Head Growth Trajectory and Neurodevelopmental Outcomes in Preterm Neonates

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abstract

OBJECTIVES: To evaluate the association between head growth (HG) during neonatal and postdischarge periods and neurodevelopmental outcomes of preterm neonates of <29 weeks gestational age.

METHODS: We conducted a retrospective cohort study of infants <29 weeks gestational age admitted between 2009 and 2011 to participating Canadian Neonatal Network units and followed by Canadian Neonatal Follow-Up Network clinics. Differences in head circumference (ΔHC) z score were calculated for 3 time periods, which include admission to discharge, discharge to follow-up at 16-36 months, and admission to follow-up. These were categorized in 1 reference group (ΔHC z score between −1 and +1) and 4 study groups (ΔHC z score of <−2, between −2 to −1, +1 to +2, and >+2). Neurodevelopmental outcomes were compared with the reference group.

RESULTS: 1973 infants met the inclusion criteria. Poor HG occurred frequently during the NICU admission (ΔHC z score <−2 in 24% infants versus 2% infants post-discharge) with a period of "catch-up" growth postdischarge. Significant neurodevelopmental impairment was higher in infants with the poorest HG from admission to follow-up (adjusted odds ratio 2.18, 95% confidence interval 1.50–3.15), specifically cognitive and motor delays. Infants with poor initial HG and catch-up postdischarge have a lower adjusted odds ratio of significant neurodevelopmental impairment (0.35, 95% CI 0.16–0.74). Infants with poor HG received a longer duration of parenteral nutrition and mechanical ventilation and had poor weight gain.

CONCLUSIONS: Poor HG during the neonatal and postdischarge periods was associated with motor and cognitive delays at 16 to 36 months.

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Dr Raghuram conceptualized and designed the study, and drafted the initial manuscript; Mr Yang conducted the initial analyses, and reviewed and revised the manuscript; Drs Church and Synnes acted as representation for the Canadian Neonatal Follow-Up Network, reviewed the initial study proposal and research ethics application, contributed to the acquisition and interpretation of data, and reviewed and revised the manuscript; Drs Cieslak and Mukerji contributed to the concept, design and interpretation of data, critically reviewed and revised the draft manuscript for intellectual content; Dr Shah reviewed the initial study proposal and research ethics

WHAT'S KNOWN ON THIS SUBJECT: There is mounting evidence to suggest that poor head growth in preterm neonates is associated with neurodevelopmental delay. It is unclear whether this association relates only to head growth within the NICU and which aspect of development is most affected.

WHAT THIS STUDY ADDS: In preterm infants of <29 weeks gestation, poor head growth both during and after NICU admission correlates with poor cognitive and motor outcomes that is mediated by nutritional and non-nutritional factors, such as prolonged invasive ventilation.

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The variable associations between head growth (HG) and neurodevelopmental outcomes of preterm neonates during early childhood and at school age have been documented[1–5]; however, studies have generally reported on small population sizes and have yielded conflicting results. Neubauer et al[2] reported that suboptimal head circumference (HC) at birth did not predict neurodevelopmental outcomes at 18 to 24 months, whereas HC at 3 months was predictive of both cognitive and psychomotor development.[2] Meanwhile, a modest association between interval HG from 1 week of age to term corrected age (CA) and cognitive outcomes at 18 months has been reported with no effect on other aspects of development in infants <33 weeks gestational age (GA).[3] Other studies have indicated that inadequate HG before 1 year of age is correlated with poor motor and cognitive outcomes, and microcephaly predicted abnormal cognitive and motor outcomes at 2 years of age.[1,6]

Although these data suggest that HC is associated with neurodevelopmental outcomes, it is unclear whether this correlation applies to HC at birth, HG during the NICU admission, or HG after discharge from the hospital. Some studies have argued that gains in HG during the NICU admission and after discharge from the hospital may be strong predictors of neurodevelopmental outcome.[2,4,7,8] Interestingly, a correlation between HC at 18 to 24 months CA and brain volume on MRI was associated with neurodevelopmental outcome.[9] Another study proposed that HG while in the NICU offers little predictive value for neurodevelopmental outcome.[10] It is also uncertain which aspect of development (ie, motor or cognitive development) is associated more with HG.[11] Our objective was to evaluate the association between HG during neonatal and postdischarge periods and neurodevelopmental outcomes between 16 and 36 months CA in preterm neonates born at <29 weeks GA.

METHODS

Design and Participants

We conducted a retrospective cohort study by using data collected for the Canadian Neonatal Network (CNN) and the Canadian Neonatal Follow-Up Network (CNFUN). The CNN and CNFUN maintain a national standardized database of neonatal diagnoses and treatments, and neurodevelopmental outcomes for infants of <29 weeks GA admitted to level III NICUs in Canada. Preterm infants of <29 weeks GA born between April 1, 2009, and September 30, 2011, who received neurodevelopmental follow-up assessments at 16 to 36 months CA for whom there was available HC measurements at admission, discharge, and follow-up were included. Infants with major congenital or chromosomal anomalies, infants with planned palliative care before delivery, those admitted to centers not participating in data collection to both networks, those born with microcephaly (HC less than third percentile for GA and sex), those with either unilateral or bilateral severe ventricular enlargement (ventricular size >15 mm measured anywhere within the ventricle on head imaging or those in which ventricular enlargement was reported with no measurements), and those with hydrocephalus requiring surgical drainage were excluded. Exclusions were preplanned to ensure that results were not confounded by conditions that may have impacted HG or by patients who may have had other causes for abnormal HG. Research ethics board approval for data collection was obtained at each site. This specific study protocol was approved by Mount Sinai Hospital's Research Ethics Board and the steering committees of both networks.

Data Collection

Neonatal outcome and demographic data were collected from the infant's medical records by trained personnel according to definitions in the CNN abstractor manual.[12] Eligible participants were identified within the CNN database and linked to the CNFUN database by using a single unique identifier.

HC *z* scores were determined at time of birth, at NICU discharge, and at follow-up assessment (ie, median 21 months, range 21.1–22.6 months) by using the Canadian population-based normal for HC at birth[13] and World Health Organization measurements of growth at 16 to 36 months CA.[14] CNFUN contains 1 recorded HC and weight measurement at follow-up. The differences between the *z* scores were calculated for 3 time periods as an estimate of HC growth velocities and wer as follows: from birth to discharge, discharge to follow-up, and birth to follow-up. Infants were categorized into the following 5 groups based on HC *z* score differences in each time period:

Group 1: *z* score difference of −1 to +1 (reference)

Group 2: *z* score difference of <−2

Group 3: *z* score difference of −1.01 to −2

Group 4: *z* score difference +1.01 to +2; and

Group 5: *z* score difference >+2.

At 16 to 36 months CA, infants were seen at participating CNFUN sites for neurodevelopmental assessment, as previously described.[15] The Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III) was administered by certified examiners to assess development. The Bayley-III is a widely used

developmental assessment scale for infants that yields cognitive, language, and motor composite scores,[16] with the mean set at 100 and a SD of 15 for each domain. Hearing and visual function were determined through physical examination, parental interviews and/or medical records. Mean (SD) *z* scores of a change in weight at all 3 times were calculated to correlate differences in HC (ΔHC) with a change in weight.

Outcomes

Primary outcomes include neurodevelopmental impairment (NDI) defined as the presence of any of the following: cerebral palsy, sensorineural or mixed hearing loss, unilateral or bilateral visual impairment, and developmental delay with a Bayley-III score <85 in any of motor, cognitive or language domains; and a significant NDI (sNDI) defined as the presence of any of the following: cerebral palsy with a Gross Motor Function Classification Scale ≥3,[17] requirement for hearing aids or cochlear implants, bilateral visual impairment (diagnosed as no response to a 1 cm object, small eye, corneal scarring, sustained sensory nystagmus, an ophthalmologist report of retinopathy of prematurity with macular drag, traction or detachment, visual acuity of 20/70 or less), or significant developmental delay with Bayley-III motor, composite, or language scores of <70. Children unable to be tested with the Bayley-III because of a significant neuroimpairment were assigned a score of <70 for sNDI and <85 for NDI based on a questionnaire provided to the examiner. Secondary outcomes consisted of individual components of the primary outcome and Bayley-III motor, cognitive, and language scores. Significant and moderate delays refer to any domain with Bayley scores <70 and <85, respectively.

Statistical Analyses

Infant characteristics, neonatal data, and neurodevelopmental outcomes of the 5 groups of infants were compared by using the Pearson's χ^2 test (categorical) and the Student's *t* test (continuous) for normally distributed variables, and the Wilcoxon rank test (continuous) for non-normally distributed data. The analysis of variance F test (continuous) was used for multiple variables. Odds ratios for primary and secondary outcomes were calculated for Groups 2 to 5 in comparison with the reference (Group 1) for each time period. Odds ratios were adjusted for confounding factors by using logistic regression analyses. These factors included GA, male sex, small for gestational age (SGA) status, Score for Neonatal Acute Physiology-II (SNAP-II) score, antenatal steroid use, and cesarean delivery. In addition, days of total parenteral nutrition (TPN), weight *z* score difference, and days on mechanical ventilation were compared between the groups. For Bayley-III composite scores, unadjusted and adjusted differences in mean scores were calculated for each group in comparison with Group 1. No adjustments were made for intermediate neonatal outcomes (including bronchopulmonary dysplasia, intraventricular hemorrhage, periventricular leukomalacia [PVL], sepsis, necrotizing enterocolitis, and patent ductus arteriosus) to avoid for over-adjustment. Generalized estimating equation models were used to account for correlation of data within centers. In a post hoc analysis, we evaluated catch-up HG. Infants in Group 2 (ΔHC < −2 *z* score) from admission to discharge were subdivided into those who had HG gains postdischarge (ΔHC *z* score difference > 0), indicating catch-up growth, and those who had no gains or a loss in HG (ΔHC *z* score difference < 0), and their neurodevelopmental outcomes were assessed. Statistical analyses were conducted by using SAS version 9.3 (SAS Institute Inc, Cary, NC), and a *P* value of .05 was considered significant.

RESULTS

Of the 3960 eligible infants, 1973 infants were included in the study population (Fig 1). Stratification of infants into groups (Table 1) revealed that poor HG was more frequent during the infant's NICU stay compared with postdischarge (ΔHC *z* score < −2, 24.2% versus 1.8%, respectively). Meanwhile, a period of catch-up growth was observed postdischarge (ΔHC *z* score +1.01 to +2, 4.0% versus 28.5%, respectively). Supplemental Figure 2 in the Supplemental Information shows the trajectory of both weight gain and HG over the 3 time points.

Table 2 outlines maternal and neonatal characteristics based on ΔHC growth from NICU admission to discharge. Differences in maternal receipt of antenatal steroids, birth weight, GA, and SGA status were noted between the groups. They also differed in the presence of ventricular enlargement (ventricular size > 10 mm on either side) at discharge, with infants having ΔHC *z* scores of <−2 or >2 displaying the highest rates (17.1% and 16.1%, respectively). Periventricular leukomalacia was also more frequent among infants in which HG velocity was higher than expected (12.3% in Group 5 versus 2.8% in Group 1, *P* < .01). Days of TPN, weight *z* score difference, and days on mechanical ventilation differed significantly in every time period, with infants that have the poorest HG displaying the longest duration of TPN and mechanical ventilation and the poorest weight gain during the NICU admission. Supplemental Tables 6 and 7 in the Supplemental Information describe baseline characteristics according to

HC growth during the other 2 time periods in which similar differences were observed between groups. However, mean weight *z* score difference correlated less strongly with HC change postdischarge and overall from admission to follow-up when compared with NICU admission.

Table 3 presents adjusted odds ratios (aORs) for the primary outcomes during each time period. Patients with the lowest HG velocity (Group 2) between NICU admission and discharge and between admission and follow-up had higher odds of sNDI (aOR 1.38, 95% confidence interval [CI] 1.01–1.89 and aOR 2.18, 95% CI 1.5–3.15, respectively). Between discharge and follow-up, the odds of sNDI were higher, but did not reach statistical significance (aOR 2.14, 95% CI 0.99–4.63). In addition, infants in Group 4 with some degree of catch-up HG had significantly lower odds of developing sNDI (aOR 0.56, 95% CI 0.33–0.93).

Table 4 displays aORs of the secondary outcomes for each group and time period. In Group 2, there was significantly higher motor and cognitive delays during all periods; moderate motor and cognitive delays were observed for most time periods, whereas language delay was only noted among those with poor HG from admission to follow-up. Infants in Group 3 with less pronounced HG from admission to follow-up showed overall moderate motor and cognitive delay and severe cognitive delay. Group 4, who had some catch-up growth, had lower odds of moderate language and severe cognitive delay when this growth occurred from admission to discharge and discharge to follow-up, respectively. Conversely, patients with the highest increase in HG during the admission to discharge period (Group 5) showed an increased risk of moderate motor delay.

Table 5 shows adjusted differences in mean Bayley-III composite scores for all groups. Mean composite motor scores varied significantly in Group 2 during all time periods, with a difference of 2 points if HG was impaired from admission to discharge, by 8 points if HG was impaired post-discharge, and by 4 points if HG was impaired throughout. This difference was also observed for composite cognitive scores for Group 2. Language scores also differed significantly in Group 2 from discharge to follow-up and overall from admission to follow-up. Group 4 had improved composite language scores when there was higher HG velocity from admission to discharge. Lower composite motor scores were observed among infants with the highest growth velocity (ΔHC *z* score > +2) from admission to discharge and from admission to follow-up. Supplemental Tables 8 through 10 in the Supplemental Information show the raw data.

Supplemental Table 11 shows the effect of catch-up growth on neurodevelopmental outcomes. Infants with the poorest HG during their admission to the NICU (ΔHC *z* score < −2) who had any HG catch-up postdischarge had a significantly lower odds of sNDI (aOR 0.35, 95% CI 0.16–0.74) and lower odds of significant motor and language

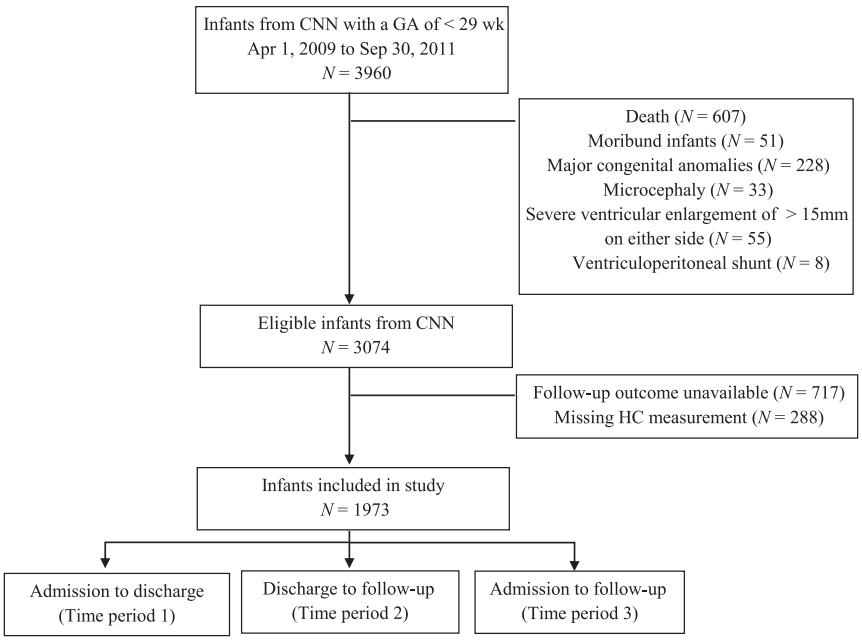

FIGURE 1
A flow diagram of study population.

TABLE 1 Study Population and Group Distribution Based on Time Period and ΔHC *z* Score

Time Period	ΔHC *z* Score				
	−1 to +1 (Group 1, Reference)	<−2 (Group 2)	−2 to −1.01 (Group 3)	+1.01 to +2 (Group 4)	>+2 (Group 5)
Admission to discharge, *N* (%)	849 (43.0)	477 (24.2)	511 (25.9)	78 (4.0)	58 (2.9)
Discharge to follow-up, *N* (%)	782 (39.6)	36 (1.8)	63 (3.2)	563 (28.5)	529 (26.8)
Admission to follow-up, *N* (%)	1037 (52.6)	216 (11.0)	218 (11.1)	333 (16.9)	169 (8.6)

TABLE 2 Maternal and Neonatal Characteristics According to Infant HC Growth Velocity During the Time Period Between NICU Admission and Discharge

	ΔHC *z* Score					*P*
	−1 to +1 Group 1 (*N* = 849)	<−2 Group 2 (*N* = 477)	−2 to −1.01 Group 3 (*N* = 511)	+1.01 to +2 Group 4 (*N* = 78)	>+2 Group 5 (*N* = 58)	
Maternal characteristics						
Maternal age, mean (SD)	31.0 (6.0)	30.5 (5.9)	30.8 (5.8)	31.0 (5.8)	30.7 (5.6)	.55
Caregiver 1 education (college+), *n* (%)	437 (55.1)	228 (54.2)	251 (53.6)	38 (50.0)	28 (51.9)	.91
Hypertension, *n* (%)	147 (17.7)	76 (16.3)	68 (13.6)	9 (11.8)	11 (19.6)	.24
Antenatal steroid, *n* (%)	767 (92.2)	409 (88.2)	445 (89.5)	65 (86.7)	46 (82.1)	.03[a]
Cesarean delivery, *n* (%)	495 (58.5)	282 (59.4)	283 (55.6)	43 (55.1)	35 (60.3)	.73
Neonatal characteristics						
Birth weight (g), mean (SD)	960 (213)	900 (233)	967 (226)	912 (206)	905 (210)	<.01
Weight *z*- core change, mean (SD)	−0.83 (0.79)	−1.52 (1.01)	−1.27 (0.68)	−0.20 (0.72)	−0.32 (1.45)	<.01
Gestational age (wk), mean (SD)	26.5 (1.3)	26.1 (1.5)	26.5 (1.4)	26.4 (1.3)	26.3 (1.4)	<.01
Sex (male), *n* (%)	460 (54.2)	247 (51.8)	249 (48.7)	45 (57.7)	33 (56.9)	.26
SGA, *n* (%)	58 (6.8)	32 (6.7)	20 (3.9)	10 (12.8)	6 (10.3)	.01
Multiple gestations, *n* (%)	237 (27.9)	138 (28.9)	138 (27.0)	27 (34.6)	19 (32.8)	.61
SNAP-II score, median (IQR)	14 (8, 19)	14 (9, 21)	14 (8, 21)	9 (7, 21)	14 (9, 19)	.17
Ventricular enlargement on head ultrasound at discharge, *n* (%)	88 (10.8)	78 (17.1)	65 (13.2)	10 (13.0)	9 (16.1)	.03[b]
PVL, *n* (%)	22 (2.8)	24 (5.6)	30 (6.5)	7 (9.2)	7 (12.3)	<.01
TPN, mean days (SD)	21.5 (14.8)	40.5 (31.5)	26.2 (17.8)	27.5 (18.6)	27.9 (15.1)	<.01
Days IPPV or HFOV, mean (SD)	13.8 (19.0)	25.0 (26.7)	13.8 (17.7)	18.4 (20.6)	23.8 (23.6)	<.01
Postnatal support						
Physical therapist	301 (46.5)	201 (52.8)	191 (52.0)	36 (59.0)	41 (78.9)	<.01
Occupational therapist	253 (39.0)	195 (51.2)	160 (43.2)	26 (44.1)	25 (48.1)	.01

HFOV, high frequency oscillatory ventilation; IPPV, intermittent positive pressure ventilation; IQR, interquartile range.

[a] Antenatal steroids refers to any antenatal steroid use.

[b] Ventricular enlargement defined as ventricular size >10 mm on either side.

TABLE 3 Neurodevelopmental Outcomes at 16–36 mo Follow-Up According to HC Growth During Various Time Periods

Outcome	Time Period	ΔHC *z* Score			
		<−2 Group 2 aOR (95% CI)	−2 to −1.01 Group 3 aOR (95% CI)	+1.01 to +2 Group 4 aOR (95% CI)	>+2 Group 5 aOR (95% CI)
sNDI	Admission to discharge	1.38 (1.01 to 1.89)	1.1 (0.79 to 1.53)	0.6 (0.27 to 1.37)	0.94 (0.42 to 2.07)
	Discharge to follow-up	2.14 (0.99 to 4.63)	0.81 (0.38 to 1.72)	0.82 (0.59 to 1.14)	1.03 (0.75 to 1.41)
	Admission to follow-up	2.18 (1.5 to 3.15)	1.31 (0.87 to 1.99)	0.98 (0.66 to 1.45)	1.09 (0.66 to 1.78)
NDI	Admission to discharge	0.98 (0.78 to 1.24)	0.96 (0.76 to 1.21)	0.56 (0.33 to 0.93)	1.43 (0.82 to 2.5)
	Discharge to follow-up	1.82 (0.89 to 3.72)	0.71 (0.41 to 1.23)	0.93 (0.74 to 1.17)	1 (0.79 to 1.26)
	Admission to follow-up	1.23 (0.9 to 1.68)	1.34 (0.99 to 1.81)	1.11 (0.86 to 1.44)	1.03 (0.73 to 1.45)

Group 1 is the reference group and all results are in relation to Group 1. The results are adjusted for GA, sex, SGA, antenatal steroid use, SNAPII score and Caesarian section.

delays (aOR 0.12, 95% CI 0.04–0.35 and aOR 0.32, 95% CI 0.12–0.79, respectively) compared with those who had catch-up HG postdischarge.

DISCUSSION

In this large population-based cohort, the rate of sNDI was higher in infants with the poorest HG from admission to follow-up compared with the reference group, primarily with motor and cognitive development. The rate of moderate motor impairment was higher in infants exhibiting the poorest HG and those with less pronounced HG delays. Infants with the poorest HG had a threefold higher risk of severe motor impairment and significantly lower composite Bayley-III scores in all development areas tested. Groups with poorer HG had higher odds of moderate and severe cognitive impairment if HG was impaired from admission to follow-up. This indicates that poor HG during the NICU admission that persists postdischarge is associated with motor and cognitive development.

Catch-up in HG during the NICU admission is associated with twofold decrease in the rate of sNDI if HG increased by 1 to 2 *z* scores. The association between HG velocity and language development were less obvious. Thus, this study adds to the body of evidence that poor HG in preterm neonates is strongly associated with neurodevelopmental outcomes.

Poor HG in preterm neonates is multifactorial. We attempted to delineate some of these causes by

TABLE 4 Developmental Outcomes at 16–36 mo Follow-Up

Outcome	Time Period	ΔHC *z* Score			
		<−2 Group 2 aOR (95% CI)	−2 to −1.01 Group 3 aOR (95% CI)	+1.01 to +2 Group 4 aOR (95% CI)	>+2 Group 5 aOR (95% CI)
Composite motor score <85	Admission to discharge	1.24 (0.91 to 1.69)	1.1 (0.81 to 1.5)	0.67 (0.32 to 1.42)	2.63 (1.45 to 4.79)
	Discharge to follow-up	2.93 (1.36 to 6.34)	1.07 (0.54 to 2.11)	1.12 (0.83 to 1.51)	1.03 (0.76 to 1.4)
	Admission to follow-up	1.67 (1.14 to 2.46)	1.55 (1.05 to 2.28)	1.33 (0.94 to 1.87)	1.4 (0.9 to 2.2)
Composite cognitive score <85	Admission to discharge	1.53 (1.08 to 2.15)	1.01 (0.7 to 1.46)	0.68 (0.28 to 1.63)	1.41 (0.65 to 3.02)
	Discharge to follow-up	3.67 (1.66 to 8.08)	0.83 (0.36 to 1.92)	0.85 (0.59 to 1.22)	1.15 (0.82 to 1.63)
	Admission to follow-up	2.23 (1.48 to 3.35)	1.77 (1.15 to 2.7)	0.91 (0.58 to 1.42)	1.49 (0.9 to 2.48)
Composite language score <85	Admission to discharge	0.94 (0.73 to 1.23)	0.94 (0.73 to 1.21)	0.5 (0.27 to 0.91)	1.15 (0.64 to 2.06)
	Discharge to follow-up	1.96 (0.92 to 4.17)	0.68 (0.36 to 1.27)	1.07 (0.84 to 1.38)	1.04 (0.81 to 1.34)
	Admission to follow-up	1.28 (0.91 to 1.79)	1.18 (0.84 to 1.64)	1.1 (0.82 to 1.46)	1 (0.68 to 1.47)
Composite motor score <70	Admission to discharge	1.89 (1.11 to 3.22)	1.37 (0.78 to 2.4)	0.7 (0.16 to 3.05)	2.24 (0.82 to 6.16)
	Discharge to follow-up	5.08 (1.95 to 13.26)	0.61 (0.14 to 2.65)	0.98 (0.57 to 1.69)	1.17 (0.69 to 2)
	Admission to follow-up	2.89 (1.65 to 5.07)	1.23 (0.6 to 2.53)	0.68 (0.31 to 1.47)	1.94 (0.96 to 3.93)
Composite cognitive score <70	Admission to discharge	2.41 (1.19 to 4.87)	0.96 (0.4 to 2.31)	1.42 (0.31 to 6.54)	1.94 (0.42 to 8.91)
	Discharge to follow-up	5.35 (1.75 to 16.4)	0.55 (0.07 to 4.23)	0.36 (0.13 to 0.98)	1.23 (0.62 to 2.43)
	Admission to follow-up	2.69 (1.24 to 5.86)	2.43 (1.06 to 5.53)	0.96 (0.35 to 2.64)	1.1 (0.32 to 3.8)
Composite language score <70	Admission to discharge	1.27 (0.85 to 1.89)	1.13 (0.76 to 1.69)	0.56 (0.19 to 1.59)	0.68 (0.24 to 1.99)
	Discharge to follow-up	2.35 (0.94 to 5.87)	0.99 (0.4 to 2.44)	0.96 (0.64 to 1.44)	1.2 (0.81 to 1.78)
	Admission to follow-up	2.07 (1.3 to 3.3)	1.56 (0.95 to 2.57)	1.2 (0.75 to 1.92)	1.1 (0.59 to 2.05)

Group 1 is the reference group and all results are in relation to Group 1. The results are adjusted for GA, sex, SGA, antenatal steroid use, SNAPII score and cesarian delivery.

TABLE 5 Adjusted Differences in Mean Bayley-III Composite Scores

Outcome	Time Period	ΔHC *z* Score			
		<−2 Group 2 ADM (95% CI)	−2 to −1.01 Group 3 ADM (95% CI)	+1.01 to +2 Group 4 ADM (95% CI)	>+2 Group 5 ADM (95% CI)
Composite motor scores	Admission to discharge	−2.07 (−3.77 to −0.36)	−0.77 (−2.39 to 0.85)	0.24 (−3.26 to 3.74)	−5.52 (−9.39 to −1.64)
	Discharge to follow-up	−7.94 (−13.03 to −2.84)	0.21 (−3.54 to 3.96)	−0.47 (−2.08 to 1.13)	−1.26 (−2.9 to 0.39)
	Admission to follow-up	−4.44 (−6.7 to −2.19)	−2.2 (−4.38 to −0.01)	−1.26 (−3.08 to 0.55)	−3.19 (−5.65 to −0.73)
Composite cognitive scores	Admission to discharge	−1.9 (−3.57 to −0.24)	0.27 (−1.32 to 1.87)	1.88 (−1.58 to 5.33)	−1.47 (−5.35 to 2.41)
	Discharge to follow-up	−8.33 (−13.4 to −3.23)	2.04 (−1.71 to 5.79)	0.31 (−1.27 to 1.88)	−1.35 (−2.96 to 0.25)
	Admission to follow-up	−5.64 (−7.83 to −3.44)	−1.84 (−3.96 to 0.29)	−2.16 (−3.95 to −0.38)	−1.22 (−3.59 to 1.16)
Composite language scores	Admission to discharge	−1.08 (−3.1 to 0.94)	−0.31 (−2.24 to 1.62)	5.16 (1.02 to 9.3)	−0.93 (−5.55 to 3.69)
	Discharge to follow-up	−6.77 (−12. 9 to −0.7)	1 (−3.55 to 5.54)	0.17 (−1.75 to 2.08)	−0.85 (−2.81 to 1.11)
	Admission to follow-up	−3.71 (−6.39 to −1.03)	−1.43 (−4.01 to 1.15)	−0.9 (−3.08 to 1.28)	0.07 (−2.84 to 2.97)

Group 1 is the reference group and all results are in relation to Group 1. The results are adjusted for GA, sex, SGA, antenatal steroid use, SNAPII score and cesarian delivery. ADM, adjusted difference in the mean.

correlating nutritional parameters, such as weight gain and TPN usage as well as head imaging findings (ie, PVL and ventriculomegaly) and mechanical ventilation. This study shows that during the NICU admission, weight gain correlates strongly with HG and infants with the poorest HG required significantly longer duration of TPN. These nutritional effects during NICU admission persisted beyond hospital discharge as evident from the ΔHC after discharge. Number of days on TPN may indicate an increased illness severity, neonatal complications, or delayed enteral feeding, which may be critical in HG and an area that warrants additional research. Most units in Canada start glucose and amino acids (1–2 g/kg per day) immediately after birth. Lipids are introduced in the next 24 hours starting between 0.5 and 1 g/kg per day, and both are increased gradually over the next 3 to 4 days at rate of 0.5 to 1 g/kg per day to reach a maximum of 3 to 4 g/kg per day. There are variations between centers in terms of increase, but the ultimate goal is similar. Previous studies have shown similar correlations between weight and HG.[1,3] Furthermore, Belfort et al[3] showed that postdischarge, increases in weight gain out of proportion to other growth parameters does not confer a neurodevelopmental advantage, also indicating that nutrition alone may not explain this association.

Neonates with the poorest HG also received more days of mechanical ventilation at all time points. We speculate that earlier extubation and increased use of noninvasive ventilation in recent neonatal practice may help reduce the duration of mechanical ventilation and promote growth; however, this needs to be studied carefully as increased work of breathing associated with noninvasive ventilation may affect growth.

Although it is difficult to make direct comparisons, studies have shown that poor postnatal HG is associated with poor motor and cognitive outcomes. Belfort et al[3] showed that HC zscore <1 SD from the mean in early infancy predicted poorer motor and cognitive outcomes. Wright and Emond[18] showed higher rates of motor and cognitive delay, cerebral palsy, abnormal neurologic examination, and sNDI were associated with poor HG while in the hospital. Despite similar findings, timing of measurement varies significantly, and therefore conclusions about when HG is most important are difficult to make. Here, it appears that although neurodevelopmental delays are associated with both predischarge and postdischarge HG, they appear to be more pronounced when HG continues to lag postdischarge. In contrast, Belfort et al[3] showed that poor HG between 1 week of life and term predicted delays in the Bayley Scales of Infant Development, Second Edition, Psychomotor Index, specifically in non-SGA infants. HG after this time period, however, had no effect on neurodevelopmental outcome. Other groups have also stressed the importance of in-hospital HG, but did not find similar associations between postdischarge HG and outcomes.[4,19,20] On the other hand, Neubauer et al[2] found that HC early in postnatal life did not correlate, whereas HC at 3 and 12 months CA correlated with both motor and cognitive outcomes, which is similar to other studies.[7,21] Additional study is warranted to determine factors that may contribute to postdischarge HG and their associations with neurodevelopment.

Catch-up growth has been shown to correlate with better outcomes.[8,21,22] Although a significant portion of infants experienced poor HG within the NICU, the majority of them displayed catch-up postdischarge, which has been consistent wih most studies. In this cohort, catch-up growth postdischarge in infants with poor initial HG was associated with improved outcomes.

Lower HC *z* scores have been associated with significantly lower brain volumes on MRI scans and higher rates of motor and cognitive impairments, including cerebral palsy.[7] Poor postnatal HG is also associated with delayed cortical maturation visable on MRI scans.[23] In our cohort, the rates of PVL and ventriculomegaly were more frequent in infants with a ΔHC *z* score >+2 than those with a ΔHC *z* score <−2. Thus, we speculate that association between persistent poor HG during the postnatal period with neurodevelopmental outcomes cannot be explained by structural changes alone.

The strengths of this study include the large population, detailed and robust data collection, detailed analysis of the implications of HG during distinct time periods, exploration of HG velocity, assessment of association with different domains of neurodevelopment, and exclusion of neonates whose HG may have been affected by underlying etiology or aberrations in HG. The limitations of our study include the retrospective, observational nature of the study, and therefore many infants were excluded because of missing data. In addition, the study relies on accurate HC measurement, which is often associated with measurement error.[18] Lastly, ∼23% patients were lost to follow-up, which could have affected our results.

Future research should focus on delineating contributors to poor postdischarge HG and the influence of factors when neonates are in the NICU on postdischarge HG. It is also important to continue to follow children with poor HG into later childhood to understand the functional implications of these findings.

CONCLUSIONS

Poor HG is strongly correlated with a greater degree of challenges in the cognitive and motor domains in preterm neonates. This is likely because of changes in brain structure that occur during the neonatal period and persists postdischarge. Additional studies are needed to better describe this association and to determine the etiology of poor HG in preterm neonates.

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ABBREVIATIONS

ΔHC: difference in head circumference
aOR: adjusted odds ratio
Bayley-III: Bayley Scales of Infant and Toddler Development, Third Edition
CA: corrected age
CI: confidence interval
CNFUN: Canadian Neonatal Follow-Up Network
CNN: Canadian Neonatal Network
GA: gestational age
HC: head circumference
HG: head growth
NDI: neurodevelopmental impairment
PVL: periventricular leukomalacia
SGA: small for gestational age
SNAP-II: Score for Neonatal Acute Physiology-II
sNDI: significant neurodevelopmental impairment
TPN: total parenteral nutrition

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