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Original Article

Comparative study on the early growth of preterm infants with the World Health Organization growth standards and the China growth charts

Shuang Liu,^{1,2} Ying Wang,¹ Xing Li,¹ Xifang Ru,¹ Tian Sang,¹ Xin Zhang¹ and Qi Feng¹ ¹Department of pediatrics, Peking University First Hospital, Beijing, ²Division of neonatology, First Affiliated Hospital of Xi'an Jiaotong University, Shaanxi, China

Abstract *Background*: This study focused on comparing the applicability and efficacy of the World Health Organization (WHO) growth standards and the China growth charts in diagnosing malnutrition and indicating nutritional interventions in preterm infants.

Methods: Six hundred and eighty-three preterm infants were involved and their anthropometric data were collected. The proportion of weight and head circumference less than the 10th percentile (P_{10}), weight less than the 25th percentile (P_{25}), and weight for length greater than the 90th percentile (P_{90}) identified by the WHO growth standards and the China growth charts were compared.

Results: At corrected age (CA) $1 \ll 2$ months (m), the proportion of head circumference $<P_{10}$ assessed by the WHO growth standards was higher than that assessed by the China growth charts by approximately 4.4% in boys and 6.6% in girls. During infancy, both boys and girls had lower proportions of weight $<P_{10}$ and weight $<P_{25}$ with the WHO growth standards than with the China growth charts: 5.1% and 5.6%, respectively, for weight $<P_{10}$ and 7.0% and 8.8%, respectively, for weight $<P_{25}$. For boys older than CA 1 m and for girls older than CA 3 m, the proportion of weight-for-length $>P_{90}$ assessed by the WHO growth standards was greater than that assessed by the China growth charts.

Conclusions: Compared with the China growth charts, the WHO growth standards can further reduce the number of diagnoses of abnormal physical growth, are more helpful in avoiding overnutrition interventions, and are more sensitive in the early detection of delayed head circumference growth.

Key words anthropometry, growth chart, infant, nutritional management, premature.

As neonatal intensive care has improved, the survival rate of preterm infants, has improved greatly in recent years. Beyond the survival rate, neonatologists and pediatricians now pay more attention to postnatal growth, nutritional status, and long-term outcomes. The physical growth of preterm infants, especially in the first year of life, is closely related to their long-term health.¹ Delayed postnatal growth is associated with neurological diseases and behavioral problems. Gaining weight abnormally quickly increases the risk for metabolic and cardiovascular disease.² Unfortunately, both delayed and rapid growth are common phenomena, with a large burden to families and society. Monitoring guided growth evaluations and nutrition-related instructions is therefore important and necessary in modern clinical practice for preterm infants.

Correspondence: Qi Feng, Professor, Department of pediatrics, Peking University First Hospital, Xi'anmen Street, Xicheng District, Beijing 100034, China. Email: fengqizf@126.com

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Growth standards and / or references are commonly used tools for monitoring infants, most of which were developed on the basis of data on full-term babies, including the international growth standards released by WHO and some other local growth references. The WHO growth standards published in 2006 were constructed based on the data collected from six countries (Brazil, Ghana, India, Norway, Oman and the USA), where the children in the WHO sample lived under an optimal growth environment (breastfed, non-smoking mother, and adequate healthcare access). Although it is obvious that the WHO growth standards are applicable for global uses, the feasibility of the WHO standards for local populations remain controversial. For example, one study in France suggested that the WHO standards were more suitable,³ whereas some studies suggested the WHO standards should be partially used for children under 2~3 years rather than of all ages,^{4,5} while some other studies preferred to use their local growth charts.^{6–8}

Generally, growth references based on full-term infants are used for preterm infants whose corrected gestational age (CGA) is older than 40 weeks.⁹ In China, the China growth charts published in 2009 are widely used. They were established based on data collected from nine cities including the north, south, west, east, and the middle of China, where all children that sampled lived in optimal environment and were given good healthcare.

Nutritional status assessments are important and are strongly dependent on the growth curves used. Different growth curves result in different assessment outcomes, which then influence the feeding protocols and even the long-term health of the infants. To provide accurate and reasonable advice on selection of growth references for improved growth outcomes of preterm babies, we therefore investigated the applicability and efficacy of the WHO growth standards and the China growth charts in monitoring the growth of Chinese preterm infants.

Methods

Study population

Preterm infants who were admitted to the neonatal intensive care unit (NICU) of Peking University First Hospital after 1 January, 2015, and were of a corrected age (CA) older than 6 m by 31 October, 2017, were included in this study. All infants were admitted to the NICU in the first 24 h of life, discharged after reaching a stable condition, and followed up in the outpatient department. Details of the follow-up rate are shown in Table S1. Infants were excluded if they died, if they were discharged against medical advice, or if they did not have any follow-up information.

The parents of the preterm infants were trained well in the caring of a baby before the infants were discharged. The parents were instructed to follow up 2–3 weeks after discharge, at CGA 40 weeks, and at CA 1, 2, 3, 6, 9, and 12 m. Physical growth assessments during follow ups were based on the Fenton preterm growth charts published in 2013 before a CGA of 40 weeks and by the China growth charts published in 2009 after term age. Nutrition-related instructions were given following related national or international recommendations and guidelines.^{10,11} The preterm infants received human milk fortifier (Similac Human Milk Fortifier) when enteral intake exceeded 50–100 mL/kg/day. Complementary food was introduced at CA 4 ~ 6 m.

Data collection

We obtained a list of eligible infants from the admission registration system. All infants' information, including the gestational age, single or multiple birth indication, growth (weight, length, and head circumference) at admission and discharge, duration of hospitalization, feeding patterns, and follow-up data at CA, were collected. As a retrospective study, in 2015, we did not apply for the ethical approval because there were no biological samples such as blood to be collected, no extra intervention applied, and no extra spending for infants.

The infants' gestational age was determined by the combination of information of their mother's last menstrual period, a fetal ultrasound scan during early pregnancy, and a physical examination at admission. The age at follow up was corrected on the basis of this information. The SECA electronic baby scale (Saikang Medical Measurement System Co. Ltd, Zhangjiagang City, Jiangsu Province, China) was used to measure the length and weight of baby. Head circumference was measured consistently over the most prominent part on the back of the head (occiput) and 1 cm above the eyebrows (supraorbital ridges) using a flexible, non-stretchable tape. All physical growth data collected during hospitalization were double checked, and the mean value was collected by NICU staff who had undergone standardized training. The data collected at the follow ups were measured by a regular nurse. The weight measurement was accurate to 0.01 kg, and the measurement of the length and head circumference was accurate to 0.1 cm. The breastfeeding ratio was calculated by the percentage of breast milk intake from the total amount of milk intake within 1 week of the follow up.

Data grouping and related definitions

The anthropometric data at the follow ups were divided into six groups: CA $0 \ll 1$ m, $1 \ll 2$ m, $2 \ll 3$ m, $3 \ll 6$ m, $6 \ll 9$ m, and $9 \ll 13$ m. The data of infants with a CGA $37 \ll 40$ weeks were included in the CA $0 \ll 1$ m group. Because there were more data on infants with a CGA of $37 \ll 38$ weeks, 61 data of which were partially excluded according to the gestational age distribution of normal fullterm infants in China.¹² As some preterm infants were followed up at a CA of more than 12 m, the upper limit of the last group was adjusted to 13 m to reduce the amount of data loss.

The physical growth of the infants at each follow up was evaluated using both the WHO growth standards and the China growth charts. The Z-score of the weight, which indicates a standard deviation from the average weight, was calculated based on the corresponding anthropometric calculator in these two growth references. The percentiles of weight, head circumference, and weight for length were also calculated, and the prevalence of growth retardation, rapid growth, and nutrient fortification timing in each age group were compared in pairs.

Growth retardation was defined as a physical growth index lower than the 10th percentile ($<P_{10}$) of the corrected age and specific sex evaluated by the WHO chart or China growth chart. Rapid weight gain was defined as a weight-for-length value higher than the 90th percentile ($>P_{90}$),¹⁰ nutrient fortification was suggested when the weight value was lower than the 25th percentile ($<P_{25}$) for appropriate for gestational age (AGA) infants and $<P_{10}$ for small for gestational age (SGA) infants.¹⁰ Malnutrition is not just a description of anthropometric parameters but also the chronicity of malnutrition, etiology, and pathogenesis, and developmental / function outcomes.¹³ In this study, we focused on nutrition intervention for preterm infants, so we take this definition for abnormal growth.

According to the ratio of breastmilk feeding, the preterm infants were selected and divided into two groups: the breast-feeding ratio larger than 75% (\geq 75%) group for the infants who had a proportion of breastfeeding that was \geq 75% at the current and previous follow-up and the breastfeeding ratio less than 25% (\leq 25%) group for the infants had a proportion of breastfeeding that was \leq 25% at the current and previous follow-up. For each group, the growth pattern was compared with the WHO and China growth references.

Statistical analysis

Descriptive statistics (medians with interquartile ranges or means with standard deviations based on the data distribution) were used for the demographic and anthropometric characteristics of premature infants.

The distribution of sex, single / multiple birth indications, and SGA infants between the follow-up group and loss to follow-up group were compared using a χ^2 test. The gestational age, weight, length, and head circumference at admission and discharge between these two subgroups were compared using an independent samples *t*-test. The duration of hospitalization was compared using a Mann–Whitney *U*-test. For all age groups and specific feeding pattern groups, the McNemar test was used to compare the prevalence of abnormal growth between the WHO growth standards and the China growth charts, and a paired *t*-test was used to compare the Zscores of the weight between these two growth references.

Analyses were performed by using the statistical package SPSS version 22.0, New York, NY, USA. P < 0.05 was considered statistically significant.

Results

Demographic characteristics and growth status of the study population

A total of 788 preterm infants fulfilled the inclusion criteria. Of these infants, 683 were discharged and followed up, while 105 were excluded. Anthropometric measurements obtained from 683 infants contained 3,147 groups of data. The flow of preterm infants involved in the study and the detailed GA distribution information of anthropometry at the follow-ups are shown in Figure 1.

Table 1 shows the demographic characteristics and physical growth status during hospitalization between preterm infants with and without follow ups. Preterm infants who did not undergo follow ups were generally more mature, heavier, and longer, and they also had shorter hospital stays.

The mean Z-scores of the weight, as evaluated by both the WHO and China's growth references, are close to or larger than 0 (Fig. 2). This result suggests that the study preterm infants generally grew well, and they are even heavier than the average.

Comparison of the prevalence of abnormal growth

Figure 3 shows the prevalence of weight growth retardation. The proportion of weight $\langle P_{10} \rangle$ assessed by the WHO growth standards was lower for preterm babies but the difference between boys and girls at CA 1 ~< 2 m was not statistically significant. Compared to the China growth charts, the WHO growth standards indicated a lower ratio of weight growth retardation, i.e. 5.1% (6.6% vs 11.7%, P < 0.001) and 5.6% (7.3% vs 12.9%, P < 0.001) less for boys and girls, respectively.

The results of delays in head circumference growth were mixed across different sexes and ages (Fig. 4). The proportion of head circumference $\langle P_{10} \rangle$ assessed by the WHO growth standards was significantly higher than that assessed by China's charts by 4.4% (10.9% vs 6.5%, P = 0.002) for boys and by 6.6% (16.1% vs 9.5%, P = 0.001) for girls at CA 1 ~< 2 m. However, for boys at CA 6 ~< 13 m and girls at CA 3 ~< 13 m, the proportion of head circumference $\langle P_{10} \rangle$ assessed by the WHO growth standards was lower than that assessed by the China growth charts. Using the WHO growth standards, the prevalence of head circumference growth retardation tended to be higher during early infancy, but it tended to be lower during later infancy.

Figure 5 shows the proportion of weight $\langle P_{25}$. During infancy, the proportion of weight $\langle P_{25}$ assessed by the WHO growth standards was lower than that assessed by the China growth charts by 7.0% (16.7% vs 23.7%, P < 0.001) for boys and by 8.8% (17.8% vs 26.6%, P < 0.001) for girls, and the difference was statistically significant at all ages except for at CA 1 ~< 2 m. This result indicates that more preterm babies may have avoided unnecessary nutrition interventions when evaluated and instructed by the WHO growth standards.

The prevalence of rapid weight gain evaluated by the WHO and China's growth references was also studied (Fig. 6). For boys older than CA 1 m and girls older than CA 3 m, the weight-for-length proportion $>P_{90}$ assessed by the WHO growth standards was statistically higher than that assessed by China's charts, suggesting that the WHO growth standards were more helpful in distinguishing infants who gained weight more quickly than they grew in length.

Growth references comparison for infants of different feeding patterns

For preterm infants with a specific feeding pattern, the weight Z-scores assessed by the WHO and China growth references were studied (Fig. 7). In the breastfeeding ratio \geq 75% group, the weight Z-scores of the two growth charts were nearly identical at CA 1 ~< 2 m, and the Z-scores deviated as CA increased. The weight Z-score assessed by the WHO standards fluctuated between 0.51~0.73 after CA 1 m, while the weight Z-score assessed by the China growth charts decreased over time. There was no evidence that the predominantly breastmilk-fed babies were more compatible with the WHO

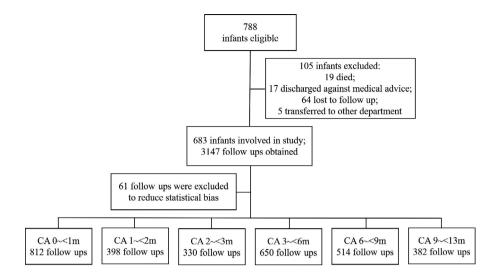


Fig. 1 Flowchart of study preterm infants and their gestational age distribution of the follow-up data. GA, gestational age.

Table 1 Comparison of the characteristics between preterm infants with and without follow ups (N = 747)

Characteristics	Follow-up group $(n = 683)$	Lost to follow-up group $(n = 64)$	$X^2/t/Z$	Р
Sex				
Boys (%)	382 (55.9)	37 (57.8)	0.084	0.772
Girls (%)	301 (44.1)	27 (42.2)		
Single birth (%)	430 (63.0)	41 (64.1)	0.031	0.861
SGA (%)	81 (11.9)	10 (15.6)	0.776	0.378
Gestational age (weeks) m \pm SD	33.3 ± 2.3	34.2 ± 1.9	-0.290	0.003*
Anthropometric data at admission				
Weight (g)	$1,956 \pm 518$	$2,144 \pm 535$	-2.762	0.006*
$m \pm SD$				
Length (cm) m \pm SD	43.1 ± 3.6	44.1 ± 3.5	-2.011	0.045*
Head circumference (cm)	30.4 ± 2.4	30.8 ± 2.4	-1.452	0.147
$m \pm SD$	JU.7 1 2.7	50.0 ± 2.4	1.452	0.147
Duration of hospitalization (days)	15.0 (11.0 ~ 29.0)	11.0 (8.0 ~ 20.0)	-3.448	0.001*
mean value(range)				
Corrected gestational age at discharge (weeks)	36.5 ± 1.3	36.5 ± 1.2	-0.054	0.957
$m \pm SD$				
Anthropometric data at discharge				
Weight (g)	$2,383\pm303$	$2,402 \pm 343$	-0.473	0.637
$m \pm SD$				
Length (cm)	46.2 ± 2.2	46.1 ± 2.5	0.143	0.886
$m \pm SD$				
Head circumference (cm) m \pm SD	32.4 ± 1.4	32.3 ± 1.4	0.449	0.653

SGA, small for gestational age.

standards. For the group with a breastfeeding ratio $\leq 25\%$, the weight Z-score fluctuated at 0 when it was assessed by the China growth charts, while it was in the range of $0.51 \sim 0.73$ when assessed by the WHO standards after CA 1 m. This result suggests that the China growth charts were more compatible than the WHO charts for predominantly formula-fed infants.

Discussion

Follow ups help monitor the growth status of preterm infants, and the growth curves used are crucial for quantitative evaluations. This study compared the similarities and differences in the WHO growth standards and the China charts, and aimed to provide reasonable advice for parents. This study showed that study preterm infants generally grew well, yet some are

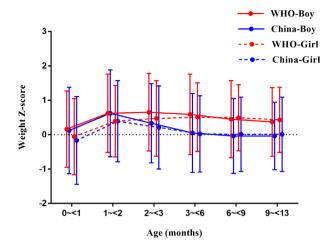


Fig. 2 Z-scores of the weight of preterm infants of different ages assessed by the WHO growth standards and the China growth charts.

slightly over-nourished, which indicates that preterm infants are prone to being overfed when the current growth charts are used. Compared to the China growth charts, the WHO standards were less likely to suggest an unnecessary nutritional intervention, as it showed a lower proportion of weight $< P_{10}$ and $< P_{25}$ and a higher proportion of weight for length $> P_{90}$.

The proportion of weight $<P_{10}$ reduced for both boys and girls, when it was evaluated by the WHO growth standards, which is consistent with the results from other groups.^{14,15} Feeding patterns play an important role in physical growth. For babies older than 6 m, breastfed infants grow slower and gain less weight than formula-fed infants.¹⁶ The WHO growth standards were established on breastfed children, where all infants were exclusively or predominantly breastfed for at least 4 m and continuously breastfed until they are 1 year

old.¹⁷ The China growth charts, however, were developed based on a population with a breastfeeding rate of 67.6% and an exclusively or predominantly breastfeeding rate until 4 m of only 47.7%.¹⁸ For infants exclusively or predominantly breastfeeding, the WHO growth standards match their growth pattern better than the local references, across different nations and regions.^{19–21} Therefore, the difference in feeding patterns could be the main reason for the less frequent diagnosis of restricted weight gain by the WHO growth standards. Besides, differences in the study population can also affect the dissimilarity between these two growth charts. In the study population of the China growth charts, low birthweight infants were not included, while 2.1% of the study population of the WHO growth standards were low birthweight infants,⁹ which obviously reduced the average growth level. Last, the China charts were developed on the basis of data on children who lived in urban areas, where children generally grow faster than in rural areas.²² In summary, using the WHO growth standards can reduce the rate of underweight infants. This effect may reduce parental anxiety concerning babies' growth and prevent the substitution of breast milk with high energy milk or with the continuous use of human milk fortifier.

It was also found in this study that the proportion of weight $<P_{25}$ assessed by the WHO growth standards was lower than that assessed by the China growth charts. The nutrition fortification will be downgraded when the baby's weight reaches or exceeds the value of P_{25} .¹⁰ As a consequence, using the WHO growth standards facilitates the early transition to breastfeeding exclusively or standard formula feeding, which avoids excessive nutrition interventions.

A higher proportion of weight for length $>P_{90}$ for boys older than CA 1 m and girls older than CA 3 m was observed, suggesting that the WHO growth standards are more sensitive than the China charts in identifying infants who are overweight or obese, which is consistent with the findings of other

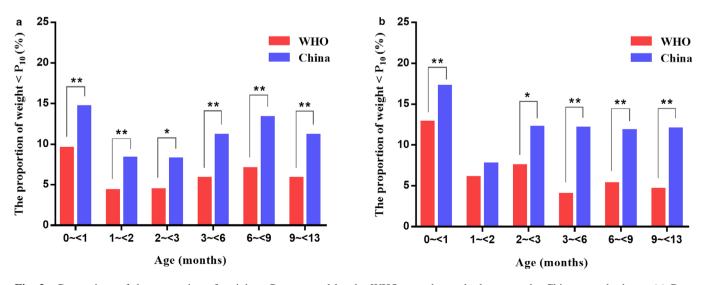


Fig. 3 Comparison of the proportion of weight $< P_{10}$ assessed by the WHO growth standards versus the China growth charts. (a) Boys and (b) girls. *P < 0.05, **P < 0.01.

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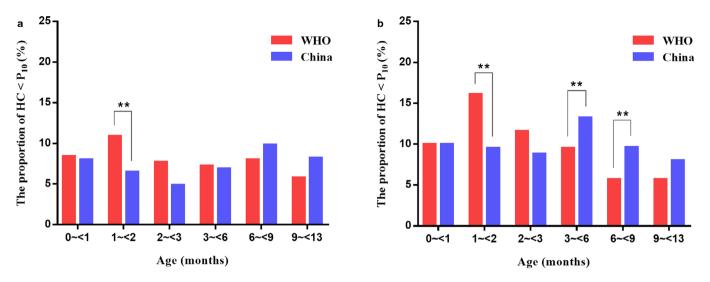


Fig. 4 Comparison of the proportion of head circumference $\langle P_{10} \rangle$ assessed by the WHO growth standards versus the China growth charts. HC = head circumference. (a) Boys and (b) girls. **P < 0.01.

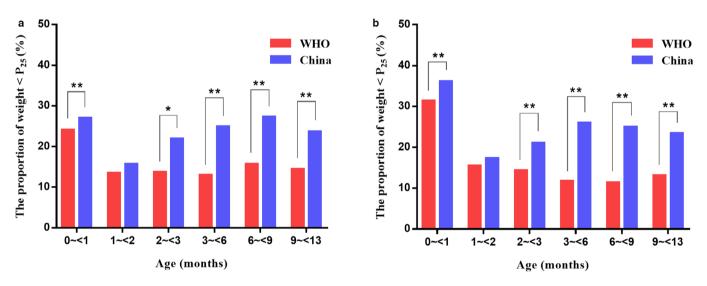


Fig. 5 Comparison of the proportion of weight P_{25} assessed by the WHO growth standards versus the China growth charts. (a) Boys and (b) girls. *P < 0.05, **P < 0.01.

studies in China and other countries worldwide.^{15,23,24} This finding is probably a result of a thin population being used for the establishment of the WHO growth standards.²⁵ Breast milk contains leptin, adiponectin, ghrelin, and other bioactive substances.²⁶ These bioactive factors regulate and promote an increase in lean body mass and prevent obesity.^{27,28} The low body mass of the infants used in the WHO growth standards may therefore be associated with their breastmilk feeding pattern.

In summary, the WHO standards describe infants who are lighter and leaner than those described by China's charts. As breastmilk is regarded as the best food for infants, the WHO standards were considered as growth under physiological conditions and were called standards rather than references. Excessive nutritional interventions in preterm infants increase the risk of metabolic disease and cardiovascular disease in adulthood. Our findings indicate that the WHO growth standards are conducive to promoting the implementation of breast feeding, to avoiding excessive nutritional interventions, consequently improving their long-term health.

Appropriate head circumference growth indirectly reflects neurological development. Our study found that the proportion of head circumference $\langle P_{10} \rangle$ assessed by the WHO standards was higher than that assessed by the China charts in growing preterm infants at an early age, i.e., CA 1 ~< 2 m, but tended to be lower during later infancy. Comparison of the head circumference Z-score in the predominantly breastfed group evaluated by these two growth references suggested similar results (Table S2), which is consistent with the results from other groups in China.²⁹ The reversal of the trend at different ages is probably a result of feeding mode. It has been found in other studies the average head circumference of exclusively

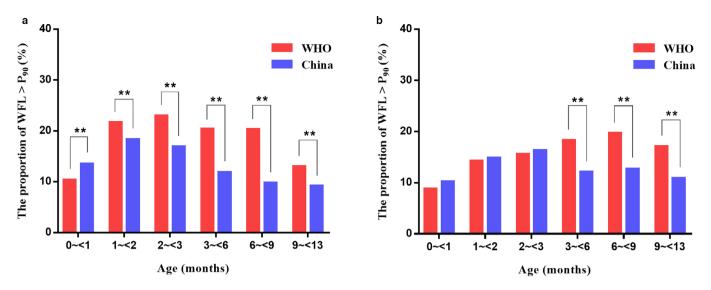


Fig. 6 Comparison of the proportion of weight-for-length > P_{90} assessed by the WHO growth standards versus the China growth charts. WFL = weight-for-length. (a) Boys and (b) girls. **P < 0.01.

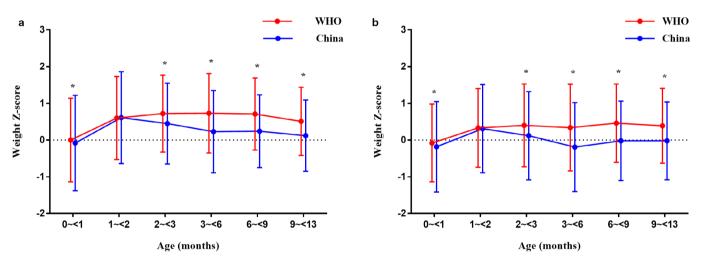


Fig. 7 Comparison of the weight Z-scores assessed by the WHO growth standards versus those assessed by the China growth charts. (a) Breastfeeding ratio $\geq 75\%$ group and (b) breastfeeding ratio $\leq 25\%$ group. *P < 0.01.

breastfed infants at 6 m of age was higher than the local reference³⁰; however, the head circumference of formula-fed children was higher than breast milk-fed children at 9 m, 12 m, 7.5 to 8 years of age.³¹ The larger head circumference in the WHO growth standards during early infancy is probably a result of its higher breastfeeding rate. Despite this, the relationship between head growth and feeding mode at different ages need to be further studied. Our study showed that the WHO growth standards were more sensitive in predicting delays in head circumference growth and in detecting infants at high risk of neurodevelopmental disorders at a very early age. This capability is critical for timely management and better outcomes.

The feasibility of the WHO growth standards and the China charts for infants of specific feeding patterns was explored in this study. As expected, preterm infants who were mainly

formula fed matched the China charts better than they matched the WHO standards. However, there is no evidence that the WHO standards are more suitable for predominantly breastfed infants. Among all breastfed infants in this study, approximately 52.0% were fed with human milk fortifier. Human milk fortifier promotes growth, and the peak in the amount of use is roughly at the CA of 3 m. From CA $0 \sim 1$ m to CA $1 \sim 2$ m, the study preterm infants grew faster than they did at other ages, which may be associated with the use of human milk fortifier. Whether the China growth charts should be widely used in less breastfed or formula-fed infants remains to be further studied. This is partly due to the fact that a higher proportion of ELBW infants and VLBW infants was seen in the breastfeeding ratio ≤25% group than in the breastfeeding ratio \geq 75% group (Table S3). Although breast milk is the best food for them, the China growth charts are more likely to underestimate their growth level, and thus will affect breast feeding to some extent.

Birthweight is a strong predictor of the postnatal growth trajectory of preterm infants, where the ELBW and VLBW infants usually receive the most attention. In this study, preterm infants who were born weighing less than 1,500 g were assessed by both the WHO standards and the China charts for the rate of abnormal growth, and similar results were obtained (Table S4).

This study compared the WHO and China's growth references in the evaluation of physical growth of growing preterm infants, where all infants involved were under systematic management in hospital, longitudinally followed up after discharge, and showed good compliance. The nutritional management of preterm infants, including the management of delayed growth, catch-up growth, and nutritional fortification, was carefully studied. The investigated difference in growth references provides a reasonable guide for the selection of growth monitoring standards in preterm infants' follow-ups.

A limitation of this study is that it might be slightly biased, as it is a one-institute study. However, despite this, it should be noted that the hospital is located in the capital of China and parents of involved preterm infants are from all over the country, including both urban areas and rural areas. The follow ups were limited to a corrected age of 12 m due to time and space reasons, and there was a lack of long-term observations in childhood, adolescence, and adulthood. A long-term follow-up study of preterm infants remains to be conducted.

Conclusions

Compared to the China growth charts, the WHO growth standards can reduce the detection rate of weight growth retardation, which relieves parental anxiety and prevents the abandonment of breastfeeding due to growth problems. The WHO growth standards are more sensitive in distinguishing infants of a weight over P_{25} and weight-for-length over P_{90} , which is helpful in preventing excessive nutritional fortification. Furthermore, the WHO growth standards are more sensitive in identifying early delays in head circumference growth, which is helpful for the detection of neural development disorders and the timely administration of interventions. Comprehensively, preterm infants benefit more from the WHO growth standards than they do from the China growth charts.

Acknowledgments

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Disclosure

The authors declare no conflict of interest.

Author contributions

S. Liu and Q. Feng conceptualized and designed the study. S. Liu, Y. Wang, X. Li, X.F. Ru, T. Sang, X. Zhang, and Q. Feng managed the preterm infants and collected the data. S. Liu and Q. Feng analyzed and interpreted the data. S. Liu and Q. Feng wrote and edited the article. All authors have read and approved the final manuscript.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1 Follow-up rate of study preterm infants.

Table S2 Comparison of head circumference Z-score with the WHO standards and the China charts in breastfeeding ratio \geq 75% group.

Table S3 The ratio of preterm infants born less than 1,500 g in breastfeeding ratio \ge 75% and \le 25% groups.

Table S4 Comparison of the proportion of abnormal growth assessed by the WHO growth standards versus the China growth charts for preterm infants born less than 1,500 g.