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Association between postnatal growth and neurodevelopmental impairment by sex at 2 years of corrected age in a multi-national cohort of very preterm children

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Abstract

Background/Aims: Extra-uterine growth restriction (EUGR) is common among very preterm (VPT) infants and has been associated with impaired neurodevelopment. Some research suggests that adverse effects of EUGR may be more severe in boys. We investigated EUGR and neurodevelopment at 2 years of corrected age (CA) by sex in a VPT birth cohort.

Methods: Data come from a population-based cohort of children born <32 weeks' gestation from 11 European countries and followed up at 2 years CA. Postnatal growth during the neonatal hospitalization was measured with: (1) birthweight and discharge-weight Z-score differences using Fenton charts (2) weight-gain velocity using Patel's model. Published cut-offs were used to define EUGR as none, moderate or severe. Neurodevelopmental impairment was assessed using a parent-report questionnaire, with standardized questions/instruments on motor function, vision, hearing and non-verbal cognition. We estimated risk ratios (RR) adjusting for maternal and neonatal characteristics overall and by sex.

Results: Among 4197 infants, the prevalence of moderate to severe impairment at 2 years CA was 17.7%. Severe EUGR was associated with neurodevelopmental impairment in the overall sample and the interaction with sex was significant. For boys, adjusted RR were 1.57 (95% Confidence Intervals (CI):1.18-2.09) for Fenton's delta Z-score and 1.50 (95%CI: 1.12-2.01) for Patel's weight-gain velocity, while for girls they were 0.97 (0.76-1.22) and 1.12 (0.90-1.40) respectively.

Conclusion: EUGR was associated with poor neurodevelopment at 2 years among VPT boys but not girls. Understanding why boys are more susceptible to the effects of poor growth is needed to develop appropriate healthcare strategies.

Key words: Extrauterine growth restriction, Neurodevelopmental impairment, Very preterm infants, Suboptimal growth

Introduction

Despite the progress made in neonatal care over the past decades, very preterm (VPT) infants, born before 32 weeks of gestational age (GA), face higher risks of neurodevelopmental impairment than children born at term.[1,2] As poor early postnatal growth, referred to as extrauterine growth restriction (EUGR), is highly prevalent in this population,[3] monitoring growth is critical for the infant's wellbeing and requires robust standards for growth assessment in the neonatal intensive care unit (NICU). A growing body of evidence relates EUGR, as measured by weight gain velocity from birth to discharge, to neurodevelopmental impairment.[4-7] Its perceived importance is illustrated by the selection of adequate weight-gain velocity by a DELPHI expert panel to be one component of a composite NICU quality score.[8]

However, there are remaining questions because previous studies were based on small single-center samples and growth velocity was not always measured in the same way or in the same populations, leading to different effects on neurodevelopment.[4-7] There is a debate about which growth standard to use: average weight gain based on Patel's exponential model[9] or birthweight and discharge-weight Z-score differences (Fenton delta Z-score) using Fenton's postnatal growth charts[10]. Another question concerns sex-specific differences. A large population-based French cohort study found that boys were more vulnerable than girls to the effects of poor growth on neurodevelopment,[11] but this has not been verified in other countries.

Our aim in this study was to investigate whether children born VPT with extrauterine growth restriction as measured by weight gain velocity between birth and discharge from their neonatal hospitalization had higher risks of neurodevelopmental impairment at 2 years of corrected age (CA) than children without EUGR, whether results were

related to the choice of weight gain velocity indicator, and if there was an interaction with sex.

Methods

Data source and population

This study uses data from the EPICE (Effective Perinatal Intensive Care in Europe) population-based cohort of births occurring between 22+0 and 31+6 weeks of gestation in 2011/2012 from 19 regions in 11 countries.[12] Perinatal and neonatal data until discharge home were abstracted from medical records using a common, predefined protocol. Data on the child's health, development and the family's social characteristics were collected using a parental questionnaire at 2 years of corrected age (CA).[13]

Country teams obtained local ethical approvals and informed consent for the follow-up study; the European database was approved by French agencies governing use of health data in medical research (CCTIRSN°13.020 and CNILN°DR-2013–194).

The study population was children surviving to two years' CA and included in the follow-up. In accordance with our previous work,[14] we excluded from the eligible population at discharge from hospital: children who were not discharged home (i.e. discharged into long-term care, N=219), those with postmenstrual age (PMA) ≥ 50 weeks (N=99) and children with missing data on discharge weight (N=121) or PMA (N=15), with severe congenital anomalies (N=61) and with outliers for Patel's weight gain velocity, defined as ± 2 SD (N=18). The 50 week limit was selected because Fenton's postnatal growth charts used in this study do not go beyond this PMA. From 6761 children

surviving to two years CA, 6259 fulfilled eligibility criteria; among them, 4197 were followed up at 2 years of CA (flow chart in Supplemental Figure 1).

Measures of postnatal extrauterine growth restriction

We used two EUGR indicators based on changes in weight between birth and discharge from the neonatal hospitalisation which are most commonly used in the scientific literature.[15-18] The first indicator was birthweight and discharge-weight Z-score differences using Fenton's postnatal growth charts (Fenton delta Z-score).[10] The second indicator uses an exponential model of growth velocity to measure the average gain in grams per kilogram (kg) of weight per day based on birthweight, discharge weight and number of days of hospitalization (Patel's weight-gain velocity).[9,19] For each indicator, infants were classified as having no, moderate or severe growth restriction based on cut-offs used in the literature and previously in the EPICE cohort.[5,11,14,18,20] For Fenton's delta Z-score, moderate and severe growth restrictions were defined as a Z-score decrease of more than 1 and 2 standard deviations SD, respectively. For Patel's these were defined as weight-gain velocity between the first quartile and the median (moderate) and less than the first quartile (severe). Finally, to measure overlap between the indicators among neonates with severe EUGR, we computed a variable with the following groups: no severe EUGR by either indicator, severe EUGR by Fenton delta Z-score only, severe EUGR by Patel's velocity only, severe EUGR by both indicators.

Neurodevelopmental assessment

At 2 years of CA (mean (SD) of 24.4 (2.5) months), the child's neurodevelopment was assessed with a standardised parental questionnaire.[21] The neurodevelopmental

impairment classification, previously published for the cohort[21] was based on five forced choice questions to ascertain gross motor function, hearing and vision impairment and standardised instruments for measuring non-verbal cognition (NVC). Severe gross motor impairment was considered if the child was unable to walk without assistance or aids or sit or hold their head up without support. Severe hearing impairment was defined if the child was deaf or had functional hearing loss requiring correction with aids but still had difficulty hearing. Severe visual impairment was defined if the child was blind or able to see light only.[21] If the child had any of the above impairments, they were classified as having severe neurosensory impairment (NSI).

NVC impairment was assessed using the Parent Report of Children's Abilities-Revised (PARCA-R)[21] in 10 of the countries and the third edition of the Ages and Stages Questionnaire (ASQ) in one country (France). We used the NVC score of the PARCA-R because the language component was not validated in all countries. Score items below 22, corresponding to scores below the 2.5th percentile[21] were classified as moderate to severe NVC impairment. The ASQ has been validated in France and assesses several components of the child's development, including problem solving. Moderate to severe NVC impairment was defined when the problem solving score was more than 2 SD below the mean. A composite primary outcome moderate to severe neurodevelopmental impairments (NDI) was computed if the child had severe NSI and/or moderate to severe NVC at 2 years CA.

Co-variables selected for the study included maternal and newborn characteristics hypothesized to affect growth and neurodevelopmental outcome: maternal age, maternal education, parity, multiple birth, mother's country of birth (foreign-born,

native-born), GA in completed weeks, small for GA (SGA),[22] sex, any severe neonatal morbidity (intraventricular hemorrhage grade III or IV, cystic periventricular leukomalacia, retinopathy of prematurity stages III–V or severe necrotizing enterocolitis needing surgery),[23] bronchopulmonary dysplasia (BPD, defined by respiratory assistance or oxygen at 36 weeks PMA), feeding at discharge (human milk only, formula only and mixed feeding) and country of birth.

Missing data were under 2.1% for most covariables, except for 5.6% for mother's origin. Missing observations ranged from 3.2% for NSI, 5.2% for the NVC and 7.2% for overall NDI.

Analysis strategy

We first described maternal and neonatal characteristics, growth indicators and neurodevelopmental outcomes and compared characteristics between girls and boys using chi-square tests for categorical variables and Student’s t-tests for independent samples for continuous variables. We also described the associations between maternal and neonatal characteristics and both growth indicators. We then estimated relative risks (RR) of NDI for the postnatal growth measures using multilevel generalized linear regression models with a Poisson distribution and robust standard error.[24] We used a multilevel model to take into consideration correlations within countries and multiples. We tested for interactions with sex and used interaction terms to calculate RR for boys and girls separately.

To account for potential bias due to loss to follow-up, we applied inverse probability weighing methods using a weight constructed for the 2-year follow up data after multiple imputation to account for missing covariates.[25] In the cohort, loss to follow-up

was associated with several maternal characteristics, including younger maternal age and being foreign-born, but not with neonatal risk factors, although children who were breastfed were more likely to be followed-up.[13] Inverse probability weights are used to balance the fact that children in the sample have different probabilities of being included because of loss to follow-up. [26] It gives higher weights to children who have characteristics associated with the probability of not-being followed up. All main results are based on weighted data with unweighted results in supplemental tables.

Three sensitivity analyses were conducted by removing (1) France because non-verbal cognition was assessed with a different instrument; (2) children with neonatal morbidities to assess the effect of EUGR on neurodevelopment in a healthier sub-population 3) SGA children as they may have different postnatal growth patterns.

All analyses were performed using STATA 15.0 (StataCorp., College Station, TX, USA).

Results

Of the 4197 children included in the study, 25.8% had mothers aged 35 years of age or older and 22% had foreign-born mothers (Table 1). At birth, 14.5% of neonates had a GA less than 27 weeks and 22.4% were born at 27 and 28 weeks; 20.2% of children were SGA. In the neonatal period, 13.2% had BPD and 10.2% had another severe neonatal morbidity; and nearly 60% received human milk at discharge home from the neonatal unit.

Overall, about 60% had moderate to severe EUGR as indicated by Fenton delta Z-score versus 51% by Patel's weight-gain velocity indicator. The distribution of severe EUGR differed, with higher prevalence for Patel weight-gain velocity compared to

Fenton delta Z-score versus (26.3% versus 14.6% respectively). The prevalence of moderate to severe NDI in the sample was 17.7%.

Differences were observed between boys and girls: girls were more often SGA, but had a lower prevalence of BPD than boys. Boys had similar postnatal EUGR as girls according to both indicators but a higher prevalence of moderate to severe NDI and NVC at 2 years.

Table 2 depicts maternal and neonatal characteristics associated with each EUGR indicator. Marked differences were observed in the strength of the associations of some risk factors with the two EUGR measures. For instance, neonates with BPD at 36 weeks had a higher prevalence of severe EUGR defined by Fenton delta Z-score, but a lower prevalence for Patel's weight-gain velocity indicator. Moreover, children identified as severely EUGR by Fenton delta Z-score were born at earlier GA, had lower birthweights and discharge weights and were discharged later than those identified as severely EUGR by Patel's weight-gain velocity. Infants born SGA were less likely to have EUGR for both indicators.

Table 3 displays the unadjusted and adjusted RR relating the two measures of EUGR to NDI for the overall sample and by the sex of the child. The unadjusted results were different between the two indicators, but adjustment on maternal and infant characteristics led to more similar results. Severely EUGR children defined by both Fenton delta Z-score and Patel's weight-gain velocity indicator had an increased risk for overall NDI (RR=1.30, 95%CI:1.02-1.65 and RR=1.33, 95%CI:1.05-1.69, respectively). Interactions with sex were significant, however, (p-values <0.01 for Fenton delta Z-score and 0.06 for Patel's weight-gain velocity). The RR for overall NDI

with severe EUGR was 1.57 (1.18 - 2.09) and 1.50 (1.12 - 2.01) for boys using the Fenton delta Z-score and Patel's weight-gain velocity indicator, respectively, while RR were 0.97 (0.76 - 1.22) and 1.12 (0.90 - 1.40) for girls. Similar results were obtained for NSI and NVC (supplemental table 3) with higher RR for NSI than NVC.

Table 4 depicts the unadjusted and adjusted RR for NDI related to the two measures for severely EUGR neonates. The prevalence of severely EUGR children by both indicators was 7.4% overall with 7.8% versus 7.0% for boys and girls respectively. After adjustment, children who were severely EUGR by both indicators had the highest RR for NDI: 1.46 (95%CI 1.16 -1.83) overall and 1.75 (95%CI: 1.31-2.33) for boys, while no excess risk was observed for girls. Boys classified with severe EUGR using Fenton's delta Z-score only also had elevated risk (1.30, 95% CI: 1.01 - 1.69), whereas no excess risk was seen for boys classified with severe EUGR by Patel's velocity measure only (1.17, 95%CI: 0.84 - 1.63).

In sensitivity analyses of the main models, the differences between weighted and unweighted models were minimal (supplemental table 1). Analyses performed by removing children from France, with neonatal morbidities and with SGA yielded similar results (supplemental table 2).

Discussion (1177/1200 words)

In this study we found an association between poor postnatal growth velocity during the neonatal hospitalisation and moderate to severe NDI at 2 years of CA in a cohort of VPT infants from 11 European countries. However, this association was only observed among boys. Similar associations were observed for boys classified as having severe EUGR by both Fenton's delta Z-score and Patel's weight-gain velocity and were most pronounced for those severely EUGR by both measures

Strengths and limitations

This study provides novel data on the association between postnatal growth and neurodevelopment from a large, population-based cohort of infants born VPT in Europe with a follow-up at 2 years' CA. Strengths of this work include the use of common inclusion criteria and standardized pretested protocols.[21] Limitations are related to the definition of growth velocity which was based on only two time points, birth and discharge. This restricts further exploration of growth patterns and may be affected by discharge policies, which differ in European countries.[27] In previous work on the prevalence of EUGR in this cohort, however, we found that adjusting for timing of discharge did not change rankings of countries.[14] We also lacked data on nutritional intake during the hospitalization, important for further understanding the mechanisms for postnatal growth and accounting for potential risk factors. Neurodevelopment was assessed by parental questionnaire at 2 years' CA and, despite good predictive value with the clinical gold standard,[28] other studies using clinical assessments as well as investigating outcomes at later ages are needed to confirm these findings. In particular, given the different developmental trajectories between boys and girls, the question is whether an association between and EUGR and neurodevelopmental outcome will persist beyond early childhood. A final point is the loss to follow-up of one-third of the cohort at 2 years' CA, although we used inverse probability weighting to address bias.

Comparison with previous studies

Our results corroborate other studies that found an association between postnatal growth velocity and neurodevelopment around 2 years' CA.[6,7,11,15] In a US study of 495 very low birth weight (VLBW) neonates, slow weight-gain velocity in the NICU was

related to poor total NDI and Mental Developmental Index (MDI) scores at 18 to 22 months of age.[6] In an Australian sample of 613 VPT infants, a positive association was found between weight-gain from week one until term and MDI and Psychomotor Developmental Index (PDI) at 18 months.[7] Similarly, in a Spanish study on VLBW infants, each Fenton delta Z-score increment from birth to 36 weeks' GA predicted MDI but not PDI at 2 years' CA. One Australian study, however, conducted on 210 VPT infants at a later time point (8 years) reported no relationship between Fenton delta Z-scores and NDI.[29] These studies did not investigate interactions by sex. However, similar to our results, a French study conducted on 2047 VPT children <33 weeks' GA found that severely growth restricted boys (Fenton delta Z-score below 2 SD), but not girls, were at greater risk of non-optimal neurodevelopment (measured by the ASQ and Brunet Lézine tests) at 2 years of age (adjusted OR of 3.2 (1.5 – 6.8) for boys and 1.8 (0.7 – 4.2) for girls).[11]

Interpretation

Most studies, including ours, on VPT postnatal growth and neurodevelopment are observational and therefore causal mechanisms remain unclear. For instance, better nutrition increases growth velocity, but it was not possible to identify whether growth velocity in itself or nutritional benefits reduce neurodevelopmental impairment. This question requires continued investigation as too rapid growth, a consequence of excessive nutritional intake in the first weeks of life, may increase metabolic diseases in later life.[30,31] Neonatal morbidities interfere with growth and are another potential explanation for poor neurodevelopment. However, they may potentially result from poor growth, and therefore may be mediators of this relationship. Nonetheless, even if poor growth serves solely as a marker of risk, this knowledge is important for identifying

children requiring closer surveillance or early intervention, for instance, post-discharge clinics focusing on growth and nutrition.[32]

Nutritional protocols which increase growth velocity and reduce morbidities for VPT neonates include early initiation of enteral feeding (<48 hours of life),[33-35] rapidly stepping-up enteral feeding volumes,[33,35-37] provision of sufficient energy and protein intakes,[35] improvements in parenteral nutrient supply with lipids and amino acids,[33,35,38] management of fresh mother's milk or milk bank availability and fortification of breastmilk with protein and other nutrients.[30,35,39] Recent research has revealed that nutritional protocols may have different impacts for boys and girls and this may be a key to explaining the sex-differential observed in our study. Lucas et al. showed that intake of unenriched formula as compared to breast milk had a negative effect on the intelligent coefficient at 8 years only among boys.[40] In a New Zealand sample of 536 VPT neonates, higher fat and enteral feed intakes during the first week of life was associated with survival without impairment among girls, but not among boys.[41] A randomized trial showed that adding docosahexaenoic acid, an omega fatty acid, to formula enhanced neurological outcomes only in girls.[42] An intervention increasing nutrients earlier during hospitalization had a positive impact on growth and MDI at 2 years for girls, whereas a positive impact was noted with higher PDI for boys.[43]

The observed sex-differential may also be explained by increased male vulnerability to neonatal morbidities, such as worse respiratory outcomes and higher risks for brain injury than girls.[41,44] As these morbidities affect growth,[45] EUGR among boys may reflect worse health status overall. Boys also have worse neurodevelopmental outcomes generally and a final reason may be that males are more vulnerable to the

adverse effects of poor growth on neurological outcomes than girls with pathogenesis mechanisms still unclear.[44]

Choice of the weight gain velocity indicator

We used two different measures of EUGR as a consensus does not exist on which indicator best captures risks associated with poor postnatal growth and both indicators are currently used in studies of growth velocity. Following adjustments for risk factors, results were fairly similar for both velocity indicators. Our analysis of the overlap between the groups found that risks were highest when boys were classified as severely EUGR by both measures and also moderately elevated when they were severely EUGR by Fenton. Fenton's delta Z-score has been considered by some researchers to be preferable because it adjusts for GA and sex,[17,46] whereas Patel's weight-gain velocity is calculated in the same manner for all neonates.[8] We do not know of any studies that have investigated the effect of combining information from both indicators. However, our findings suggest that using both velocity assessments may allow for better identification of children at risk of later neurodevelopmental problems and should be investigated in future studies.

Conclusion

In our study, we found an association between severe postnatal growth restriction among VPT infants, measured by their weight gain velocity during hospitalization, and the risk of neurodevelopmental impairment at 2 years' CA only among boys. This finding underscores the importance of understanding factors such as sex-specific differences in growth and nutrition to promote healthy growth during the neonatal hospitalization for long-term neurodevelopment.

ABBREVIATIONS:

EUGR: extra-uterine growth restriction

IVH: intraventricular hemorrhage

PVL: periventricular leukomalacia

ROP: retinopathy of prematurity

NEC: necrotizing enterocolitis

BPD: bronchopulmonary dysplasia

SGA: small for gestational age

PMA: postmenstrual age

NSI: neurosensory impairment

NVC: non-verbal cognition

NDI: neurodevelopmental impairment

CA: corrected age

GA: gestational age

VPT: very preterm

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Authorship contribution

JZ, RER, PHJ and MN conceptualized the study and produced a first draft. RER, JZ, PHJ, MN, RFM, HB, PVR, PP, MC, RC, MZ and ESD contributed to the research design and acquisition or management of data. All authors also participated in interpreting the data, revising the manuscript critically for important intellectual content and read and approved the final version of the manuscript.

Conflicts of interest

The authors have no conflicts of interest to disclose.

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Table 1: Maternal, neonatal, growth and neurodevelopmental characteristics at 2 years of CA of the overall sample and by sex

Sample characteristics		Total N=4197		Boys N=2219		Girls N=1978		P-value
Maternal								
Maternal age (years)								0.27
<25	N/%	512	14.9	293	15.7	219	13.9	
25-34	N/%	2459	59.3	1300	59.1	1159	59.5	
35+	N/%	1217	25.8	621	25.1	596	26.6	
Maternal education								0.18
Low	N/%	811	20.0	415	19.5	396	20.6	
Intermediate	N/%	1704	42.1	879	41.3	825	43.0	
High	N/%	1536	37.9	836	39.3	700	36.4	
Mother's origin								0.41
Foreign-born	N/%	752	21.9	380	21.3	372	22.6	
Native-born	N/%	3209	78.1	1714	78.7	1495	77.4	
Parity								0.29
Nulliparous	N/%	2521	56.8	1335	57.7	1186	55.8	
Multiparous	N/%	1632	43.2	862	42.3	770	44.2	
Multiple birth								0.37
Singletons	N/%	2813	68.5	1,506	69.2	1,307	67.8	
Twins or more	N/%	1384	31.5	713	30.8	671	32.2	
Neonatal								
Gestational age (wks)	Mean SD	28.9	(2.0)	28.9	(1.9)	28.8	2.0	0.11
by sub-group:								0.024
23-24	N/%	130	3.1	70	3.1	60	3.1	
25-26	N/%	492	11.4	227	9.7	265	13.6	
27-28	N/%	951	22.4	518	23.3	433	21.4	
29-30	N/%	1516	36.5	823	37.1	693	35.8	
31	N/%	1108	26.6	581	26.8	527	26.4	
Birthweight (g)	Mean SD	1259	(367)	1300	(365)	1212	(365)	<0.01
SGA								0.03
<3 centile	N/%	860	20.2	436	19.1	424	21.5	
3-10 centile	N/%	497	11.9	245	11.0	252	12.9	
>10 centile	N/%	2840	67.9	1538	69.8	1302	65.7	
Any severe morbidity *								0.92
No	N/%	3722	89.8	1962	89.8	1760	89.7	
Yes	N/%	400	10.2	216	10.2	184	10.3	
BPD at 36 wks								0.03
No	N/%	3610	86.8	1879	85.5	1731	88.2	
Yes	N/%	503	13.2	299	14.5	204	11.8	
Feeding at discharge								0.84
Human milk only	N/%	1239	27.8	667	28.2	572	27.3	
Mixed feeding	N/%	1363	31.1	711	30.8	652	31.4	
Formula only	N/%	1517	41.2	800	41.0	717	41.3	
Discharge PMA (wks)	Mean SD	37.9	(2.6)	37.9	(2.7)	37.9	(2.6)	0.71

Postnatal growth								
Discharge weight (g)	Mean SD	2506	(506)	2576	(525)	2426	(472)	<0.01
Fenton Delta Z Score								
Not EUGR	N/%	1693	40.3	917	41.6	776	38.78	0.12
Moderate EUGR	N/%	1903	45.1	998	44.8	905	45.5	
Severe EUGR	N/%	601	14.6	304	13.6	297	15.72	
Patel's weight-gain Velocity								0.19
Not EUGR	N/%	2098	49.2	1074	47.9	1024	50.8	
Moderate EUGR	N/%	1050	24.5	572	25.5	478	23.3	
Severe EUGR	N/%	1049	26.3	573	26.7	476	25.9	
Neurodevelopment								
Moderate to severe neurodevelopment impairment (NDI)								
No	N/%	3239	82.3	1647	79.5	1592	85.5	<0.01
Yes	N/%	655	17.7	404	20.5	251	14.5	
Severe neurosensory impairment (NSI)								
No	N/%	3868	94.7	2031	94.0	1837	95.5	0.08
Yes	N/%	196	5.3	119	6.0	77	4.46	
Moderate to severe non-verbal cognition (NVC)								
No	N/%	3402	84.7	1735	82.1	1667	87.6	<0.001
Yes	N/%	578	15.3	361	17.9	217	12.4	

* defined as a composite of IVH grade III or IV, cystic PVL, ROP stages III–V or severe necrotizing enterocolitis needing surgery;
Note: severe NSI defined as severe gross motor impairment or severe hearing impairment or severe visual impairment; moderate to severe NVC defined as scores below the 2.5th percentile in the Parent Report of Children's Abilities-Revised or scores below 2 SD from the mean in the Ages and Stages Questionnaire; NDI defined as one or combined severe NSI and/or moderate to severe NVC;
BPD: bronchopulmonary dysplasia; SGA: small for gestational age; PMA: postmenstrual age; EUGR: extra-uterine growth restriction

Table 2. Maternal and neonatal characteristics associated with postnatal extrauterine growth restriction

Characteristics		Fenton delta Z Score				Patel's weight-gain velocity			
		None	Moderate	Severe	P Value	None	Moderate	Severe	P value
Maternal									
Maternal age (years)									
<25	%	43.5	43.8	12.7	0.19	49.9	26.2	23.9	0.53
25-34	%	39.0	45.3	15.7		48.6	24.5	26.9	
35+	%	40.9	45.9	13.3		50.4	22.9	26.7	
Maternal education	%				<0.01				<0.01
Low	%	47.1	39.8	13.1		55.1	24.7	20.2	
Intermediate	%	39.7	44.9	15.4		48.3	23.8	27.9	
High	%	36.7	49.0	14.3		46.4	25.7	28.0	
Mother origin									
Foreign-born	%	43.7	41.4	14.9	0.07	51.9	24.0	24.1	0.25
Native-born		38.8	46.6	14.6		48.3	24.7	27.1	
Parity									
Nulliparous	%	41.4	44.4	14.3	0.35	50.9	24.8	24.3	<0.01
Multiparous	%	38.8	46.2	15.0		47.1	23.9	29.0	
Multiple birth									
Singletons	%	38.4	45.7	15.9	<0.01	49.7	23.0	27.3	<0.01
Twins or more	%	44.4	43.9	11.8		48.2	27.7	24.2	
Neonatal									
Gestational age (wks)	Mean SD	29.4 (1.8)	29.0 (1.9)	27.3 (2.1)	<0.01	28.5 (2.1)	28.7 (2.0)	29.8 (1.6)	<0.01
By sub-group :					<0.01				<0.01
23-24	%	22.8	29.1	48.1		63.1	24.7	12.2	
25-26	%	23.2	40.5	36.3		64.6	26.1	9.4	
27-28	%	31.8	47.2	21.0		58.3	28.7	13.0	
29-30	%	44.3	47.3	8.4		48.0	24.6	27.4	
31	%	51.2	44.3	4.5		35.0	20.0	45.0	
Birthweight (g)	Mean SD	1281 (342)	1297 (379)	1080 (348)	<0.01	1095 (303)	1274 (328)	1551 (324)	<0.01
SGA									
<3 centile	%	51.8	37.9	10.3	<0.01	81.4	13.5	5.0	<0.01
3-10 centile	%	50.1	39.1	10.9		58.4	26.5	15.0	
>10 centile	%	35.1	48.4	16.5		38.0	27.3	34.6	
Any severe morbidity									
No	%	42.2	45.9	11.9	<0.01	49.8	23.8	26.3	0.04
Yes	%	21.0	39.4	39.6		44.1	30.1	25.7	
BPD at 36 wks									
No	%	41.6	46.2	12.2	<0.01	47.8	24.1	28.1	<0.01
Yes	%	32.5	38.8	28.7		60.2	25.7	14.1	
Feeding at discharge									
Human milk only	%	32.0	52.6	15.5	<0.01	41.7	24.4	34.0	<0.01

Mixed feeding	%	47.3	40.2	12.5		57.4	24.8	17.9	
Formula only	%	38.4	45.4	16.2		46.0	24.0	30.0	
Discharge PMA (wks)	Mean	37.5	37.6	39.7	<0.01	38.0	38.2	37.2	<0.01
	SD	(2.3)	(2.5)	(3.2)		(2.3)	(2.9)	(2.9)	
Discharge weight (g)	Mean	2640	2420	2399	<0.01	2583	2548	2322	<0.01
	SD	(532)	(456)	(501)		(486)	(548)	(457)	

SGA: small for gestational age; BPD: broncho-pulmonary dysplasia; PMA: postmenstrual age

Table 3: Unadjusted and adjusted risk ratios between postnatal growth restriction and neurodevelopmental impairment (NDI) at 2 years of the overall sample and by sex using multilevel model with interaction term

	Fenton's delta Z Score				Patel's weight-gain velocity			
EUGR	N	NDI N (%)	unadj RR RR (95%CI)	adj RR^ RR (95%CI)	N	NDI N (%)	unadj RR RR (95%CI)	adj RR^ RR (95%CI)
Overall								
None	1569	237 (15.6)	Reference	Reference	1949	319 (16.9)	Reference	Reference
Moderate	1769	275 (16.5)	1.04 (0.83 - 1.29)	1.01 (0.83 - 1.24)	966	167 (18.8)	1.06 (0.88 - 1.27)	1.11 (0.95 - 1.29)
Severe	556	143 (27.4)	1.77 (1.33 - 2.34)	1.30 (1.02 - 1.65)	979	169 (17.7)	1.05 (0.84 - 1.32)	1.33 (1.07 - 1.69)
Boys								
None	839	140 (17.6)	Reference	Reference	990	176 (18.6)	Reference	Reference
Moderate	928	164 (18.0)	1.04 (0.73 - 1.48)	1.06 (0.78 - 1.43)	524	114 (23.0)	1.21 (0.92 - 1.59)	1.26 (0.97 - 1.63)
Severe	284	100 (37.7)	2.23 (1.55 - 3.22)	1.57 (1.18 - 2.09)	537	114 (20.5)	1.18 (0.90 - 1.54)	1.50 (1.12 - 2.01)
Girls								
None	730	97 (13.2)	Reference	Reference	959	143 (15.1)	Reference	Reference
Moderate	841	111 (14.8)	1.04 (0.88 - 1.23)	0.95 (0.71 - 1.29)	442	53 (13.6)	0.83 (0.67 - 1.03)	0.91 (0.72 - 1.16)
Severe	272	43 (16.9)	1.23 (1.00 - 1.50)	0.97 (0.76 - 1.22)	442	55 (14.5)	0.85 (0.63 - 1.14)	1.12 (0.90 - 1.40)

^ Co-variables included in the adjusted models: mother's age, maternal education, foreign born mothers, gestational age, child's sex, multiples, any severe morbidity (defined as a composite of intraventricular hemorrhage grade III or IV, cystic periventricular leukomalacia, retinopathy of prematurity stages III–V or severe necrotizing enterocolitis needing surgery), bronchopulmonary dysplasia (BPD), parity, small for gestational age (SGA) and feeding at discharge

Note: Interaction terms p-values were: <0.01 (Sex X Fenton's delta Z score (Overall)) and 0.06 (Sex X Patel's weight-gain velocity (Overall))

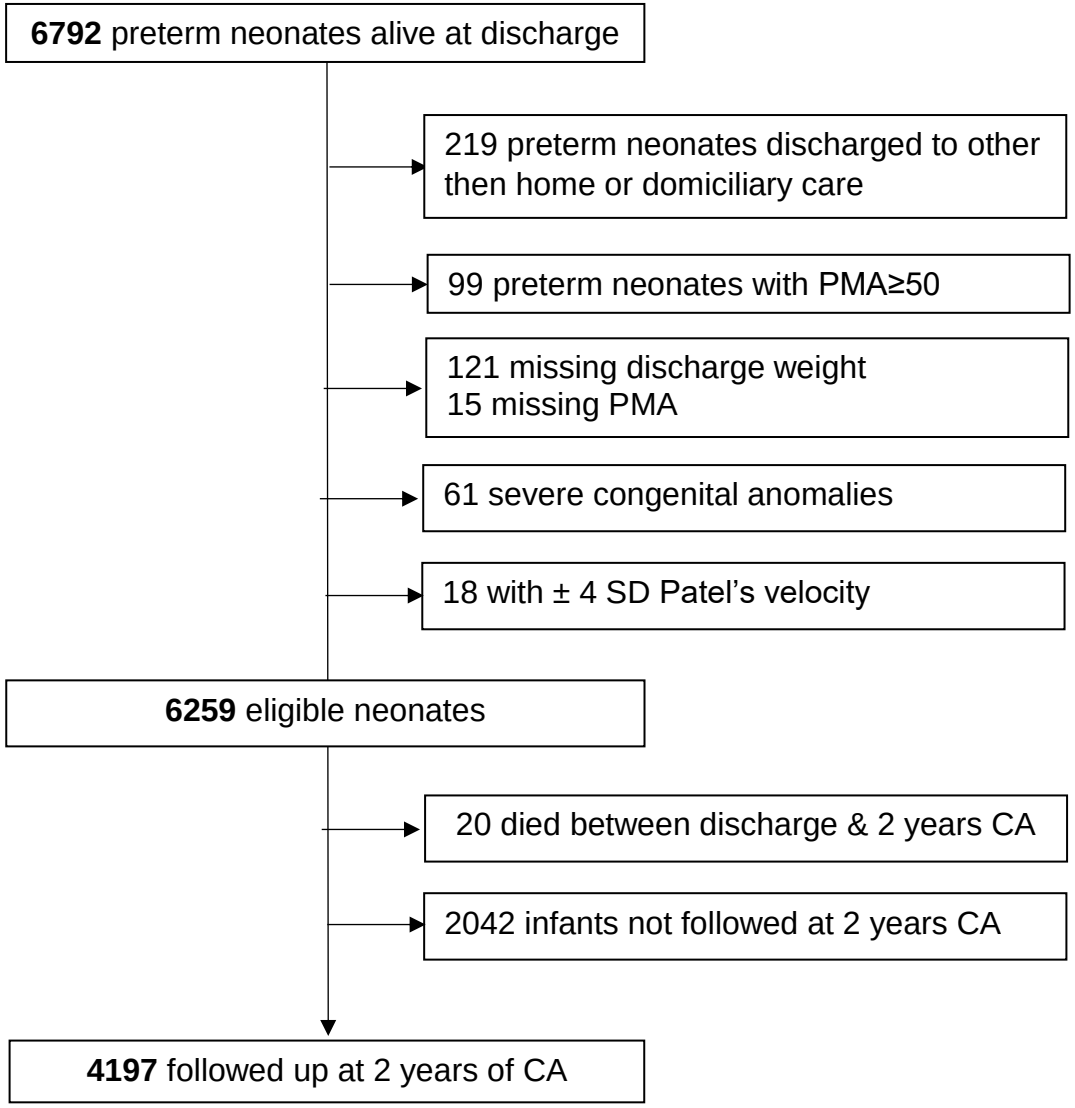
Table 4: Unadjusted and adjusted risk ratios between severe postnatal growth restriction, defined by both indicators, and neurodevelopmental impairment (NDI) at 2 years of the overall sample and by sex using multilevel model with interaction term

Severe EUGR	N	Prevalence %	NDI n (%)	unadj RR RR (95%CI)	adj RR^ RR (95%CI)
Overall					
Not severe	2649	68.0	418 (62.4)	Reference	Reference
Fenton only	266	6.8	68 (10.6)	1.71 (1.32 - 2.22)	1.09 (0.82 – 1.44)
Patel only	689	17.7	94 (15.2)	0.87 (0.65 - 1.16)	1.22 (0.94 - 1.58)
Both severe	290	7.4	75 (11.8)	1.65 (1.36 - 2.00)	1.46 (1.16 – 1.83)
Boys					
Not severe	1391	67.8	247 (61.2)	Reference	Reference
Fenton only	123	6.0	43 (10.6)	2.12 (1.63 - 2.78)	1.30 (1.01 - 1.69)
Patel only	376	18.3	57 (13.6)	0.83 (0.59 - 1.17)	1.17 (0.84 - 1.63)
Both severe	161	7.8	57 (14.7)	2.08 (1.61 - 2.68)	1.75 (1.31 - 2.33)
Girls					
Not severe	1258	68.3	171 (64.4)	Reference	Reference
Fenton only	143	7.8	25 (10.7)	1.36 (1.03 - 1.78)	0.96 (0.69 - 1.34)
Patel only	313	17.0	37 (17.8)	0.91 (0.66 - 1.24)	1.14 (0.88 - 1.49)
Both severe	129	7.0	18 (7.1)	0.99 (0.74 - 1.31)	1.03 (0.78 - 1.36)

^ Co-variables included in the adjusted models: mother's age, maternal education, foreign born mothers, gestational age, child's sex, multiples, any severe morbidity (defined as a composite of intraventricular hemorrhage grade III or IV, cystic periventricular leukomalacia, retinopathy of prematurity stages III–V or severe necrotizing enterocolitis needing surgery), bronchopulmonary dysplasia (BPD), parity, small for gestational age (SGA) and feeding at discharge

Note: Interaction terms p-values were: <0.01 (Sex X Fenton's delta Z score (Overall)) and 0.06 (Sex X Patel's weight-gain velocity (Overall))

Supplemental figure 1. Study population flow chart



Supplemental Table 1: Maternal, neonatal, growth and neurodevelopmental characteristics at 2 years of CA overall and by newborns' sex

		Total N=4197			Boys N=2219			Girls N=1978			P-value
Maternal characteristics											
Maternal age (years)											0.27
<25	N/%/%^	512	12.2	14.9	293	13.2	15.7	219	11.1	13.9	
25-34	N/%/%^	2459	58.7	59.3	1.300	58.7	59.1	1.159	58.7	59.5	
35+	N/%/%^	1217	29.1	25.8	621	28.1	25.1	596	30.2	26.6	
Maternal education											0.18
Low	N/%/%^	811	20.0	20.0	415	19.5	19.5	396	20.6	20.6	
Intermediate	N/%/%^	1704	42.1	42.1	879	41.3	41.3	825	43.0	43.0	
High	N/%/%^	1536	37.9	37.9	836	39.3	39.3	700	36.4	36.4	
Mother origin											0.41
Foreign-born	N/%/%^	752	19.0	21.9	380	18.2	21.3	372	19.9	22.6	
Native-born	N/%/%^	3209	81.0	78.1	1.714	81.9	78.7	1.495	80.1	77.4	
Parity											0.29
Nulliparous	N/%/%^	2521	60.7	56.8	1.335	60.8	57.7	1.186	60.6	55.8	
Multiparous	N/%/%^	1632	39.3	43.2	862	39.2	42.3	770	39.4	44.2	
Multiple pregnancy											0.37

No	N/%/%^	2813	67.0	68.5	1.506	67.9	69.2	1.307	66.1	67.8	
Yes	N/%/%^	1384	33.0	31.5	713	32.1	30.8	671	33.9	32.2	
Neonatal											
Gestational age (wks)	Mean(SD)/ Mean^(SD^)	28.9(2.0)	28.9(2.0)		28.9(2.0)	28.9(1.9)		28.8(2.0)	2.8(2.0)		0.11
Birthweight (g)	Mean(SD)/ Mean^(SD^)	1252.4(366.2)	1258.7(367.4)		1290.0(365.9)	1299.9(364.7)		1210.0(362.0)	1212.0(364.8)		<0.01
SGA (europeristat)											0.03
<3 centile	N/%/%^	860	20.5	20.2	436	19.7	19.1	424	21.4	21.5	
3-10 centile	N/%/%^	497	11.8	11.9	245	11	11.0	252	12.7	12.9	
>10 centile	N/%/%^	2840	68	67.9	1.538	69.3	69.8	1.302	65.8	65.7	
Any severe morbidity*											0.92
No	N/%/%^	3722	90.3	89.8	1.962	90.1	89.8	1.760	90.5	89.7	
Yes	N/%/%^	400	9.7	10.2	216	9.9	10.2	184	9.5	10.3	
BPD at 36 wks											0.03
No	N/%/%^	3610	87.8	86.8	1.879	86.3	85.5	1.731	89.5	88.2	
Yes	N/%/%^	503	12.2	13.2	299	13.7	14.5	204	10.5	11.8	

Feeding at discharge											0.84
Human milk only	N/%/%^	1239	30.1	27.8	667	30.6	28.2	572	29.5	27.3	
Mixed feeding	N/%/%^	1363	33.1	31.1	711	32.6	30.8	652	33.6	31.4	
Formula only	N/%/%^	1517	36.8	41.2	800	36.7	41.0	717	36.9	41.3	
Dicharge PMA(wks)	Mean(SD)/ Mean^(SD^)	37.9(2.6)	37.9(2.6)		37.9(2.7)	37.9(2.7)		37.9(2.5)	37.9(2.6)		0.93
Postnatal growth											
Discharge weight (g)	Mean(SD)/ Mean^(SD^)	2511.1(499.6)	2505.7(506.4)		2579.2(522.4)	2576.2(525.0)		2434.6(461.0)	2425.9(471.6)		<0.01
Fenton Delta Z Score											
Not EUGR	N/%/%^	1693	40.3	40.3	917	41.3	41.6	776	39.2	38.8	0.12
Moderate EUGR	N/%/%^	1903	45.3	45.1	998	45.0	44.8	905	45.8	45.5	
Severe EUGR	N/%/%^	601	14.3	14.6	304	13.7	13.6	297	15.0	15.7	
Patel’s weight-gain velocity											0.19
Not EUGR	N/%/%^	2098	50	49.2	1.074	48.4	47.9	1.024	51.8	50.8	
Moderate EUGR	N/%/%^	1050	25	24.5	572	25.8	25.5	478	24.2	23.3	

Severe EUGR	N/%/%^	1049	25	26.3	573	25.8	26.7	476	24.0	25.92	
Neurodevelopment											
Moderate to severe neurodevelopment impairment (NDI)											
No	N/%/%^	3239	83.2	82.3	1647	80.3	79.5	1592	86.4	85.52	<0.01
Yes	N/%/%^	655	16.8	17.7	404	19.7	20.5	251	13.6	14.48	
Severe neurosensory impairment (NSI)											
No	N/%/%^	3868	95.2	94.7	2031	94.5	94.0	1837	96	95.54	0.08
Yes	N/%/%^	196	4.8	5.3	119	5.5	6.0	77	4	4.46	
Moderate to severe non-verbal cognition (NVC)											
No	N/%/%^	3402	85.5	84.7	1735	82.8	82.1	1667	88.5	87.6	<0.01
Yes	N/%/%^	578	14.5	15.3	361	17.2	17.9	217	11.5	12.4	

* Defined as a composite of IVH grade III or IV, cystic PVL, ROP stages III–V or severe necrotizing enterocolitis needing surgery

^Weighted data

Supplemental table 2. Sensitivity analyses

	Main analysis^			Main analysis			Sensitivity 1			Sensitivity 2			Sensitivity 3		
Postnatal growth	RR	95%CI		RR	95%CI		RR	95%CI		RR	95%CI		RR	95%CI	
Overall															
Fenton Delta Z Score															
Not EUGR															
Moderate EUGR	1.01	0.82	1.23	1.01	0.83	1.24	1.08	0.87	1.34	1.02	0.79	1.31	1.11	0.93	1.32
Severe EUGR	1.28	1.00	1.63	1.30	1.02	1.65	1.37	1.03	1.83	1.32	1.04	1.68	1.34	1.04	1.74
Patel's weight-gain velocity															
Not EUGR															
Moderate EUGR	1.09	0.93	1.28	1.11	0.95	1.29	1.15	0.96	1.38	1.03	0.85	1.24	1.18	1.03	1.35
Severe EUGR	1.25	1.00	1.56	1.33	1.05	1.69	1.42	1.08	1.86	1.21	0.90	1.64	1.23	1.07	1.42
Boys															
Fenton Delta Z Score															
Not EUGR															
Moderate EUGR	1.09	0.81	1.47	1.06	0.78	1.43	1.06	0.73	1.54	1.07	0.76	1.50	1.24	0.96	1.60
Severe EUGR	1.53	1.15	2.04	1.57	1.18	2.09	1.66	1.18	2.34	1.46	0.97	2.20	1.69	1.22	2.33
Patel's weight-gain velocity															
Not EUGR															

Moderate EUGR	1.25	0.97	1.62	1.26	0.97	1.63	1.29	0.93	1.79	1.14	0.86	1.51	1.40	1.08	1.83
Severe EUGR	1.42	1.08	1.87	1.50	1.12	2.01	1.59	1.13	2.25	1.32	0.91	1.91	1.44	1.21	1.70
Girls															
Fenton Delta Z Score															
Not EUGR															
Moderate EUGR	0.89	0.67	1.18	0.95	0.71	1.29	1.11	0.87	1.41	0.96	0.67	1.36	0.94	0.71	1.24
Severe EUGR	0.93	0.76	1.13	0.97	0.76	1.22	1.02	0.79	1.30	1.15	0.88	1.51	0.91	0.73	1.14
Patel's weight-gain velocity															
Not EUGR															
Moderate EUGR	0.88	0.70	1.09	0.91	0.72	1.16	0.98	0.74	1.29	0.88	0.60	1.28	0.90	0.68	1.21
Severe EUGR	1.02	0.83	1.24	1.12	0.90	1.40	1.19	0.94	1.51	1.07	0.77	1.48	0.98	0.79	1.21

* Sensitivity 1: removing France from the countries; Sensitivity 2: Removing neonates with any morbidity and BPD; Sensitivity 3: Removing neonates who are SGA (<10th) at birth

^Unweighted data

Supplemental table 3: Unadjusted and adjusted risk ratios between postnatal growth restriction by components of neurodevelopmental impairment (NDI) composite at 2 years of the overall sample and by sex

	Fenton's delta Z Score				Patel's weight-gain velocity			
		NDI	unadj RR	adj RR		NDI	unadj RR	adj RR
	N	N (%)	RR (95%CI)	RR (95%CI)	N	n (%)	RR (95%CI)	RR (95%CI)
Neurosensory impairment (NSI)								
Overall								
None	1642	55 (3.4)	Reference	Reference	2027	79 (5.2)	Reference	Reference
Moderate	1843	79 (4.8)	1.36 (0.92 - 2.00)	1.22 (0.82-1.81)	1016	58 (6.4)	1.52 (0.88 -2.63)	1.32 (0.76 -2.31)
Severe	579	62 (11.9)	3.74 (2.47 - 5.65)	1.83 (1.07-3.11)	1021	60 (6.2)	1.55 (0.92 -2.63)	1.93 (1.14 -3.29)
Boys								
None	885	31 (3.9)	Reference	Reference	1034	40 (4.6)	Reference	Reference
Moderate	969	47 (5.0)	1.46 (0.89 -2.39)	1.39 (0.86-2.23)	553	36 (6.7)	1.63 (0.84 -3.18)	1.40 (0.72 -2.76)
Severe	296	41 (15.2)	4.99 (3.36 - 7.43)	2.25 (1.36-3.73)	563	43 (7.7)	2.21 (1.31 -3.74)	2.63 (1.43 -4.86)
Girls								
None	757	24 (2.8)	Reference	Reference	993	38 (3.8)	Reference	Reference
Moderate	874	32 (4.5)	1.23 (0.77 -1.95)	1.01 (0.57-1.77)	463	22 (6.1)	1.34 (0.77-2.32)	1.25 (0.68 -2.29)
Severe	283	21 (8.5)	2.52 (1.30 - 4.90)	1.32 (0.64 -2.73)	458	17 (4.4)	0.84 (0.35 -2.04)	1.17 (0.55 -2.48)

Non-verbal cognition impairment (NVC)								
Overall								
None	1603	216 (13.9)	Reference	Reference	1994	282 (14.5)	Reference	Reference
Moderate	1807	237 (13.9)	0.96 (0.75 - 1.24)	0.95 (0.77 -1.17)	989	149 (16.7)	1.06 (0.90 -1.27)	1.16 (0.99-1.36)
Severe	570	125 (23.5)	1.70 (1.25 - 2.32)	1.24 (0.97 -1.60)	997	147 (15.4)	1.03 (0.83 -1.27)	1.38 (1.05 -1.80)
Boys								
None	863	130 (15.8)	Reference	Reference	1017	157 (15.8)	Reference	Reference
Moderate	943	140 (14.9)	0.95 (0.63 - 1.42)	0.96 (0.69 -1.36)	536	106 (21.1)	1.26 (0.99-1.60)	1.37 (1.05 -1.77)
Severe	290	91 (34.0)	2.23 (1.47 - 3.40)	1.56 (1.13 2.14)	543	98 (18.6)	1.15 (0.89 -1.49)	1.55 (1.12-2.15)
Girls								
None	740	86 (11.7)	Reference	Reference	977	125 (12.8)	Reference	Reference
Moderate	864	97 (12.8)	1.01 (0.83 - 1.22)	0.93 (0.66 -1.30)	453	43 (9.5)	0.78 (0.59 -1.02)	0.91 (0.69 -1.20)
Severe	280	34 (13.1)	1.07 (0.90 - 1.28)	0.86 (0.69 -1.06)	454	49 (10.8)	0.85 (0.67 -1.07)	1.15(0.93-1.44)

^ Co-variables included in the adjusted models: mother's age, maternal education, foreign born mothers, gestational age, child's sex, multiples, any severe morbidity (defined as a composite of intraventricular hemorrhage grade III or IV, cystic periventricular leukomalacia, retinopathy of prematurity stages III–V or severe necrotizing enterocolitis needing surgery), bronchopulmonary dysplasia (BPD), parity, small for gestational age (SGA) and feeding at discharge

Note: Interaction terms p-values were: <0.01 (Sex X Fenton's delta Z score (Overall)) and 0.06 (Sex X Patel's weight-gain velocity (Overall))