

ARTICLE



Postnatal weight trajectories drives better head circumference growth in preterm infants ≤ 32 weeks: a multicenter Latin American cohort study

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BACKGROUND: Postnatal weight loss is nearly universal in preterm infants, and its relationship to head circumference (HC) growth remains incompletely characterized. Growth standards were recently updated with the Fenton 2025 charts, which modify Z-score parameters compared to the 2013 version.

OBJECTIVE: To evaluate the association between postnatal weight trajectory and HC growth from birth to discharge in preterm infants ≤ 32 weeks of gestation across a large multicenter Latin American cohort, using Fenton 2025 growth standards.

METHODS: This observational cohort study by secondary analysis of a prospective cohort study using data from EpicLatino, a quality improvement registry of 35 neonatal intensive care units (NICUs) across Latin America and the Caribbean (2015–2024). Infants ≤ 32 weeks admitted within 48 h of birth were included. The exposure was the change in weight Z-score (Fenton 2025) from birth to discharge, categorized into 10 groups at 0.4-unit intervals. The primary outcome was the change in HC Z-score (Fenton 2025). Multivariable linear regression with average marginal predictions was used, adjusting for gestational age, necrotizing enterocolitis (NEC), sepsis, SNAP-II score, length of stay, treated patent ductus arteriosus, Apgar score at 5 min, HC Z-score at birth, and outborn status.

RESULTS: 3926 infants were included (analytical sample $n = 3757$). Median gestational age was 30 [IQR 29–32] weeks. Adjusted HC Δ Z-score ranged from -0.34 (95% CI -0.38 to -0.30) in infants with weight Δ Z-score > 0 , to -2.71 (95% CI -2.83 to -2.58) in those with weight Δ Z-score ≤ -3.2 . All group comparisons were statistically significant ($p < 0.001$). The model explained 37.6% of the variance in HC growth.

CONCLUSIONS: Postnatal weight trajectory is independently and progressively associated with HC growth in preterm infants ≤ 32 weeks across Latin America. Supporting weight recovery toward birth Z-score is a key nutritional target to promote adequate HC growth in the NICU.

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INTRODUCTION

Adequate postnatal growth is a recognized priority in the care of preterm infants. While weight gain is the most widely monitored growth parameter in neonatal intensive care units (NICUs), head circumference (HC) growth may be a more direct reflection of brain development and is associated with long-term neurocognitive outcomes [1, 2]. In preterm infants, postnatal growth restriction — defined as a decline in weight Z-score between birth and discharge—is nearly universal and has been linked to reduced HC growth and adverse neurodevelopmental trajectories [3, 4].

The dose-response relationship between the magnitude of postnatal weight loss and HC growth has received limited attention, particularly in low- and middle-income countries where preterm

birth rates are highest and nutritional management may differ substantially from high-income settings [5]. Latin America is a region that remains underrepresented in neonatal nutrition research despite bearing a disproportionate burden of preterm birth [6].

A methodological complexity has been introduced by the 2025 revision of the Fenton preterm growth charts, the most widely used reference for this population [7]. This update revised Z-score includes parameters for weight and HC across gestational ages, meaning that growth classifications derived from the 2013 version are not directly equivalent. Prior associations between weight trajectory and HC outcomes derived from Fenton 2013 require re-examination under the updated standard.

Using data from EpicLatino, a multicenter prospective registry of 35 NICUs across Latin America and the Caribbean spanning ten

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years (2015–2024), we evaluated the association between postnatal weight trajectory — categorized into 10 Δ Z-score groups using Fenton 2025—and HC growth from birth to discharge, after adjustment for clinical confounders.

METHODS

Study design and setting

This was a observational cohort study by secondary analysis of a multicenter prospective cohort study using data from EpicLatino, a quality improvement registry modeled after the Canadian Neonatal Network. The registry prospectively collects standardized clinical data from participating NICUs in Latin America and the Caribbean. Data from 8 countries and 35 units contributed to this analysis, covering admissions from January 2015 through December 2024. Each participating unit obtained ethics committee approval under the framework of the EpicLatino registry.

Participants

We included liveborn infants with gestational age ≤ 32 weeks admitted to a participating NICU within 48 h of birth. Infants were excluded if they had intraventricular hemorrhage, major congenital malformations, implausible or missing weight or HC measurements at birth or discharge, or death before discharge. Readmissions were excluded; only the index admission was analyzed.

Growth assessment and Z-score calculation

Weight and HC were recorded at birth and at hospital discharge. Z-scores for both measurements were calculated using the Fenton 2025 preterm growth charts, which provide sex-specific, gestational-age-adjusted reference values from 22 to 50 weeks of corrected age. [7] Fenton 2025 was selected to apply the most current reference standard available and to avoid misclassification associated with the Z-score recalibration introduced by this revision.

The primary exposure was postnatal weight trajectory, defined as the change in weight Z-score from birth to discharge ($\text{Weight } \Delta \text{ Z-score} = \text{Z-score at discharge} - \text{Z-score at birth}$). The primary outcome was the

analogous change in HC Z-score ($\text{HC } \Delta \text{ Z-score}$). Weight Δ Z-score was categorized into 10 groups using 0.4-unit intervals, with the reference category defined as Δ Z-score > 0 (weight Z-score at discharge close to weight Z-score at birth).

Covariates

The following variables were included as confounders based on clinical plausibility: gestational age at birth (weeks, continuous); necrotizing enterocolitis (NEC) (binary); positive blood/CSF culture, (binary); Score for Neonatal Acute Physiology-II (SNAP-II, continuous); length of hospital stay (days, continuous); treatment of patent ductus arteriosus (PDA) with medication or surgical ligation (binary); Apgar score at 5 min (continuous); HC Z-score at birth (Fenton 2025, continuous); and outborn status (binary).

Statistical analysis

Baseline characteristics are presented as median [interquartile range] for continuous variables and as count (%) for categorical variables. The association between Weight Δ Z-score group and HC Δ Z-score was evaluated using multivariable linear regression, with Weight Δ Z-score > 0 as the reference category. Adjusted average marginal predictions of HC Δ Z-score were estimated for each weight group by setting the group indicator to each value in turn while holding all other covariates at their observed values. Heteroskedasticity-robust standard errors (HC3) were used. The proportion of variance explained was assessed with R^2 . Observations with missing data in any covariate were excluded via listwise deletion ($n = 169$, 4.3%). Analyses were conducted in Python 3.12 using the statsmodels library. The study is reported following the STROBE guidelines for cohort studies.

RESULTS

Study population

A total of 3926 infants met the inclusion criteria. Baseline characteristics are presented in Table 1. Median gestational age was 30 weeks [IQR 29–32]; 49.6% of infants were born at 32 weeks. Male sex accounted for 53.8% of the cohort and 4.8% were outborn. Positive blood cultures were documented in 611 infants

Table 1. Baseline characteristics of the study population.

Characteristic	Value	Missing, <i>n</i> (%)
Total infants, <i>n</i>	3926	—
Gestational age, weeks — median [IQR]	30 [29–32]	0
23–24 weeks, <i>n</i> (%)	25 (0.6%)	
25–27 weeks, <i>n</i> (%)	198 (5.0%)	
28–29 weeks, <i>n</i> (%)	657 (16.7%)	
30–31 weeks, <i>n</i> (%)	1098 (28.0%)	
32 weeks, <i>n</i> (%)	1948 (49.6%)	
Male sex, <i>n</i> (%)	2111 (53.8%)	8 (0.2%)
Outborn, <i>n</i> (%)	190 (4.8%)	0
Birth weight, g — median [IQR]	1390 [1120–1670]	0
Weight Z-score at birth (Fenton 2025)—mean (SD)	−0.43 (1.16)	0
HC Z-score at birth (Fenton 2025)—mean (SD)	0.00 (1.11)	0
Apgar score at 5 min—median [IQR]	8 [7–9]	87 (2.2%)
SNAP-II score—median [IQR]	5 [0–17]	70 (1.8%)
Necrotizing enterocolitis, <i>n</i> (%)	189 (4.8%)	15 (0.4%)
Positive blood culture, <i>n</i> (%)	611 (15.6%)	15 (0.4%)
Treated patent ductus arteriosus, <i>n</i> (%)	624 (15.9%)	0
Length of stay, days—median [IQR]	42 [30–61]	0
Weight Δ Z-score (birth to discharge)—mean (SD)	−0.86 (1.02)	0
HC Δ Z-score (birth to discharge)—mean (SD)	−0.92 (1.30)	0

Z-scores calculated with Fenton 2025 preterm growth charts.

HC head circumference, IQR interquartile range, SD standard deviation, SNAP-II Score for Neonatal Acute Physiology-II, NEC necrotizing enterocolitis, PDA patent ductus arteriosus.

(15.6%), NEC stage $\geq$ II in 189 (4.8%), and treated PDA in 624 (15.9%). Median length of stay was 42 days [IQR 30–61]. Mean Weight Δ Z-score was -0.86 (SD 1.02) and mean HC Δ Z-score was -0.92 (SD 1.30). The distribution of infants across weight trajectory groups is shown in Table 2; the largest groups were those with moderate weight loss (Δ Z-score >-0.8 to ≤-0.4 , $n = 658$, and >-1.2 to ≤-0.8 , $n = 665$).

Association between weight trajectory and HC growth

After adjustment for all covariates, adjusted HC Δ Z-score declined progressively with increasing postnatal weight loss across all 10 groups (Table 2, Fig. 1). Infants with Weight Δ Z-score >0 had a predicted HC Δ Z-score of -0.34 (95% confidence interval [CI] -0.38 to -0.30). Predicted values declined to -0.49 (group 2),

-0.75 (group 3), -0.94 (group 4), -1.13 (group 5), -1.28 (group 6), -1.72 (group 7), -1.89 (group 8), -2.24 (group 9), and -2.71 (95% CI -2.83 to -2.58) in infants with the most severe weight loss (Weight Δ Z-score ≤-3.2). All group estimates were statistically significant ($p < 0.001$) figs. 2, 3.

The multivariable model had an R^2 of 0.376. HC Z-score at birth was the covariate with the strongest adjusted association with HC Δ Z-score ($\beta = -0.43$, 95% CI -0.46 to -0.39 , $p < 0.001$). Length of stay was inversely associated with HC Δ Z-score ($\beta = -0.011$ per day, 95% CI -0.013 to -0.008 , $p < 0.001$). SNAP-II score was also inversely associated ($\beta = -0.008$ per point, 95% CI -0.012 to -0.005 , $p < 0.001$). Gestational age, NEC, sepsis, treated PDA, outborn status, and Apgar score at 5 min were not independently associated with HC Δ Z-score after full adjustment.

Table 2. Adjusted average marginal predictions of HC Δ Z-score by postnatal weight trajectory group.

Weight Δ Z-score Group	N	Adjusted HC Δ Z-score	SE	95% CI	p
>0	646	-0.34	0.008	-0.38 to -0.30	<0.001
> -0.4 to ≤ 0	529	-0.49	0.008	-0.54 to -0.45	<0.001
> -0.8 to ≤ -0.4	658	-0.75	0.008	-0.79 to -0.72	<0.001
> -1.2 to ≤ -0.8	665	-0.94	0.008	-0.98 to -0.90	<0.001
> -1.6 to ≤ -1.2	517	-1.13	0.008	-1.18 to -1.09	<0.001
> -2.0 to ≤ -1.6	334	-1.28	0.008	-1.34 to -1.23	<0.001
> -2.4 to ≤ -2.0	179	-1.72	0.008	-1.79 to -1.64	<0.001
> -2.8 to ≤ -2.4	103	-1.89	0.008	-1.99 to -1.79	<0.001
> -3.2 to ≤ -2.8	61	-2.24	0.008	-2.37 to -2.11	<0.001
≤ -3.2	65	-2.71	0.008	-2.83 to -2.58	<0.001

Bold row (>0): reference group. Adjusted for gestational age, necrotizing enterocolitis, sepsis (positive blood culture), SNAP-II score, length of stay, treated patent ductus arteriosus, Apgar score at 5 min, HC Z-score at birth (Fenton 2025), and outborn status. $N = 3757$. Z-scores calculated with Fenton 2025 preterm growth charts.

HC head circumference, Δ Z-score change in Z-score from birth to discharge, SE standard error, CI confidence interval.

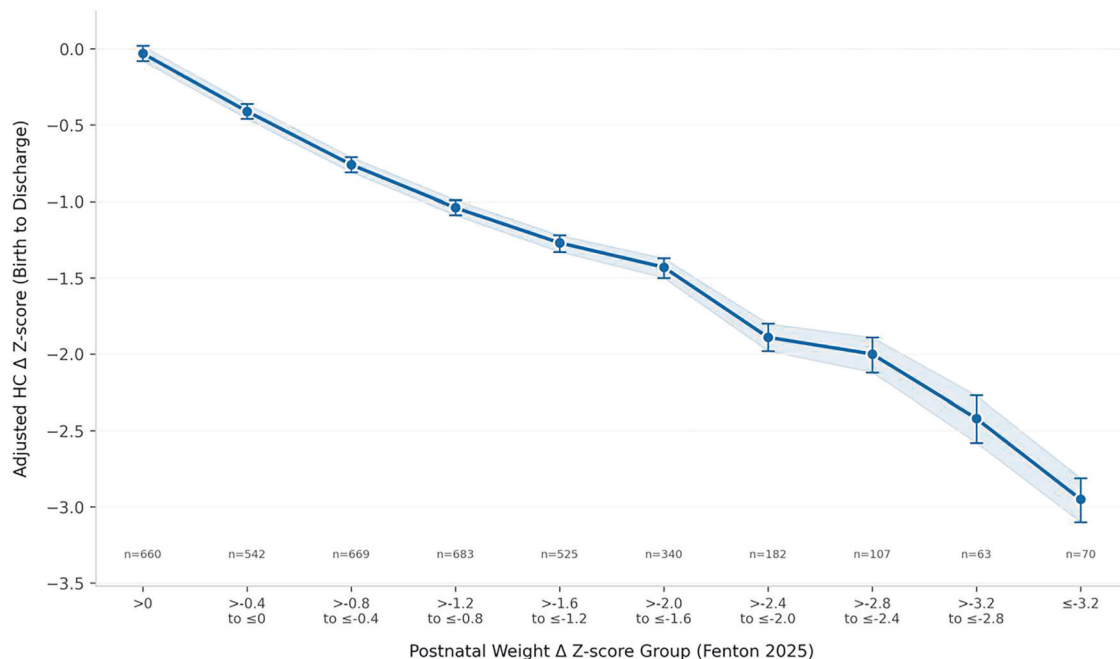


Fig. 1 Adjusted average marginal predictions of HC Δ Z-score (birth to discharge) across 10 postnatal weight trajectory groups (Fenton 2025). Each point represents the adjusted marginal prediction with 95% confidence interval (shaded area). Reference group: Weight Δ Z-score >0 . Linear regression with cluster-robust standard errors by center, adjusted for gestational age, necrotizing enterocolitis, sepsis, SNAP-II score, length of stay, treated patent ductus arteriosus, HC Z-score at birth, weight Z-score at birth, and outborn status. $N = 3841$. $R^2 = 0.446$. HC head circumference, Δ Z-score change in Z-score from birth to discharge, CI confidence interval.

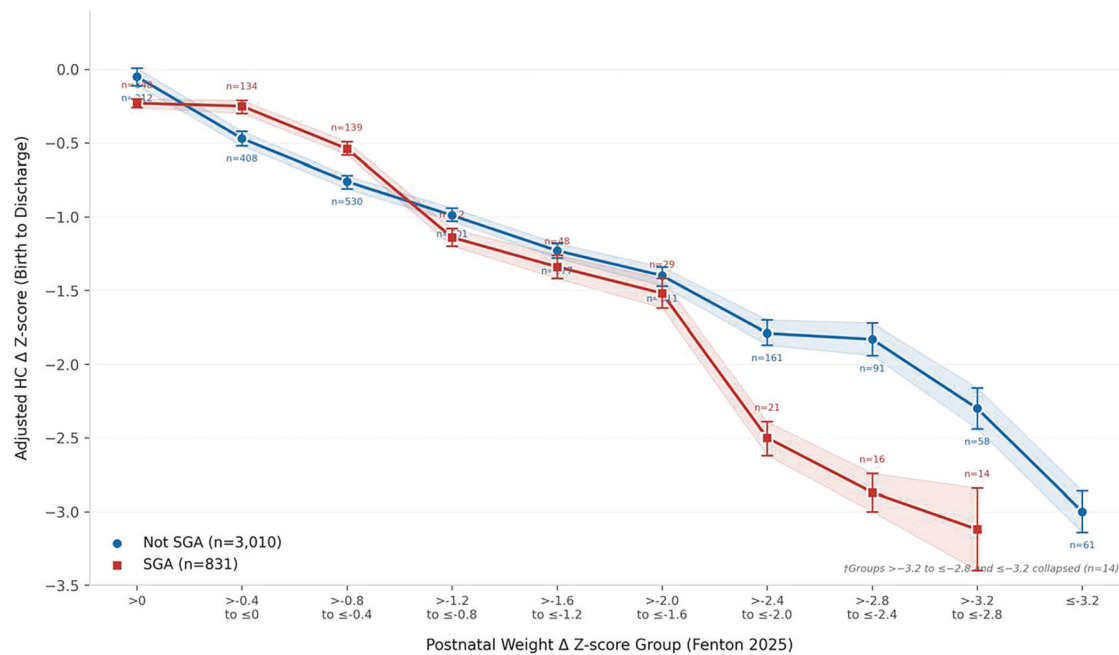


Fig. 2 Adjusted average marginal predictions of HC Δ Z-score by postnatal weight trajectory group, stratified by SGA status. Circles: Not SGA (weight Z-score at birth ≥ -1.28 SD, $n = 3010$); squares: SGA (weight Z-score at birth < -1.28 SD, below 10th percentile, Fenton 2025, $n = 831$). Not SGA model adjusted for gestational age, necrotizing enterocolitis, sepsis, SNAP-II score, length of stay, treated patent ductus arteriosus, HC Z-score at birth, weight Z-score at birth, and outborn status. SGA model adjusted for the same covariates excluding HC Z-score and weight Z-score at birth. Cluster-robust standard errors by center. Shaded areas and error bars represent 95% confidence intervals. †Last two SGA groups collapsed ($n = 14$) due to small sample size. HC head circumference, Δ Z-score change in Z-score from birth to discharge, SGA small for gestational age.

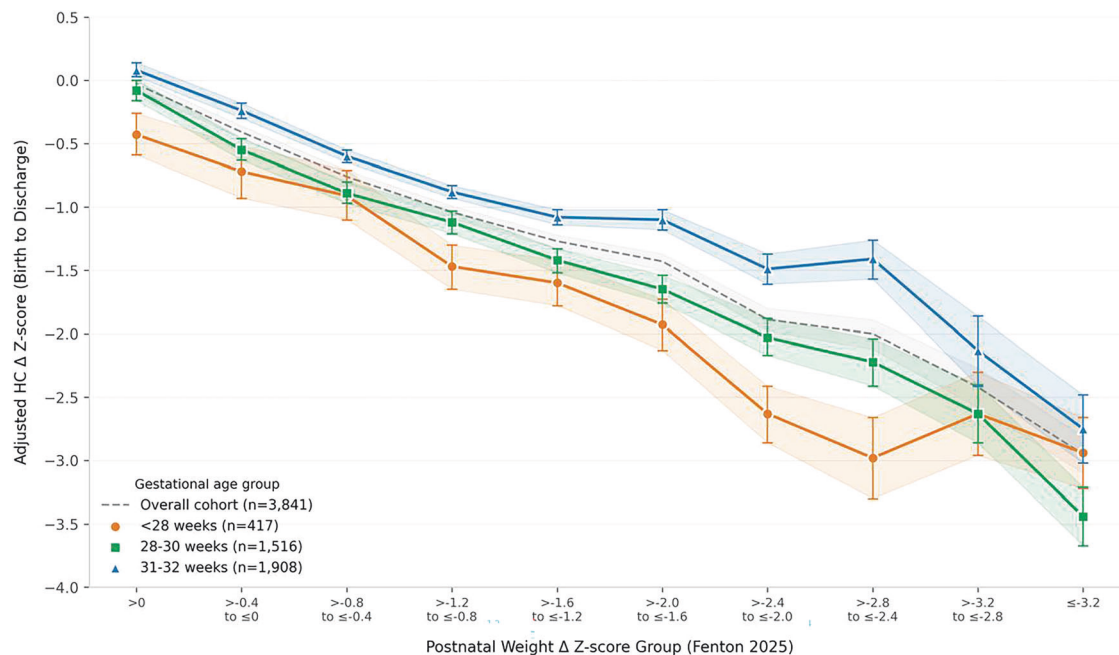


Fig. 3 Adjusted average marginal predictions of HC Δ Z-score by postnatal weight trajectory group, stratified by gestational age: <28 weeks ($n = 417$, orange circles), 28–30 weeks ($n = 1516$, green squares), and 31–32 weeks ($n = 1908$, blue triangles). Dashed gray line: overall cohort estimate ($n = 3841$) with 95% CI for reference. All models adjusted for necrotizing enterocolitis, sepsis, SNAP-II score, length of stay, treated patent ductus arteriosus, HC Z-score at birth, weight Z-score at birth, and outborn status, with cluster-robust standard errors by center. Gestational age was excluded as a covariate within each stratum as it is the stratification variable. Shaded areas and error bars represent 95% confidence intervals. HC head circumference, Δ Z-score change in Z-score from birth to discharge.

DISCUSSION

In this cohort of 3926 preterm infants ≤ 32 weeks from 35 NICUs across Latin America, postnatal weight trajectory was independently and progressively associated with HC growth from birth to discharge. This association was present across the entire range of weight loss categories and persisted after adjustment for gestational age, illness severity, morbidities, and HC Z-score at birth.

The magnitude of the association is clinically relevant. The difference in predicted HC Δ Z-score between the reference group (Weight Δ Z-score > 0) and the most severe weight loss group (≤ -3.2) was approximately 2.4 Z-score units. HC growth in infancy is strongly correlated with brain volume and subsequent neurodevelopmental outcomes, [1, 2] and a difference of this magnitude—exceeding two standard deviations—is likely to translate into meaningful differences in neurodevelopment. Even mild weight loss (Δ Z-score > -0.4 to ≤ 0) was associated with lower HC growth compared to infants who maintained or bordered their birth weight Z-score, a finding that argues against the clinical assumption that small amounts of postnatal weight loss are inconsequential for brain growth.

The negative coefficient for HC Z-score at birth ($\beta = -0.43$) reflects regression to the mean: infants born with a higher HC Z-score tend to have a greater decline, and vice versa. This is an expected statistical phenomenon in repeated measurements of Z-scores and does not imply that a high HC at birth is harmful. Controlling for this effect is essential to isolate the independent contribution of weight trajectory to HC change, which our model achieves.

The independent inverse association of length of stay with HC Δ Z-score warrants consideration. Longer NICU stays may reflect greater cumulative morbidity and nutritional challenges as well as costs that are not fully captured by the covariates included in the model. Alternatively, extended hospitalization may represent prolonged exposure to the NICU environment—with its attendant nutritional and metabolic demands—beyond what can be attributed to illness severity alone. The directionality of this relationship should not be interpreted as evidence that early discharge promotes HC growth; rather, it likely reflects residual confounding by disease burden.

The use of Fenton 2025 as the reference standard is a key methodological feature of this analysis. The 2025 revision introduced updated parameters that modify Z-score assignments relative to the 2013 version. As a consequence, the numerical results reported here are not directly comparable to prior studies using Fenton 2013, including an earlier version of this work presented in PAS 2026 poster form. Investigators applying these findings in clinical or research contexts should verify which version of the Fenton charts is in use.

EpicLatino provides a distinctive platform for this analysis: a large, prospectively collected, standardized dataset from a region systematically underrepresented in neonatal nutrition literature. Most available evidence comes from high-income country registries in which nutritional protocols, population characteristics, and institutional resources may differ substantially from Latin American NICUs. Our results provide region-specific estimates that can inform nutritional guidelines in this context.

Several limitations should be acknowledged. Listwise deletion was used for missing covariate data (4.3%), which may introduce bias if data are not missing at random. Positive blood culture was used as a proxy for sepsis, and clinical sepsis episodes without bacteremia would be misclassified. Nutritional intake data—including parenteral nutrition volumes, enteral feeding advancement protocols, and breast milk availability—were not available in the registry and represent important unmeasured confounders. HC at discharge may not be the most clinically meaningful endpoint; outcomes at 18–24 months corrected age would better capture the neurodevelopmental implications of HC growth.

Another key limitation of this study is the presence of survivor bias, as only patients who survived were included. Deceased patients were excluded because their shorter follow-up would have yielded incomplete z-score data, potentially underestimating growth faltering in the full cohort. Finally, participating units are not a random sample of NICUs in the region, and generalizability to facilities without quality improvement infrastructure is uncertain.

In summary, postnatal weight trajectory is strongly and independently associated with HC growth across all severity categories in preterm infants ≤ 32 weeks across Latin America. These findings support the clinical goal of minimizing postnatal weight Z-score decline as a nutritional target to promote brain growth in the NICU.

DATA AVAILABILITY

The data that supports the findings of this study are not publicly available because this data belongs to 35 units of Latin America and the Caribbean and there is a confidential agreement with them, but are available from the corresponding author upon request.

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AUTHOR CONTRIBUTIONS

Conceptualization ABH, PVH, CF, HO, MB, and CV. Data curation ABH, PVH. Formal analysis ABH and PVH. Investigation ABH and PVH. Methodology ABH and PVH. Project administration ABH, PVH, HO, CF, MB, and CV. Validation ABH, PVH, HO, CF, MB, and CV. Visualization ABH, PVH, HO, CF, MB, and CV. Writing—original draft ABH and PVH. Writing—review & editing ABH and PVH.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICAL APPROVAL

The EpicLatino Neonatal Network registry has Institutional Review Board approval at each participating site. Data are anonymized before submission to the central

database. This secondary analysis of de-identified data was considered exempt from individual informed consent, in accordance with international guidelines (Declaration of Helsinki, CIOMS) and national regulations on human subject research. Data handling complied with applicable confidentiality and data protection standards. Conjoint Health Research Ethics Board (CHREB) at the University of Calgary has issued an approval No REB21-1518_REN4 for the Database for EpicLatino.

STATEMENT ON ARTIFICIAL INTELLIGENCE USE

Artificial intelligence tools (ChatGPT, OpenAI, Claude) were used to assist with language editing, formatting suggestions, and organization of sections (e.g., abstract, methods, discussion). No content was reviewed by AI. The authors reviewed, revised, and take full responsibility for the content of the manuscript.

ADDITIONAL INFORMATION

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