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Factors affecting early childhood growth in hypoxic-ischemic encephalopathy treated with hypothermia

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Abstract

INTRODUCTION: There is an extensive body of research regarding neurological outcomes following neonatal hypoxic-ischemic encephalopathy (HIE) treated with therapeutic hypothermia (TH), with limited data on growth outcomes. We examined perinatal characteristics associated with postnatal growth in this population.

METHODS: Convenience cohort of 66 infants with HIE who underwent TH and participated in follow-up at 24 months of age were included. Regression modeling including perinatal anthropomorphics, markers of HIE, and systemic injury was used to evaluate growth at 24 months.

RESULTS: Birth head circumference was associated with weight ($p = 0.036$). MRI severity, pH at admission and birth head circumference were associated with height ($p = 0.043$, $p = 0.015$

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AUTHOR CONTRIBUTIONS

Srishti Jayakumar participated in the data collection for the project, as well as analysis and writing of this manuscript. Vera Joanna Burton participated in the conceptualization and data collection for the project, as well as analysis and writing of this manuscript. Jamie Perin participated in the analysis and reviewed this manuscript. Daniella Asafu-Adjaye participated in data collection for the project and reviewed this manuscript. Elizabeth Cristofalo participated in the conceptualization and data collection for this project and reviewed the manuscript. Frances Northington participated in the conceptualization of this project and reviewed the manuscript. Raul Chavez-Valdez Northington participated in the conceptualization of this project and reviewed the manuscript. Mary Leppert participated in the conceptualization of this project and reviewed the manuscript. Marilee Allen participated in the conceptualization of this project and reviewed the manuscript. Gwendolyn Gerner participated in the conceptualization and data collection for the project, as well as analysis and writing of this manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

STATEMENT OF ETHICS

Study approval statement: The study was approved by the Institutional Review Board at Johns Hopkins University School of Medicine (IRB00133750). Written consent was obtained for the use of study participant data. This is not a clinical trial nor did it contain any experiments with animals.

and $p = 0.043$ respectively). MRI severity and length of intubation were associated with head circumference ($p = 0.038$ and $p < 0.001$ respectively).

CONCLUSION: There was a significant association between specific early factors and growth at 24 months among infants with HIE treated with TH.

INTRODUCTION

Neonatal hypoxic-ischemic encephalopathy (HIE) is one of the most common causes of perinatal brain injury and affects between 1.5 and 6 per 1000 live births [1, 2]. Since therapeutic hypothermia (TH) became standard of care for moderate to severe HIE [3], the majority of available literature has focused on neurological and developmental outcomes in this population. Few studies have described growth outcomes in this population despite risk for feeding problems and systemic injury that could negatively impact growth and potentially be a mediating factor of long-term developmental outcomes. The Eunice Kennedy Shriver National Institute for Child Health and Human Development (NICHD) trial reported slow growth (weight, length and head circumference) at 18–22 months and 6–7 years age in a cohort of term moderate to severe HIE survivors with moderate to severe cerebral palsy (CP) compared to those without CP [4]. Although Preeti et al. described anthropometric measures at one year of age following HIE, the study included neonates who had not undergone TH [5]. To our knowledge, there is no literature describing the association between neonatal characteristics and follow-up growth at 2 years of age in neonates who have been treated with TH.

The potential for systemic injury following perinatal hypoxic-ischemic insults has been well-described, with involvement of at least one system (renal, cardiac, hepatic or pulmonary) in up to nearly 100% of participants in some studies [6, 7]. The relationship between markers of systemic injury and neurodevelopmental outcomes following HIE has been explored. Acute kidney injury (AKI) in asphyxiated newborns has been shown to be a predictor of abnormal brain MRI at 7 to 10 days of age in some studies [8, 9] while hepatic, pulmonary and cardiac involvement have not been shown to be significant predictors of neuroimaging findings [6]. However, the association of systemic injury with anthropometric outcomes in neonates with HIE treated with hypothermia has not been well studied.

The goal of this study was to examine whether there are associations between neonatal variables and anthropometric measurements at twenty-four months of age in neonates who had undergone TH for HIE. Given the high prevalence of multisystem involvement, we evaluated neonatal variables including birth anthropometrics, early markers of HIE, and markers potentially reflecting systemic injury while controlling for sex and socioeconomic factors.

MATERIALS AND METHODS

Study design and participants

A prospective convenience sample of neonates with moderate to severe HIE who underwent treatment with TH in the neonatal intensive care unit at Johns Hopkins Hospital between

2010 and 2015 was utilized. All study participants completed a comprehensive follow-up evaluation at 24 months of age.

Institutional clinical protocol was followed during TH. Eligibility for hypothermia was based on clinical exam using the modified Sarnat criteria [10, 11] and blood gas obtained from the umbilical cord or during the first hour of life with pH <7.00 or a base deficit > 16 mmol/L. In the absence of available blood gases or pH < 7.15 or base deficit > 10 mmol/L, additional criteria were used to facilitate the diagnosis of HIE including an Apgar score of less than 5 at 10 min of life, requirement of ventilator assistance at or greater than 10 min of life, and history of an acute perinatal event. Infants born at 35 weeks or greater and those with a birth weight of 1.8 kg or greater were included in the study, as they met criteria for TH. Exclusion criteria comprise neonates with genetic abnormalities, in-utero drug exposure or prenatal infections, neonates ineligible for TH or those in foster care. Approval was obtained from the institutional research board at the home institution.

Independent variables

Neonatal characteristics collected included birth weight (grams), length (cm) and head circumference (cm), gestational age (weeks) and sex. Factors relating to HIE included pH (obtained from cord blood or within the first hour of life), base excess (obtained from cord blood or within the first hour of life), Apgar scores at one and five minutes of life and brain MRI at 10 to 16 days of life, categorized using the NICHD classification. Per NICHD criteria, categories included 0-normal; 1A-minimal cerebral lesions only with no involvement of basal ganglia (BG), thalamus (T), anterior limb of the internal capsule (ALIC) or posterior limb of the internal capsule (PLIC), and no area of watershed infarction; 1B-more extensive cerebral lesions without basal ganglia and thalamic (BGT), PLIC or ALIC involvement or infarction; 2A-any BGT, ALIC or PLIC involvement or watershed infarction noted without any other cerebral lesions; 2B-involvement of either BGT, ALIC or PLIC or area of infarction and additional cerebral lesions; and 3-cerebral hemispheric devastation [12, 13]. Additional factors related to more systemic injury were also recorded, including total duration of intubation (in days) required for respiratory support excluding intubation used for the purpose of a procedure, peak creatinine and alanine transaminase levels during the neonate's NICU stay, and mode of feeding at discharge classified as oral, gavage feeds, gastric tube (G-tube) feeds, or combined feeds. Additionally, type of feeds during the NICU admission including breastmilk, formula or combined feeds were recorded. Lastly, two well-established proxies that included family insurance status (private vs. medical assistance) and census tract median income using the family's address at time of the delivery [14, 15] were used to estimate socioeconomic status.

Dependent variables

Beginning in 2010, standard of care for neonates undergoing TH for HIE began including referral for neurodevelopmental follow-up upon discharge. These neonates were followed serially and included a comprehensive evaluation between 18–30 months. Outcomes included in this study are anthropometrics collected at the 24-month visit and included weight, height and head circumference recorded as percentiles and Z-scores.

Statistical analysis

Statistical analysis was completed using the software R Version 4.0. Descriptive statistics for neonatal characteristics were summarized using mean and standard deviation, median and interquartile range as appropriate. Since percentiles are bounded by 0 and 1 and likely not normally distributed, we used Z scores to estimate predictors of growth outcomes instead of percentiles. Assumptions for linear regression using Z scores for anthropometric outcomes were checked using the White test for heteroscedasticity, the Anderson Darling test to check normality and visual examination of the residuals to gauge linearity of the data. We used linear regression to explore the relationship between potential predictors and anthropometric outcomes at 24 months of age. These results were adjusted for birth anthropometric Z scores in order to investigate post-natal growth that would be more related to HIE. Results were also adjusted for sex and census-tract median income that might also impact post-natal growth. p value < 0.05 was considered statistically significant.

RESULTS

Sample characteristics

42 infants of an initial cohort of 66 neonates who underwent TH completed follow-up evaluation at 24 months of age. 9 (13.6%) out of 66 were deceased at the time of follow-up. Mean gestational age for our cohort was 38.9 weeks with a mean birth weight of 3273.8 g, mean birth length of 50 cm and mean head circumference of 34 cm. While 45% of our participants had a normal MRI (Grade 0), 17% had either NICHD Grade 2 A or 2B and 10% had NICHD Grade 3. Participant characteristics are summarized in Table 1.

Predictors of head circumference at 24 months

Mean head circumference Z score at 24 months of age was −0.17. Birth anthropometrics and gestational age were not significant predictors of head circumference at 24 months. MRI NICHD grade was significantly associated with head circumference outcomes ($p < 0.001$), with increasing severity of MRI predicting lower head circumference Z scores (Fig. 1). This association remained significant after adjusting for birth head circumference Z score as well as sex and census-tract median income ($p < 0.001$). pH, base deficit and Apgar scores were not predictive of head circumference outcomes. Duration of intubation in the NICU was also a significant predictor of head circumference at 24 months ($p = 0.022$), with an increase in the number of days of intubation predicting lower head circumference Z scores at 24 months. This association remained significant even after adjusting for birth head circumference Z scores as well as sex and census-tract median income ($p = 0.025$). Duration of intubation was significantly correlated with MRI with a multicollinearity value of 0.476. Interestingly, neither marker of systemic injury, peak creatinine nor alanine transaminase levels in the first 24 h of life predicted head circumference outcomes. Mode of feeding during the NICU admission and type of feeding at discharge also did not predict head circumference outcomes. These results are summarized in Table 2.

Predictors of weight at 24 months

While birth weight and birth length were not significantly associated with weight at 24 months, birth head circumference was found to be a significant predictor of weight Z scores at 24 months of age ($p = 0.039$), with each centimeter increase in head circumference associated with an increase in the weight Z score (Fig. 2). This significance persisted after adjusting for sex and census-tract median income ($p = 0.036$). Gestational age did not predict weight Z scores in this cohort of term infants. Factors related to hypoxic injury including pH, base deficit, Apgar scores and MRI NICHD grades were not significant predictors of weight outcomes at 24 months. Duration of intubation in the NICU was not related to weight at 24 months. Importantly, markers of systemic injury including peak creatinine and alanine transaminase levels did not correlate with weight outcomes. Additionally, neither the type of feeding during admission nor mode of feeding at discharge predicted weight outcomes at 24 months of age. These results are summarized in Table 3.

Predictors of height at 24 months

Birth head circumference was a significant predictor of height Z scores at 24 months after adjusting for sex and census-tract median income ($p = 0.043$), with increase in birth head circumference predicting higher height Z scores. MRI NICHD grades reflecting greater anatomic involvement were significantly associated with lower height Z scores ($p = 0.017$), which remained statistically significant after adjusting for birth length Z score as well as sex and median income ($p = 0.043$) (Fig. 3). pH (obtained from cord blood or during the first hour of life) was also a significant predictor of height outcomes ($p = 0.017$), which persisted after adjusting for birth length Z score, sex, and median income ($p = 0.015$). Specifically, a greater degree of acidosis was associated with lower height Z scores at 24 months. Apgar scores and base deficit did not appear to be significant predictors of height. Additionally, markers of systemic injury, mode of feeding in the NICU and type of feeding at discharge did not significantly predict height, nor did the duration of intubation in the neonatal period. These results are summarized in Table 4.

DISCUSSION/CONCLUSION

Feeding and growth are factors closely monitored in the neonate after the acute phases of HIE and treatment with TH and are considered when determining when to discharge from the NICU. Even after discharge from the NICU, feeding and growth are closely monitored as a marker of overall health, and factors that are important for neurodevelopment. This study aimed to identify factors during the neonatal course following HIE treated with TH that relate to later growth outcomes. Specifically, we examined early anthropometric measurements, markers of HIE, and biomarkers of systemic injury and the associations with later anthropometric outcomes at age 24 months.

Neonatal growth characteristics, specifically birth anthropometric measurements including head circumference, weight and length, did not generally predict later growth at age 24 months. This is not completely unexpected given that birth weight and height only have mild correlations with later growth in the general population [16]. In contrast, we observed that birth head circumference was associated with weight and height at age 24 months in our study.

Previously, suboptimal head growth in the first year of life was found to be associated with the pattern of brain lesions on neonatal brain MRI that included severe white matter, basal ganglia and thalamic involvement [16, 17]. Consistent with this existing body of literature [16, 17], we observed that worse MRI NICHD grade predicted smaller head circumference at age 24 months. This is likely related to a combination of reduced brain volumes secondary to early neurologic injury and subsequent atypical neurodevelopment, leading to a smaller head circumference by age 24 months. Of note, approximately 10% of our sample with moderate to severe HIE treated with TH met criteria of microcephaly by age 24 months, while Mercuri and colleagues observed that 50% of children who had HIE at birth and did not undergo TH, developed microcephaly by age 12 months. Therefore, TH mitigates the overall risk for severe neurologic injury resulting in microcephaly, as has been reported previously [18]. Building on these findings, we observed that longer duration of intubation was also associated with significantly smaller head circumference by age 24 months. Interestingly, our analyses revealed that our predictors of head circumference at age 24 months, MRI NICHD scores and days of intubation are moderately correlated (0.48). Therefore, it is possible that more severe neurologic injury leads to worse pulmonary function (i.e., central causes of respiratory problems) and/or worse pulmonary injury (i.e., persistent pulmonary hypertension). Given the evidence that fetal hypoxemia associated with severe HIE exacerbates pulmonary vasoconstriction [19], we speculate that increased length of intubation reflects more extensive cerebral injury and subsequent poor head growth; however, additional work is needed to delineate the mechanism involved in this association.

Our study did not reveal associations between markers of systemic injury, including renal and hepatic injury, and growth outcomes following HIE treated with hypothermia. Biomarkers including acidic pH and higher MRI NICHD grades predicted smaller height, in line with the themes described in the literature [4, 20].

Strengths

This study is one of the very few in the literature which describes comprehensive anthropometric outcomes at 24 months of age in a population who has undergone TH, in addition to reviewing the impact of neonatal characteristics on multiple outcomes. This study is amongst the first to describe the association of three a priori domains, including systemic injury, with anthropometric outcomes.

Limitations

One limitation of this study is that the prospective study cohort was a convenience sample of neonates who were able to follow-up within a 2-year period, which can introduce selection bias and may affect our findings. Another limitation is the non-availability of data regarding parental anthropometric measurements, which was not recorded in the electronic medical record. This represents an important area for exploration in future research. Additionally, the peak creatinine values in this study reflect the highest values during the neonate’s NICU stay, including the first 24 h. Thus, peak creatinine may have been impacted by maternal levels and not provided the most precise measure of systemic injury following HIE. Future directions may involve exploring the duration of this peak after the second day of life and its association with growth outcomes.

Conclusion

This study found that like in general populations, birth anthropometrics did not correlate well with growth at 2 years of age. The exception was head circumference, where a smaller head circumference was associated with lighter weight and shorter height. In this HIE cohort, both, more severe MRI NICHD grades and longer duration of intubation predicted lower head circumference at 24 months of age. More work is needed to determine if longer duration of intubation is related to severity of illness associated with worse brain injury or as a marker of systemic injury as other markers of systemic injury evaluated were not associated with growth at 2 years in this study. More acidic pH and worse MRI NICHD scores, reflecting increased severity of HIE, were associated with lower height at 24 months of age. This information can aid clinicians in counseling parents regarding later growth outcomes in infants with HIE who have undergone TH. This data is amongst the first of its kind and adds important evidence to the limited literature on long-term growth outcomes in this population.

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DATA AVAILABILITY

The dataset of which this paper is based is a small pilot sample and is not retained or publicly archived.

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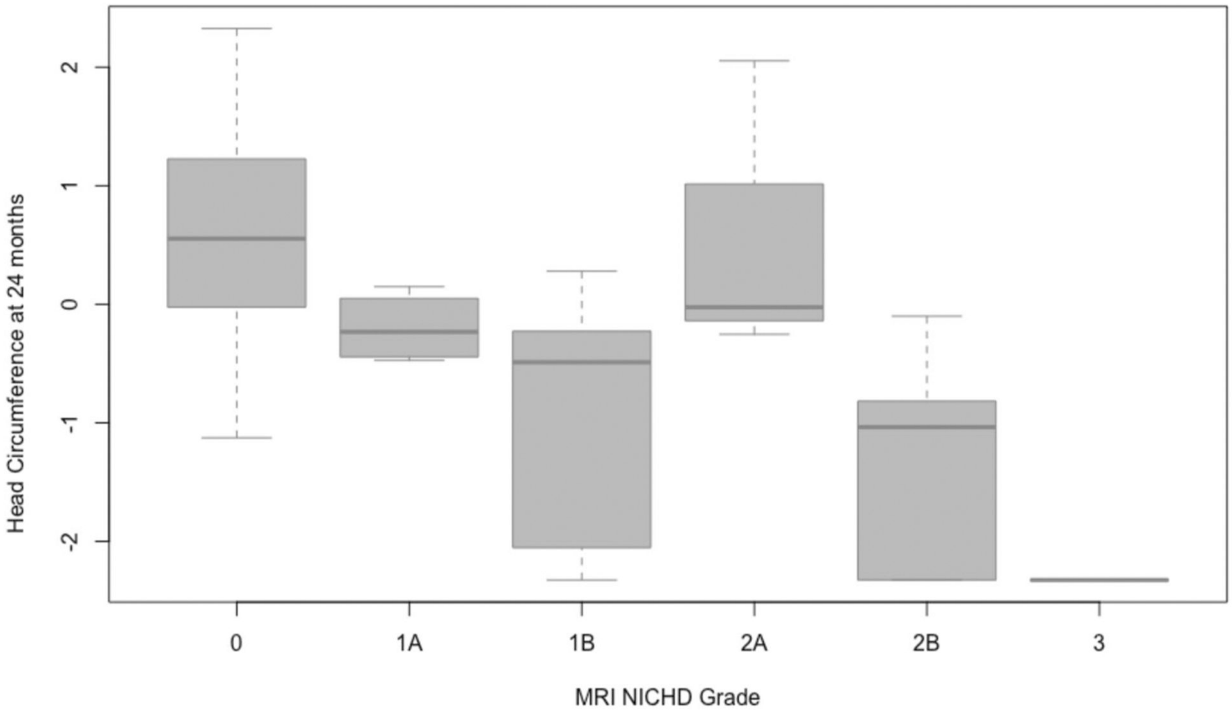

Fig. 1. MRI NICHD grade is significantly associated with head circumference at 24 months.
Figure 1 includes box and whisker plots showing the association between MRI NICHD grade obtained at 10–16 days of life following therapeutic hypothermia (TH) and head circumference at 24 months. MRI NICHD grade was significantly associated with head circumference outcomes ($p < 0.001$), with increasing severity of MRI predicting lower head circumference Z scores, which persisted after adjusting for sex and census-tract median income.

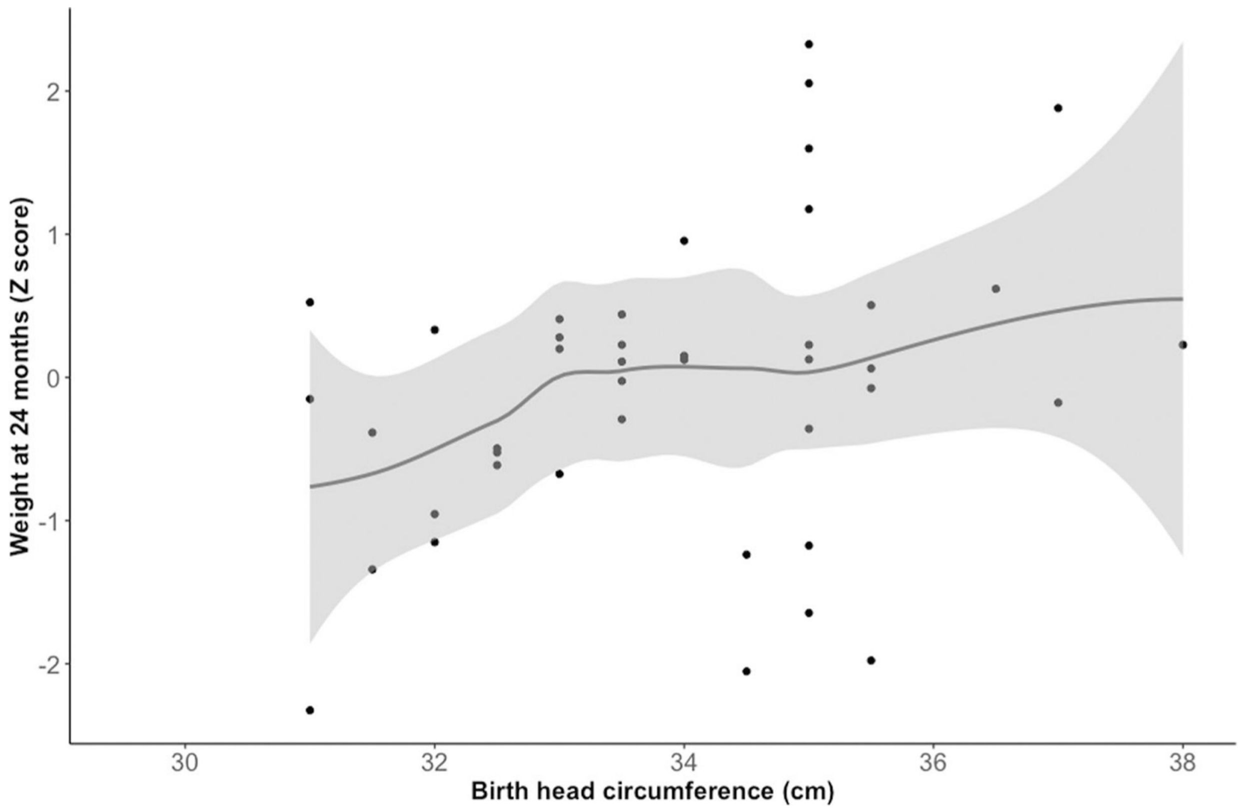

Fig. 2. Birth head circumference in neonates with HIE significantly predicts weight at 24 months.

Figure 2 includes a scatterplot showing the relationship between birth head circumference and weight Z scores at 24 months of age. Birth head circumference was found to significantly predict weight Z scores at 24 months ($p = 0.039$), which persisted after adjusting for sex and census-tract median income. Each centimeter increase in head circumference associated with an increase in the weight Z score.

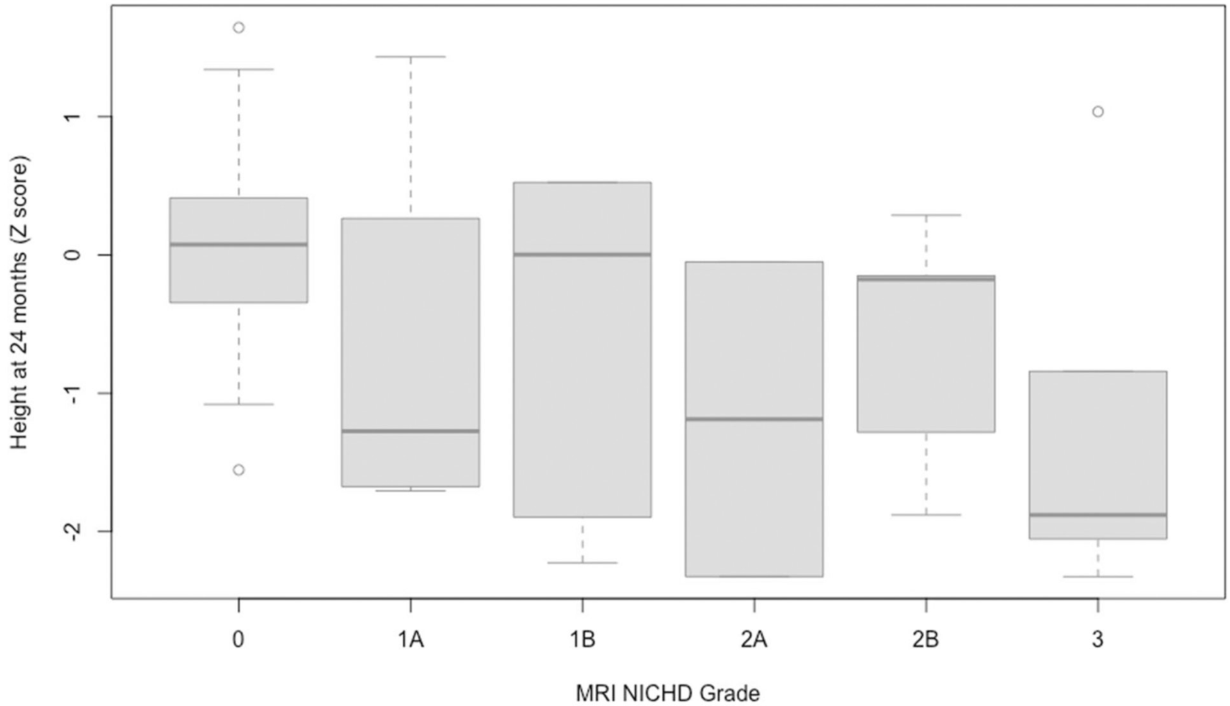

Fig. 3. MRI NICHD grade significantly predicts height at 24 months.

Figure 3 includes box and whicker plots showing the association between MRI NICHD grades and height Z scores at 24 months of age. MRI NICHD grades reflecting greater anatomic involvement were significantly associated with lower height Z scores ($p = 0.017$), which remained statistically significant after adjusting for birth length Z score as well as sex and median income ($p = 0.043$).

Table 1.

Participant characteristics.

Characteristics	Total	Mean	SD	*N* (%)
Base Deficit	57	−16.2	6.6	
pH	64	6.9	0.2	
Apgar score ≤ 5 (1 min)	66			63 (95%)
Apgar score ≤ 5 (5 min)	66			49 (74%)
Apgar score ≤ 5 (10 min)	59			31 (53%)
Peak ALT	66	254.7	788.0	
Peak creatinine	66	1.0	0.5	
Gestational age (weeks)	66	38.9	1.7	
Birth weight (g)	66	3273.8	554.2	
Birth head circumference (cm)	66	34.0	1.8	
Birth length (cm)	66	50.0	3.4	
Duration of intubation (days)	66	6.0	9.6	
Mode of nutrition	58			
Breastmilk (1)				29 (50%)
Formula (2)				10 (17%)
Combined (3)				19 (33%)
Census tract median income (thousands)	66	68.2	30.3	
Feeding	58			
By mouth (1)				46 (79%)
NG or NJ Tube (2)				6 (10%)
G-Tube (3)				3 (5%)
Combined (4)				3 (5%)
MRI	58			
0				26 (45%)
1A				4 (7%)
1B				12 (21%)
2A				3 (5%)
2B				7 (12%)
3				6 (10%)
Sex	66			
Males				37 (56%)
Females				29 (44%)
Growth outcomes at 24 months				
G-Tube	39			4 (10%)
Head circumference (Z score)	40	−0.17	1.28	
Weight (Z score)	42	−0.07	1.04	
Height (Z score)	41	−0.37	1.12	

Table 2.

Factors associated with head circumference at 24 months.

		Unadjusted			Adjusted for sex, median income and baseline head circumference Z score		
Factor	**Total**	**Beta**	**95% CI**	***P***	**Beta**	**95% CI**	**p**
Formula	40	−0.46	(−1.67, 0.74)	0.453	−0.41	(−1.61, 0.79)	0.511
Combined	40	0.12	(−0.76, 1.00)	0.790	0.43	(−0.46, 1.33)	0.349
Duration of intubation	40	−0.05	(−0.08, −0.01)	**0.022**	−0.04	(−0.08, 0.00)	**0.038**
Birth head circumference (cm)	40	0.12	(−0.10, 0.33)	0.305	0.11	(−0.15, 0.37)	0.400
Birth length (cm)	40	−0.04	(−0.15, 0.07)	0.477	−0.06	(−0.19, 0.07)	0.365
MRI NICHD Grade	38	−0.48	(−0.66, −0.30)	**<0.001**	−0.47	(−0.67, −0.28)	**<0.001**
Mode of feeding at discharge	40	−0.22	(−0.69, 0.25)	0.365	−0.26	(−0.73, 0.21)	0.291
Birth weight (g)	40	0.00	(0.00, 0.00)	0.874	0.00	(0.00, 0.00)	0.577
Gestational age	40	−0.06	(−0.36, 0.23)	0.677	−0.14	(−0.45, 0.17)	0.381
Peak creatinine	40	0.08	(−0.57, 0.73)	0.806	0.06	(−0.60, 0.72)	0.854
Peak ALT	40	0.00	(0.00, 0.00)	0.618	0.00	(0.00, 0.00)	0.300
Apgar score (1 min)	40	0.21	(−0.02, 0.43)	0.080	0.23	(−0.01, 0.46)	0.066
Apgar score (5 min)	40	0.12	(−0.06, 0.29)	0.216	0.18	(−0.01, 0.36)	0.077
Apgar score (10 min)	36	0.02	(−0.21, 0.24)	0.894	0.08	(−0.17, 0.32)	0.552
pH	40	−0.64	(−3.38, 2.10)	0.650	−0.58	(−3.38, 2.22)	0.686
Base deficit	35	0.00	(−0.06, 0.06)	0.977	0.00	(−0.06, 0.06)	0.968

Table 3.

Factors associated with weight at 24 months.

Factor	Total	Unadjusted			Adjusted for sex, median income and baseline weight Z score		
		Beta	95% CI	*P*	Beta	95% CI	*P*
Formula	42	−0.60	(−1.50, 0.31)	0.203	−0.38	(−1.33, 0.57)	0.437
Combined	42	−0.16	(−0.86, 0.54)	0.654	−0.09	(−0.82, 0.63)	0.802
Duration of intubation	42	−0.02	(−0.05, 0.01)	0.316	−0.02	(−0.05, 0.01)	0.311
Birth head circumference (cm)	42	0.19	(0.02, 0.37)	**0.039**	0.23	(0.02, 0.44)	**0.036**
Birth length (cm)	42	0.06	(−0.04, 0.15)	0.244	0.06	(−0.05, 0.17)	0.298
MRI NICHD Grade	40	−0.11	(−0.28, 0.06)	0.200	−0.11	(−0.28, 0.06)	0.214
Mode of feeding at discharge	42	−0.01	(−0.42, 0.41)	0.980	0.02	(−0.39, 0.44)	0.909
Birth weight (g)	42	0.00	(0.00, 0.00)	0.056	0.00	(0.00, 0.00)	0.064
Gestational age	42	0.04	(−0.19, 0.26)	0.744	−0.12	(−0.39, 0.15)	0.380
Peak creatinine	42	0.06	(−0.47, 0.58)	0.837	0.10	(−0.43, 0.64)	0.702
Peak ALT	42	0.00	(0.00, 0.00)	0.898	0.00	(0.00, 0.00)	0.859
Apgar score (1 min)	42	0.03	(−0.15, 0.21)	0.756	0.04	(−0.14, 0.23)	0.653
Apgar score (5 min)	42	0.02	(−0.13, 0.18)	0.772	0.04	(−0.12, 0.20)	0.652
Apgar score (10 min)	38	−0.07	(−0.25, 0.12)	0.477	−0.07	(−0.26, 0.12)	0.472
pH	42	0.34	(−1.79, 2.48)	0.756	0.32	(−1.85, 2.49)	0.772
Base deficit	37	0.00	(−0.05, 0.05)	0.936	0.01	(−0.04, 0.07)	0.670

Table 4.

Factors associated with height at 24 months.

Factor	Total	Unadjusted			Adjusted for sex, median income and baseline length Z score		
		Beta	**95% CI**	***P***	**Beta**	**95% CI**	***P***
Formula	41	−0.86	(−1.79, 0.08)	0.080	−0.87	(−1.86, 0.13)	0.096
Combined	41	−0.56	(−1.30, 0.18)	0.145	−0.48	(−1.28, 0.33)	0.253
Duration of Intubation	41	−0.03	(−0.06, 0.01)	0.105	−0.03	(−0.06, 0.00)	0.099
Birth head circumference (cm)	41	0.13	(−0.06, 0.32)	0.184	0.23	(0.01, 0.44)	**0.043**
Birth length (cm)	41	0.01	(−0.09, 0.11)	0.871	0.04	(−0.07, 0.15)	0.449
MRI NICHD grade	39	−0.22	(−0.40, −0.05)	**0.017**	−0.19	(−0.37, −0.01)	**0.043**
Mode of feeding at discharge	41	−0.11	(−0.50, 0.29)	0.598	−0.10	(−0.50, 0.29)	0.618
Birth weight (g)	41	0.00	(0.00, 0.00)	0.466	0.00	(0.00, 0.00)	0.259
Gestational age	41	0.06	(−0.18, 0.30)	0.620	−0.01	(−0.29, 0.27)	0.971
Peak creatinine	41	0.15	(−0.42, 0.71)	0.610	0.05	(−0.54, 0.63)	0.879
Peak ALT	41	0.00	(0.00, 0.00)	0.826	0.00	(0.00, 0.00)	0.703
Apgar score (1 min)	41	0.07	(−0.12, 0.26)	0.476	0.11	(−0.08, 0.31)	0.271
Apgar score (5 min)	41	0.00	(−0.16, 0.16)	0.997	0.05	(−0.11, 0.22)	0.548
Apgar score (10 min)	37	−0.12	(−0.31, 0.07)	0.237	−0.09	(−0.28, 0.11)	0.398
pH	41	2.62	(0.56, 4.69)	**0.017**	2.74	(0.63, 4.85)	**0.015**
Base deficit	37	0.04	(−0.02, 0.09)	0.185	0.03	(−0.02, 0.09)	0.234