Original article

Postnatal growth in preterm infants: A comparative analysis for gestational age of underweight versus normal weight and small versus normal head size

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Abstract. *Introduction:* Head circumference (HC) is considered a reflection of intracranial volume and brain size, influencing early infant growth. *Objectives:* We conducted a two-year study on 65 preterm infants (Gestational Age, GA: 33.5 ± 2.2 weeks, birth weight 1.5-2.5 Kg) categorized at birth into underweight z-score (WAZ <-2) and normal weight z-score (WAZ> -2) groups. They were further divided by head circumference for gestational age z-score (HCZ) (<-1 vs.>-1). *Results:* Preterm infants with birth WAZ <-2 displayed significant improvements in WAZ at 6 and 12 months, transitioning from -2.8 to -1.5 and -1.1, respectively. Although there was an initial decrease in length-for-age z-score (LAZ), during the first 6 months, these infants exhibited catch-up, improving from -1.5 to - 0.2 Z-score. Weight-for-length z-score (WLZ) improved from -5 at birth to -0.6, -0.84, and -0.47 at 6, 12, and 24 months, respectively. Preterm infants with birth WAZ> -2 experienced a decrease in WAZ during the first 6 months but gradually increased afterward. LAZ initially decreased but improved in subsequent months. WLZ exhibited an upward trend. At birth, infants with smaller HCZ were shorter and lighter, and this trend persisted throughout the first and second year of follow-up. *Conclusion:* Rapid catch-up in WAZ and LAZ was more pronounced during the first year in preterm infants born underweight for their gestational age. However, by the end of the second year, those with small HCZ at birth were shorter and lighter at 2 years compared to those with HCZ>-1. (www.actabiomedica.it)

Key words: Preterm, postnatal growth, follow-up

Introduction

Intrauterine growth restriction (IUGR) remains a significant concern in perinatal medicine, prompting ongoing research in this area. The postnatal growth patterns of newborns with small size at birth, often indicative of IUGR, and those born with small head size, reflecting brain volume, represent an essential area of study for understanding neonatal growth, development, and long-term health outcomes (1-3).

Small size at birth serves as a sentinel event in the neonatal journey, reflecting a complex interplay of genetic, environmental, and maternal factors. It is widely recognized that infants born with IUGR have a higher risk of long-term growth problems and metabolic diseases (4,5).

Moreover, studies have indicated that preterm infants who develop metabolic syndrome later in life tend to have a smaller size at birth and a greater increase in weight Z-scores from term to 2.5 years (6).

Additionally, an examination of growth in extremely preterm children born in England in 1995 and 2006 revealed improvements in weight, height, and body mass index (BMI), but no corresponding improvement in head growth (7).

The head size of neonates is intricately linked to brain volume and neurodevelopment, making it a crucial parameter for assessing growth and health. Intrauterine growth restriction affects the volume of brain structures, as measured by quantitative magnetic resonance imaging (MRI). Data suggests that IUGR induces a distinct brain pattern of structural changes that persist at 1 year of life and is associated with specific developmental difficulties (8-10).

Notably, infants of very preterm birth with IUGR exhibit a relative volumetric decrease in gray matter in limbic regions and a relative increase in frontoinsular, temporal-parietal, and frontal areas compared with peers of very preterm birth who were appropriate for gestational age (AGA) (11,12).

Furthermore, microcephaly, associated with a reduction in brain tissue volumes, especially deep nuclear gray matter, suggests a selective vulnerability of these babies for growth and developmental delay. Poor postnatal head growth in preterm infants becomes more evident by 2 years and is strongly associated with poor neurodevelopmental outcomes and cerebral palsy (13).

The primary aim of this study was to investigate the postnatal growth patterns of preterm infants with varying birth weights for gestational age z-score (WAZ) and head circumferences z-score for gestational age (HCZ).

Methods

Sixty-five preterm infants born at Hamad Medical Corporation Doha (Qatar), between 2017 - 2018, were included in our retrospective study. Their mean gestational age (GA) was 33.5 ± 2.2 weeks and birth weights ranged from 1.5 to 2.5 Kg.

At birth, these infants were categorized into two distinct groups: Group 1 (WAZ <-2) (no = 18) and Group 2 (WAZ> -2) (no = 47). Additionally, they were further stratified into 2 subgroups based on head circumference for gestational age (HCZ): HCZ <-1 (no=24) and HCZ> -1 (no=42). To assess growth trajectories, we evaluated various growth parameters, including weight-for-age z-score (WAZ), length-for-age z-score (LAZ), and weight-for-length z-score (WLZ), at 6, 12, and 24 months.

Gestational age was recorded as per obstetrical estimates based on first-trimester ultrasonography or if not available, by the date of the last menstrual period.

Weight was taken at birth, using an electronic weighing scale with an accuracy of ± 5 grams, with a baby being unclothed. Length and head circumference (HC) were taken within 12-24 hours of age using standard techniques. Subsequently, measurements were repeated at discharge and at 3, 6, 12, 18 and 24 months of corrected age. To improve follow-up, periodic reminders were sent to parents through telephonic calls.

All LBW infants were started on enteral feeds as soon as possible after birth. All infants had a birth weight <2,500 grams and all with a birth weight >1,500 grams. Enteral feeds were increased gradually to a volume of 180 mL/kg/day. Breast milk was the preferred milk for the premature infants but also formula was used to supplement it. Once the infant reached 100 mL/kg/day of enteral feeds, expressed breast milk was fortified with human milk fortifier to make a caloric content of 80 Cal/100 mL, to achieve a target calorie of 110-130 cal/kg/day. Developmentally supportive care was routinely provided to all the neonates.

Z-scores for each anthropometric parameter before 40 weeks post menstrual age (PMA) were computed using Fenton's reference. Infants below the 10^{th} centile were categorized as small for gestational age (SGA). For term gestation and beyond, Z-scores were computed using the new WHO growth standard available to: www.who.int/tools/child-growth-standards/who-multicentre-growth-reference-study.

Statistical analysis

Statistical analysis was done using SPSS version 17.0. Comparisons were made using independent t-test, paired t-test and repeated measure ANOVA, as applicable. The nonparametric Wilcoxon test was used when the data was not normally distributed. A P value < 0.05 was considered statistically significant.

Ethics

The study was approved by the Institutional Review Board and Hamad Medical Center Ethics Committee of Doha (Qatar) (MRC-01-21-277).

Results

Preterm infants with birth WAZ <-2 increased their WAZ at 6, 12, and 24 months from -2.83 to -1.49, to -1.07 and to - 0.70 Z-score., respectively. While preterm infants with birth WAZ> -2 had decreased WAZ during the first 6 months from -0.48 to -1.35 Z-score. This was followed by a gradual increase of WAZ at 12 and 18 months (-0.48 and -0.28), but at 24 months the registered mean WAZ value was -0.37 (Table 1 and Figure 1).

In group 1 (WAZ<-2) after an initial decrease in LAZ during the first 6 months of life (from -1.48 to -1.71 Z-score.) presented a catch-up during the following 18 months (from -1.48 at birth to -0.16, after 24 months), on the other hand, Group 2 (WAZ>-2) showed a significant decrease in LAZ during the first 6 months (from -0.04 to -1.68 Z-score.). Moreover, during the following 18 months, LAZ increased to -1.09, -0.91 and -0.51 at 12, 18, and 24 months, respectively (Table 1 and Figure 2).

In group 1 WLZ increased markedly from birth to 6, 12, and 24 months (-4.95, -0.56, - 0.84, and -0.47 Z-score, respectively) and Group 2 WLZ also increased from -3.96 at birth to -0.42, -0.12, 0.25 and -0.10 Z-score. at 6, 12, 18 and 24 months, respectively. Despite the significantly decreased LAZ and WLZ scores in the group with WAZ <-2 at birth, at two years none of the growth parameters (WAZ, LAZ, and WLZ) differ significantly between the two groups (Table 1 and Figure 3).

Among preterm infants with WAZ <-2, the head circumference for gestational age (HCZ) at birth was comparable to that of preterm infants with WAZ> -2. However, by the end of the second year, HCZ for infants with WAZ <-2 was significantly smaller than those with WAZ> -2 at birth. Furthermore, at birth, preterm infants with smaller HCZ were significantly shorter and lighter compared to those with larger HCZ In the group with HCZ <-1 at birth, HCZ showed substantial improvement, increasing from -1.8 at birth to -1.49, -1.08, -0.56, and -0.4 Z-score at 6, 12, 18, and 24 months. This represented a remarkable catch-up of

Table 1. Changes of birth weights for gestational age Z-score (WAZ <-2 vs. WAZ> -2), length-for-age z-score (LAZ) and weight-for-length Z-score (WLZ) in 65 preterm infants during the first 2 years.

		At Birth				After 6 Months		
		Gestaz. Age	**WAZ**	**LAZ**	**WLZ**	**WAZ**	**LAZ**	**WLZ**
WAZ <-2	**Mean**	36*	(-2.83) *	(-1.48) *	-4.95	-1.49	-1.71	-0.56
N= 18	**SD**	2.50	0.38	0.51	2.61	0.91	1.08	1.63
WAZ>-2	**Mean**	33.14	-0.48	-0.04	-3.96	-1.35	-0.68	-0.42
N= 47	**SD**	1.68	0.96	1.26	1.14	1.28	1.17	1.41
	P-value	0.0079*	<0.000001*	<0.000001*	0.323	0.703	0.949	0.846

After 12 Months			After 18 Months			After 24 Months		
WAZ	**LAZ**	**WLZ**	**WAZ**	**LAZ**	**WLZ**	**WAZ**	**LAZ**	**WLZ**
-1.07	-0.84	-0.84	-0.95	-0.75	-1.20	-0.70	-0.16	-0.47
1.09	1.11	1.33	1.19	34.29	1.45	1.41	1.25	1.01
-0.48	-1.09	-0.12	-0.28	-0.91	0.25	-0.37	-0.51	-0.10
1.37	1.35	1.19	1.34	1.33	1.15	1.32	1.73	1.41
0.177	0.585	0.264	0.152	0.77	0.084	0.522	0.569	0.507

Legend: *P:<0.05 among the two groups

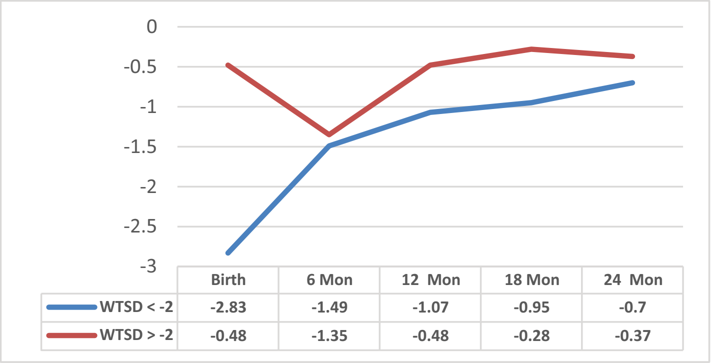

Figure 1. Postnatal growth in weights for age Z-score, comparing (WAZ <-2 vs. WAZ> -2), in 65 preterm infants during the first 2 years.

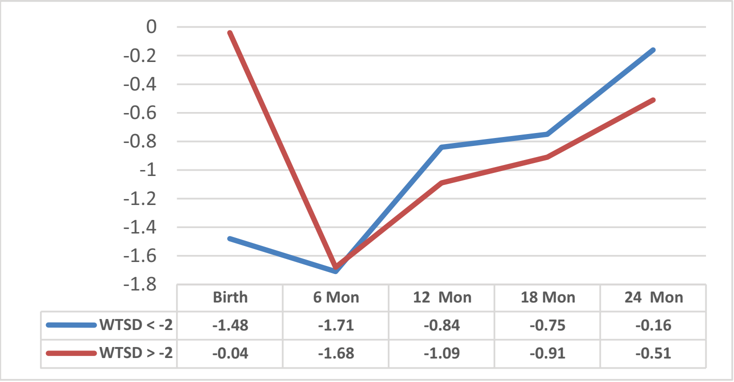

Figure 2. Postnatal growth in length for age Z-score (LAZ) for infants born (WAZ <-2 vs. WAZ> -2), in 65 preterm infants during the first 2 years.

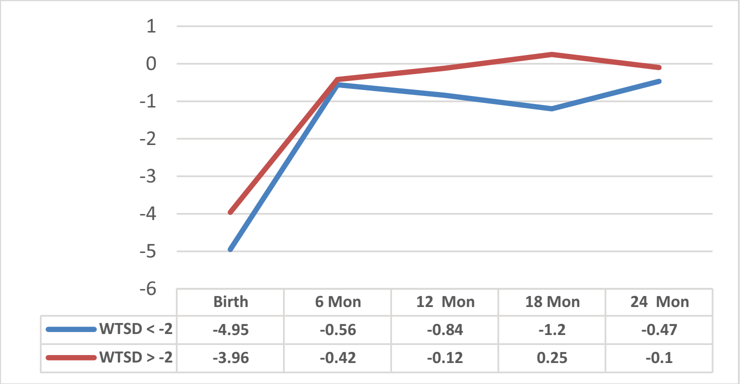

Figure 3. Postnatal growth in weight for length for age Z-score (WLZ) for infants born (WAZ <-2 vs. WAZ> -2), in 65 preterm infants during the first 2 years.

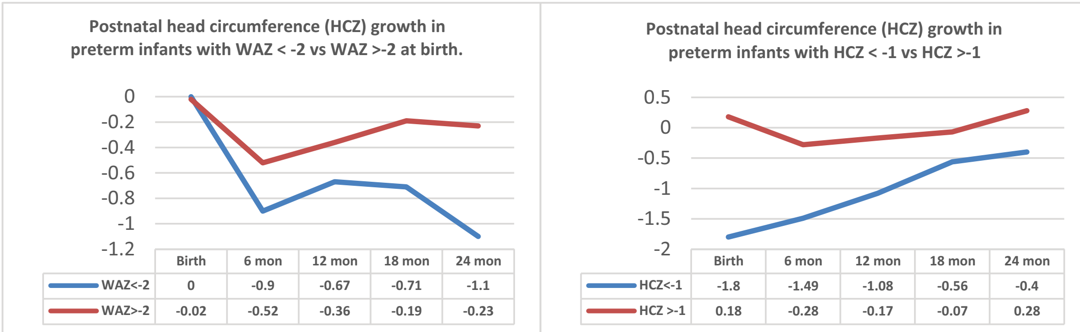

Figure 4. Postnatal growth in head circumference for age Z-score (HCZ) in 65 preterm infants during the first 2 years.

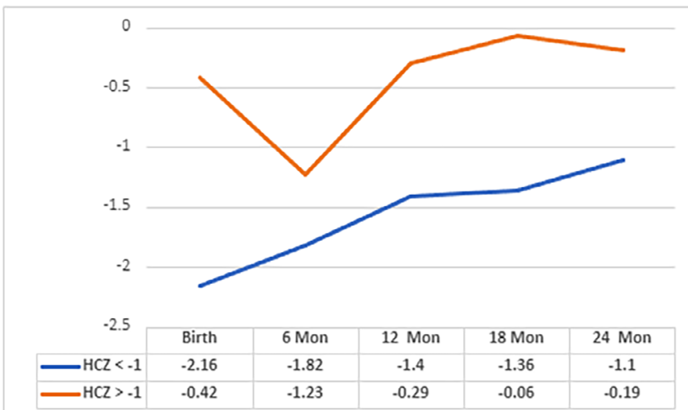

Figure 5. Mean weight gain in the first 2 years for preterm infants born with head circumference for gestational age (HCZ) <-1 versus HCZ> -1.

1.4 SD over the two-year study period. Nevertheless, at 2 years, the HCZ remained significantly smaller compared to infants with HCZ> -1 at birth (Figure 4). WAZ also showed a similar trend, increasing from -2.16 at birth to -1.82, -1.4, -1.36, and -1.1 Z-score. at 6, 12, 18, and 24 months, respectively (Figure 5).

Despite an initial decline in LAZ during the first 6 months, infants with HCZ>-1 displayed catch-up growth in LAZ, transitioning from -2.04 at 6 months to -1.06 Z-score in the second half of the first year. During their second year, LAZ remained stable, indicating normal growth (Figure 6 and Table 2).

Preterm infants with HCZ> -1 at birth exhibited normal head growth during the first two years of life, ultimately achieving a normal HCZ at the end of the second year. They experienced WAZ catch-up, improving from -1.23 to -0.3 Z-score at the end of the first year. Furthermore, their WAZ remained stable, indicating normal weight gain during the second year. LAZ demonstrated progressive improvement, starting from -2.5 at birth and reaching -1.57, -1.04, -0.75, and -0.25 Z-score at 6, 12, 18, and 24 months, respectively. At the end of the second year, preterm infants with HCZ <-1 at birth remained significantly lighter, shorter, and had smaller head sizes compared to those with HCZ> -1 (Table 2).

Discussion

Extensive research has developed into postnatal growth patterns in infants with small size at birth and

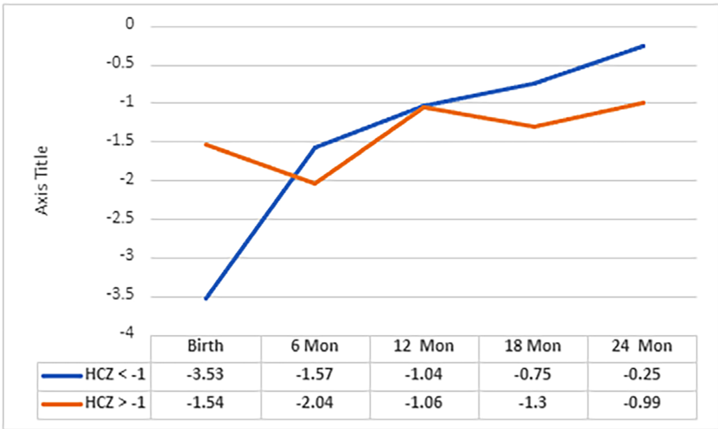

Figure 6. Mean length gain in the first 2 years for preterm infants born with head circumference for gestational age (HCZ) <-1 versus HCZ> -1.

Table 2. Postnatal growth (WAZ, LAZ and HCZ) in preterm infants with head circumference for gestational age (HCZ) <-1 versus HCZ>-1 at birth.

		At Birth				After 6 Months		
		Gestational Age	WAZ	LAZ	WLZ	WAZ	LAZ	WLZ
HCZ <-1	Mean	34.77*	-2.16*	-1.54*	-4.76	-1.82	-2.04	-0.72
N= 24	SD	1.70	0.81	0.62	2.12	1.06	1.45	1.53
HCZ>-1	Mean	32.89	-0.42	-2.53	-2.90	-1.23	-1.57	-0.34
N= 42	SD	1.72	1.05	1.28	1.14	1.25	1.05	1.40
	P-value	<0.01	<0.0001	<0.01	0.183	0.0961	0.138	0.485
After 12 Months			After 18 Months			After 24 Months		
WAZ	LAZ	WLZ	WAZ	LAZ	WLZ	WAZ	LAZ	WLZ
-1.4*	-1.06	-1.1*	-1.36*	-1.10	-0.99*	-1.1 *	-0.99*	-0.50
1.02	1.67	1.08	1.02	1.34	1.22	1.07	1	1.27
-0.29	-1.04	0.11	-0.06	-0.75	0.40	-0.19	-0.25	0.00
1.32	1.17	1.12	1.28	1.31	1.10	1.33	1.1	1.38
0.0024	0.971	0.004	0.000614	0.15	0.0059	0.0146	0.02	0.327

those born with small head sizes, shedding light on the intricate interplay of genetic factors, environmental influences, nutritional strategies, and the dynamic evolution of growth parameters in these vulnerable neonates.

In our study, we have explored the postnatal growth of preterm infants, with a particular focus on weight-for-age z-score (WAZ), length-for-age z-score (LAZ), weight-for-length z-score (WLZ), and head circumference-for-age z-score (HCZ) in relation to their birth weight for gestational age (GA) as well as HCZ. The insights derived from our findings provide a valuable perspective on the progression of these parameters over the first two years of life in this vulnerable population.

WAZ and LAZ growth

A mounting body of evidence supports the notion that both the intrauterine environment and early-life growth can influence the development of chronic non-communicable diseases, such as type 2 diabetes mellitus and cardiovascular disease. Our study reveals that preterm infant with a birth WAZ <-2 displayed remarkable improvements in WAZ at 6 and 12 months, reaching values of -1.49 and -1.07 Z-score, respectively. They exhibited rapid weight gain during the first 6 months, particularly when compared to their counterparts with WAZ> -2.

This pattern of rapid catch-up growth in weight aligns with research conducted by Cole et al. (14), involving an analysis of growth data for 5,009 infants born between 22 - 31 weeks' gestation, which reported a similar trend, highlighting the significance of early growth dynamics. Additionally, although LAZ showed a tendency to decrease during the first 6 months, preterm infants continued to catch up in length from the 6th month to the end of 2 years. This trend is consistent with observations made by Raaijmakers et al.(15) in a study of 82 extremely low birth weight (ELBW) infants. Similarly, in large Chinese cohort the majority of AGA/LGA preterm infants achieved growth targets during the first 3 months, echoing the findings in our study that indicated catch-up growth occurring at around 6 months (16-18). Furthermore, the research by Altigani et al.(19), involving 71 infants with a mean gestational age of 32 weeks and a mean birth weight of 1,805 kg, demonstrated a drop in weight, length, and head circumference shortly after birth, followed by catch-up growth during the first 24 weeks of postnatal life.

Our findings at 2 years revealed that only 12.3% of preterm infants had LAZ <-2, and 15.4% had Wt-SDS <-2. Notably, there was no statistical significance in WAZ, LAZ, and WLZ between the two groups that began with different WAZ at birth. The rapid catch-up growth in weight and length observed during the first year aligns with previous research findings, such as those reported by Campisi et al. (20), who reviewed 11 studies and indicated that a significant percentage of small for gestational age (SGA) infants exhibited catch-up growth by the age of 2 years.

In further support of our study, research conducted by Yeşinel et al. (21), involving 117 preterm babies born at a gestational age of 32 weeks or below with birth weights of 1,500 g or below found that 87.2% reached or exceeded their target height percentile (THP) by 3 years of age.

Albertsson-Wikland et al. (22) studied the growth of 111 infants born with WAZ<-2 SDS and reported that 87% of children born with SGA showed full catch-up growth within the first 2 years of life.

Our study showed that infants born with WAZ <-2 had a significant catch-up in LAZ during the first 2 years (from -1.48 to -0.16 Z-score). Additionally, González-García et al. (23) studied the growth of 92 very low birth weight (LBW) infants, and at 2 years, the prevalence of short stature (LAZ <-2) was 15.2%, with a significant increase in LAZ to -0.74. Furthermore, Toftlund et al. (24) investigated the growth of 281 premature infants with a median gestational age of 30 weeks and reported a fast catch-up in weight during the first 2 months of life. Preterm infants born small for gestational age compared to those born appropriate for gestational age demonstrated continuous catch-up growth until 6 years of age.

However, Vizzari et al (25) examined the growth of 175 late preterm infants with birth weights below the 10th percentile, revealing that 34% of them did not achieve weight recovery at 36 months. Their study indicated that infants who had not regained weight at 12 months were at a higher risk of not regaining weight even at 36 months.

In our study, infants with WAZ <-2 at birth exhibited higher linear catch-up growth Z-score (LAZ) during the first 6 months compared to those with WAZ> -2, with catch-up growth in LAZ continuing during the second year of life. These findings align with research by Sinha et al. (26), who studied 8,360 low birth weight (LBW) infants and compared the growth of small for gestational age (SGA)-LBW and appropriate for gestational age (AGA)-LBW infants. SGA-LBW infants exhibited significantly higher linear growth velocity during the 3- to 6-month period. Deng et al. (27) found that SGA-preterm infants increased their LAZ (catch-up) early, starting from the first months postnatally, compared to AGA preterm infants, who began to increase their LAZ after 2-3 months (27).

Our study highlighted that the total gain in LAZ (catch-up) during the first year (+0.64 SD) and the second year (+0.6 SD) was significantly higher in the

WAZ <-2 group compared to the group with WAZ> -2 at birth (only +0.5 SD during the second year). These results were consistent with those reported by Deng et al. (27), who found that LAZ increased by 0.9 SD in the SGA-preterm group during the first year, compared to a minimal increase in LAZ in the AGA-preterm group (+0.2 SD).

WLZ growth

One particularly noteworthy finding in our study was the significant increase in weight-for-length z-score (WLZ) observed in preterm infants with WAZ <-2 during the first 6 months. This rapid WLZ improvement paralleled the pattern observed in their WAZ, signifying faster weight gain than length gain during this early stage of life. Deng et al. (27) also reported a fast increase in WLZ during the first 6 months, corroborating our findings.

Our results are in line with reports by Martinez et al. (28), suggesting that early nutritional interventions can effectively address these growth challenges in preterm infants.

HCZ growth

Brain volume is a critical determinant of head size at term. Notably, small head size is associated with a reduction in brain tissue volumes, particularly in deep nuclear gray matter, suggesting a selective vulnerability (12,13, 29).

Our study revealed that preterm infants with WAZ <-2 at birth had significantly smaller head sizes at 2 years of age compared to those with WAZ>-2, indicating slower head growth during the first two years of life. These observations align with previous research findings that emphasize the emergence of poor postnatal head growth in preterm infants by 2 years of age, which is strongly associated with unfavorable neurodevelopmental outcomes. Furthermore, a positive correlation has been reported between higher head growth and improved neurodevelopmental outcomes (30-32).

In our study, preterm infants with birth HCZ <-1 exhibited a significant increase in their HCZ, progressing from a mean of -1.8 at birth to a mean of -0.4 Z-score at 24 months (Figure 4). This growth represented a notable catch-up of 1.4 standard deviations (SD) over the span of two years. However, at 2 years of age, their HCZ was notably smaller, and they were significantly lighter and shorter compared to those with HCZ>-1 at birth. These findings are corroborated by the data presented by Deng et al. (27), who reported significantly higher HCZ values in AGA-preterm infants compared with SGA preterm infants. Despite the catch-up growth in HCZ observed in 33% of SGA-preterm infants versus 12% of AGA-preterm infants, the HCZ of the SGA-preterm group remained significantly smaller compared to the AGA-preterm group at the end of the second year.

It is worth noting that a singular study has reported that 71% of children born with congenital microcephaly were no longer considered to be microcephalic at 24 months (33). However, a separate study involving 488 children born at less than 32 weeks gestation found that 57.8% were categorized as having suboptimal head growth (>1 SD below the mean) at the 2-year follow-up (34).

These findings collectively highlight the potential utility of monitoring HCZ as a valuable indicator not only of linear growth but also of brain development in preterm infants.

In summary, preterm infants with WAZ <-2 at birth demonstrated significant improvements in WAZ over the first two years, with substantial gains in the first 6 months. Weight-for-length z-score (WLZ) also showed marked improvement. However, infants with WAZ <-2 were shorter at 2 years compared to those with WAZ>-2. Preterm infants with WAZ> -2 gradually improved their WAZ at 12, 18, and 24 months, along with an increase in length-for-age z-score (LAZ) after the initial 6 months. Notably, catch-up growth in LAZ was significantly higher in infants with WAZ <-2. Infants with WAZ <-2 at birth displayed similar head circumferences z-score (HCZ) to infants with WAZ>-2. However, by the end of the second year, those with WAZ <-2 exhibited significantly smaller HCZ. Despite catch-up growth in WAZ, LAZ, and HCZ, preterm infants with HCZ <-1 at birth were still lighter, shorter, and had smaller head sizes compared to those with HCZ>-1 at the end of the second year.

Conflict of Interest Statement: Each author declares that he or she has no commercial associations (e.g., consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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