLSS package v5.1.2.

## 2.3. Role of the funding source

The funders had no role in the study design, data collection and analysis, preparation of the manuscript and decision to publish.

## 3. Results

After application of the selection criteria and the cleaning process, 157,762 children (69,558; 44% girls) with at least one HC measurement between birth and five years were included in this analysis (Supplementary Figure 3). The total number of HC measurements was 973,869 and decreased from 656,664 before one year to 8575 during the fourth year, with a mean number of 6.2 (SD 4.2) measurements per child.

The HC growth charts from birth to age five years for girls and boys obtained by modelling and their comparison with their empirical SD values are in Fig. 1. The inspection of worm plots (Supplementary Figure 4) showed good internal fit because they were close to zero regardless of age and sex.

The comparison of the HC growth charts with data from the ELFE birth cohort showed good external fit (Fig. 2). Mean ELFE HC z-scores based on the new HC growth charts were globally close to zero SD for girls and boys from birth to 30 months. Mean HC z-scores for girls and boys were, respectively,  $-0.06$  and  $-0.04$  SD at birth;  $-0.05$  and  $0.00$  SD at 6 months; and  $-0.10$  and  $-0.05$  SD at one year. The visual

comparison of new HC growth charts showed a satisfactory overlay of the modelled SD curves with empirical SD values from the ELFE birth cohort (Fig. 3).

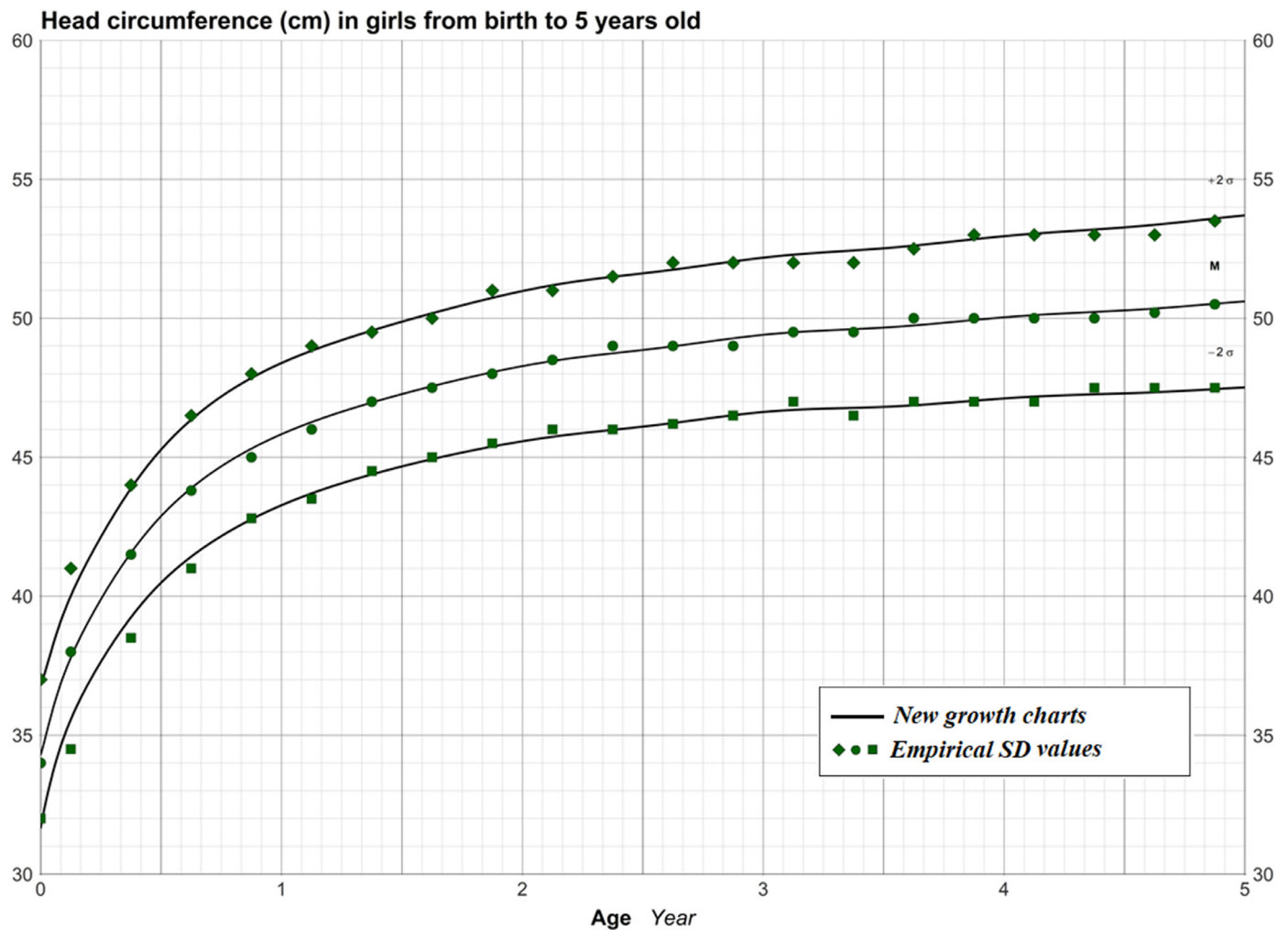
The comparison of the HC z-scores for the new HC growth charts with previous French or WHO growth charts from birth to five years is presented in Fig. 2. For previous French growth charts, mean HC z-scores for girls and boys were, respectively,  $0.09$  and  $0.26$  SD at birth;  $-0.76$  and  $-0.57$  SD at six months;  $-0.42$  and  $-0.20$  SD at one year; and  $-0.21$  and  $0.02$  SD at five years. For WHO growth charts, mean HC z-scores were  $-0.60$  SD from birth to five years, with a maximal mean z-score of  $-0.84$  SD around two years and no sex difference. Indeed, for girls and boys, mean HC z-scores were, respectively,  $-0.31$  and  $-0.26$  SD at birth;  $-0.58$  and  $-0.53$  SD at six months;  $-0.75$  and  $-0.68$  SD at one year; and  $-0.47$  and  $-0.48$  SD at five years. This difference in z-scores is reflected in the different HC growth charts presented in Fig. 3. The previous French and WHO growth charts were shifted down, on average, as compared with the new HC charts.

## 4. Discussion

### 4.1. Main findings and interpretation

We constructed and validated new national calibrated HC growth charts from birth to age five years with data for contemporary children. The HC of contemporary children was slightly greater than the one from previous French or WHO growth charts, which suggests a positive secular trend since the 1960s and regional specificities. This secular trend seemed to be more pronounced in girls and to narrow with age. Previous French growth charts had lower median and  $\pm 2$  SD curves than the new HC growth charts, which indicates that children born in the 1960s had a smaller HC compared to children born in the 2000s, especially in the first two years of life. This gap between HC growth charts suggests greater HC prenatal growth and accelerated HC growth during the first year of life for children born in the 2000s as compared with those born in the 1960s. This positive secular trend in HC between the 1960s and 2000s is consistent with a positive secular trend recently shown in height in France [26] and concordant with the well-known correlation between height and HC [27]. Indeed, a comparison of new growth charts to previous French charts for children from one month to five years revealed an average difference of  $-0.70$  SD for height [26]. This positive secular trend in HC has also been described in many countries between the 1920s and 2000s in Europe, Asia, the United States and Africa [17, 18, 24, 25, 33-36]. Several hypotheses related to environmental factors (nutritional quality and access, general child health or socioeconomic conditions) have been suggested to explain this trend [15, 37-39].

Our results also suggest that the secular trend decreased with age for both sexes and was more pronounced in girls. At five years, girls born in the 2000s had a slightly higher mean HC than those born in the 1960s (difference of  $0.20$  SD), whereas boys had the same mean HC (difference of  $0.02$  SD). We previously described the same slight sex difference in comparing new French and previous French height charts, with a mean height difference of  $-0.79$  SD for girls and  $-0.68$  SD for boys at five years [26]. The previous French growth charts relied on a non-representative sample from only one French region and with favourable nutrition and socioeconomic conditions. Thus, children included in the development of previous French growth charts were likely to have a mean HC higher than the general population of children born in the 1960s, which would lead to an underestimation of the secular trend in our study. The selection bias that occurred for the derivation of the previous French growth charts may have been differential regarding sex, thus explaining why the secular trend was more pronounced in girls. However, we cannot rule out that boys with conditions affecting HC growth were over-represented in our study sample.



**Fig. 1.** Head circumference growth charts compared to empirical standard deviation (SD) values, for girls (a) and boys (b), from birth to five years. The empirical SD values for head circumference were calculated by grouping data by three-month intervals.

The difference between new French and WHO HC growth charts was greater than that observed with previous French charts. This gap increased with age and was maximal at  $-0.70$  SD, on average, at two years for both sexes. This result confirms the regional specificities observed in other studies [20], mainly explained by genetic differences [40]. This geographical variability appeared to have a stronger effect on HC than the secular trend, contrary to what was observed for height [26]. A recent meta-analysis in 26 different countries found that median WHO values for HC were below those for many countries, thus leading to 54% of outliers [20], and suggests that the use of an international HC growth chart seems not appropriate, as also suggested for height and weight [14, 20, 23].

The choice of adopting prescriptive or descriptive growth charts has been widely debated in the overall context of growth monitoring for which the main objective is to early detect severe conditions. Contrary to the WHO, which has proposed prescriptive growth charts (or standards), we generated here new descriptive growth charts (or references). Previous studies have shown that the performance of algorithms proposed for defining abnormal growth can be strongly modified by the kind of growth chart used (standards vs references), which highlights the need for calibration of growth charts to the target population to improve performance [23, 41, 42].

#### 4.2. Strengths and limitations

With an automated approach, we produced updated and calibrated national HC growth charts from birth to five years by using a large and national contemporary sample. The growth charts were validated by comparison to a national population-based sample. This novel big-data approach applied to data routinely collected in clinical practice appeared to be less time-consuming and costly than classical ad-hoc cross-sectional surveys. However, some limitations deserve to be discussed. First, HC was less routinely measured by physicians as children become older. Unfortunately, we were not able to collect data allowing to compare the general characteristics of children measured or not after a certain age to explore potential selection bias. Second, the recruitment in primary-care physicians might have introduced a potential selection bias by selecting children with higher socioeconomic status and better nutrition, which may overestimate the new national HC growth charts and limit their generalization to the French population. This bias was limited by the additional recruitment of general practitioners [26]. We did not collect any information on socioeconomic status, which prevented from better characterizing this potential bias. Third, data regarding any congenital or acquired condition affecting HC growth were not available. We addressed this limitation by excluding data for children with an excessive number of HC measurements and by applying a data-cleaning process.



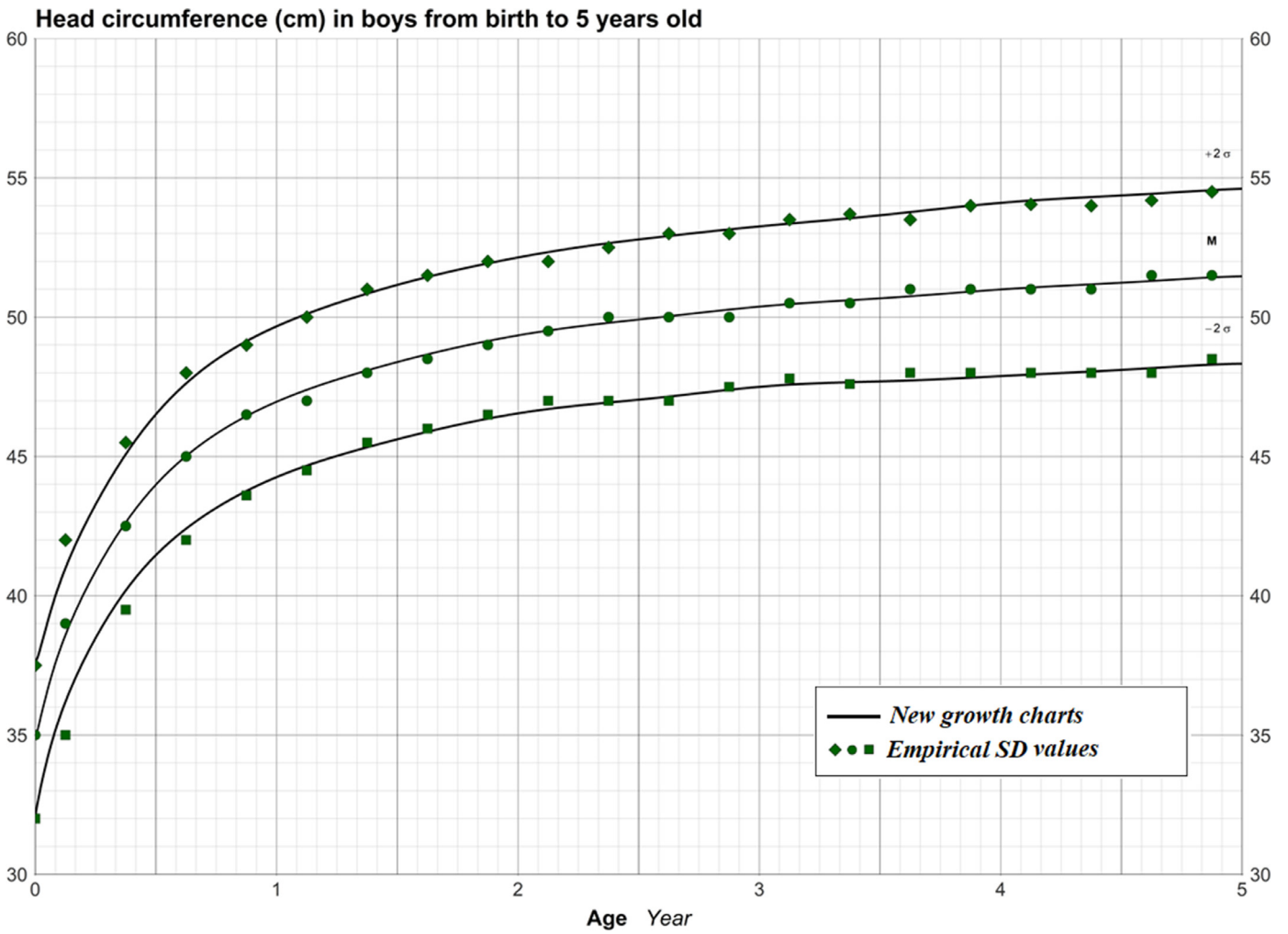


Fig. 1. Continued.

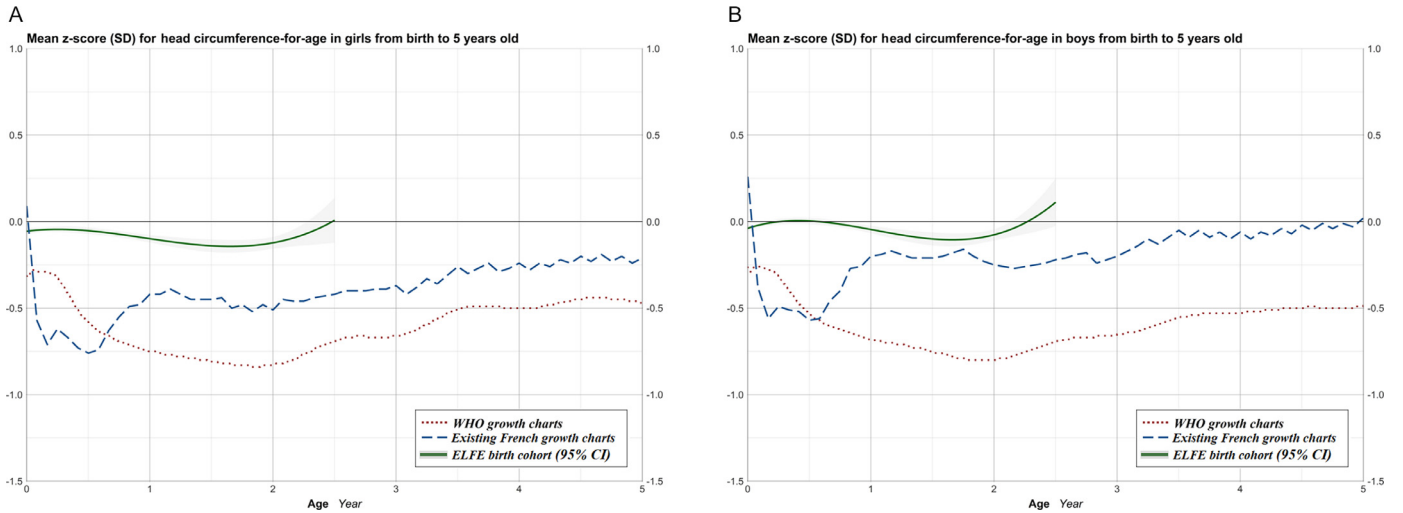
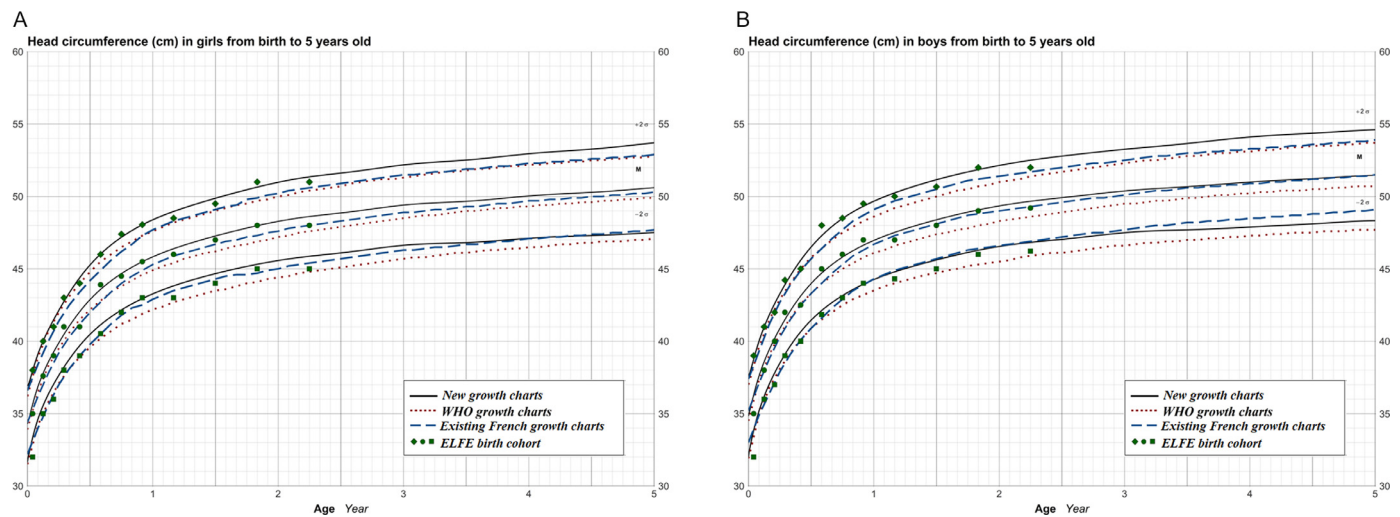


Fig. 2. Mean head circumference z-scores-for-age (in SD) from the ELFE birth cohort, and previous French and WHO growth charts, based on new head circumference growth charts, for girls (a) and boys (b), from birth to five years.

The mean head circumference z-scores-for-age of data from the ELFE birth cohort are represented graphically by using spline curves. Note: a difference of 1 SD is equivalent to a difference of 1.1, 1.1, 1.2 and 1.3 cm for girls and 1.1, 1.2, 1.2 and 1.2 cm for boys, at birth, six months, one and five years, respectively. 95% CI, 95% confidence interval.



**Fig. 3.** Head circumference growth charts compared to empirical SD values from the ELFE birth cohort, and previous French and WHO growth charts, for girls (a) and boys (b), from birth to five years. The empirical SD values from the ELFE birth cohort were calculated by grouping data by one-month intervals from birth to four months, two-month intervals from four to 12 months, four-month intervals from 12 to 24 months, and six-month intervals from 24 to 30 months.

Furthermore, the design we selected may have introduced a bias if children with a higher number of measurements differed from those with a lower number. We intended to partially limit this bias by randomly selecting a limited number of measurements per child and per age range before two years. Fourth, we were not able to include a random effect in our models to take into account the dependency between observations because of computational limitations. As recently mentioned by Cole [43], some study designs, such as ours, use longitudinal data as if they were cross-sectional ones. This approach can affect the precision in studies with limited sample size, because they rely on a lower number of children for a given number of measurements. However, we included a very large number of children in our study. Fifth, owing to the reduced number of HC measurements collected in the ELFE birth cohort after 30 months, we could not perform any external validation between 30 months and five years. Thus, we cannot exclude that for measurements collected after 30 months, there is an over-representation of children with conditions affecting HC growth or better socio-economic conditions. Finally, variations in the HC definition and techniques of measurements amongst participating physicians were likely responsible for some of the observed differences, as reported worldwide [44], because of the lack of standardization of growth monitoring practices [14]. However, routine HC measurement has been described as a reliable and reproducible measurement [45].

## 5. Conclusion

We successfully produced and validated national, calibrated, paediatric HC growth charts from birth to five years by using a novel big-data approach applied to data routinely collected in clinical practice. Comparison with previous French national and WHO growth charts confirmed a positive secular trend since the 1960s and regional specificities, which justified the updating of the previous French growth charts. This new tool will allow for optimizing HC monitoring.

## Contributors

BH, AW, MC, and PS conceived the study. AW provided data, organised the promotion and participation of healthcare professionals. BF was responsible for the extraction, the medical observatory, and data processing. MB, BH and PS performed the statistical analysis. MT, SNG, AW, TB, DS, and MAC provided expertise. MB, BH, MC and

PS drafted the manuscript. All authors approved the protocol and the final version of the manuscript.

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The ELFE birth cohort is a joint project between the French Institute for Demographic Studies (INED, *Institut national d'études démographiques*) and the National Institute of Health and Medical Research (INSERM, *Institut national de la santé et de la recherche médicale*), in partnership with the French blood transfusion service (EFS, *Établissement français du sang*), the France Public Health (*Santé publique France*), the National Institute for Statistics and Economic Studies (INSEE, *Institut national de la statistique et des études économiques*), the French Ministry of Health (DGS, *Direction générale de la santé*), the Ministry for the Environment (DGPR, *Direction générale de la prévention des risques*), the Ministry of Health and Social Affairs (DREES, *Direction de la recherche, des études, de l'évaluation et des statistiques*), the Ministry of Culture (DEPS, *Département des études, de la prospective et des statistiques*), and the National Family Allowance Fund (CNAF, *Caisse nationale des allocations familiales*), with the support of the Ministry of Higher Education and Research (INJEP, *Institut national de la jeunesse et de l'éducation populaire*). Via the RECONAI platform, it receives a government grant managed by the National Research Agency under the investments for the future programs (ANR-11-EQPX-0038).

## Declaration of conflict of interest

BH, AW, MC, BF and PS are co-owners of the patent for the new national French AFPA/Inserm/CGM growth charts. All remaining authors declare no competing interests.

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### Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.lanpe.2021.100114.

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