# Relationships between Early Nutrition, Illness, and Later Outcomes among Infants Born Preterm with Hyperglycemia

Juan David Gonzalez Villamizar, MD[1], Jacob L. Haapala, MPH[2], Johannah M. Scheurer, MD[1], Raghavendra Rao, MD[1], and Sara E. Ramel, MD[1]

**Objective** To evaluate the effects of hyperglycemia on body composition and neurodevelopment, and how early nutrition and illness modify these relationships in infants born preterm.

**Study design** Prospective data were collected from infants born <32 weeks of gestational age (N = 97), including inpatient days of hyperglycemia (blood glucose >150 mg/dL) and nutrient intake. Body composition was measured at discharge and 4 months' postmenstrual age (PMA). Bayley Scales of Infant Development III (BSID-III) were administered at 12 months' PMA. Linear regression analysis was performed, adjusting for birth gestational age. Associations between hyperglycemia, body composition, and BSID-III were analyzed in models accounting for first-week nutrition and early illness severity via Score for Neonatal Acute Physiology-II.

**Results** Mean birth gestational age was 27.8 (SD 2.4) weeks. Hyperglycemia occurred in 48.5% of infants. Hyperglycemia for ≥5 days was negatively associated with fat mass and fat free mass z scores at discharge, and fat free mass z score at 4 months' PMA ($P < .05$ all). Hyperglycemia for ≥5 days was negatively associated with cognition, language, and motor scores on the BSDI at 12 months ($P \leq .01$ all). Associations with body composition and BSID-III were diminished when models included first week nutrition yet remained unchanged when illness severity was included.

**Conclusions** In infants <32 weeks, ≥5 days of hyperglycemia is associated with decreased lean mass at 4 months' PMA and poorer neurodevelopmental outcome at 12 months' PMA. These associations may be mediated by decreased first week nutrition, potentially related to reduced glucose infusion rate for management of hyperglycemia. *(J Pediatr 2020;223:29-33)*.

Neonatal hyperglycemia (blood glucose concentration >150 mg/dL) is common in infants with very low birth weight (VLBW), particularly during the first 2 weeks of postnatal life, with a reported incidence of 30%-80%.[1-3] Hyperglycemia in this population is associated with increased death and morbidities such as sepsis,[4,5] retinopathy of prematurity,[6] necrotizing enterocolitis,[7] and intraventricular hemorrhage (IVH).[8]

Less is known about longer-term complications of neonatal hyperglycemia in infants with VLBW. Decreased body weight, length, and head circumference have been demonstrated in infants with hyperglycemia out to 2 years of postmenstrual age (PMA).[9] Decreased adiposity at 4 months' corrected age has been noted in infants with hyperglycemia for 5 or more days in the first 2 weeks after birth, compared with those without hyperglycemia.[10] Hyperglycemia during the neonatal period also may have significant effects on the developing brain; it is associated with decreased white matter at term age.[11] One study found associations with abnormal neurodevelopment and behavior out to 2 years' corrected age,[4] and another did not find any associations.[9]

The relationship between hyperglycemia and poorer long-term outcomes is complex. Nutrient intake, illness-related factors (ie, clinical instability, inflammatory states), and management strategies for hyperglycemia have all been implicated as mediators of these associations.[9,12,13] Although early illness and instability can influence long-term growth and neurodevelopment,[14] this is not always a modifiable factor. Early provision of adequate protein and caloric intake is associated with improved growth and long-term neurodevelopmental outcomes[15,16]; however, early nutrient intake is often restricted in infants with hyperglycemia through reduction of glucose infusion rates (GIR).

| | |
|---|---|
| BSID-III | Bayley Scales of Infant Development III |
| DOL | Days of life |
| FFM | Fat free mass |
| GIR | Glucose infusion rate |
| IVH | Intraventricular hemorrhage |
| PMA | Postmenstrual age |
| SNAP-II | Score for Neonatal Acute Physiology-II |
| VLBW | Very low birth weight |

From the [1]Division of Neonatology, Department of Pediatrics, School of Medicine; and [2]Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, MN

Supported in part by the University of Minnesota Foundation, Minneapolis, MN; and the March of Dimes Foundation (12-FY13-295). The authors declare no conflicts of interest.

Portions of this study were presented at the Pediatric Academic Societies annual meeting, April 24-May 1, 2019, Baltimore, Maryland.


https://doi.org/10.1016/j.jpeds.2020.04.038

The objective of this study was to determine the influence of early nutritional provision and illness on the relationships between early hyperglycemia and later growth and neurodevelopmental outcomes. We hypothesized that infants born preterm with VLBW and hyperglycemia would have decreased fat free mass z scores at hospital discharge and 4 months' PMA and lower scores on the Bayley Scales of Infant Development III (BSID-III) at 12 months' PMA, and that these relationships would be driven by decreased nutrient intake rather than critical illness in the first week of life.

## Methods

A retrospective post hoc analysis was performed on data collected from a prospective study of infants recruited at the neonatal intensive care unit of the University of Minnesota Masonic Children's Hospital from February 2012 to June 2016. Inclusion criteria included birth weight <1500 g and appropriate for gestational age status, between the 10th and 90th percentile at birth on the Fenton Growth Curve.[17]

Exclusion criteria included infants born with a congenital anomaly that would affect growth, enrollment in an interventional research study, or non–English-speaking parents/guardians (interpreters were not available at follow-up study visits). Infants who lived out of state also were excluded from recruitment due to inability to reliably attend outpatient visits. Written informed consent was obtained from the parents. The study protocol was approved by the University of Minnesota institutional review board.

Blood glucose was measured at least daily during the first week of life and later as clinically indicated. When additional glucose measures were obtained clinically, these values also were collected and used for this analysis. Inpatient hyperglycemia days were recorded, as defined, by 1 or more blood glucose measurements >150 mg/dL (>8.3 mmol/L). Infants were distributed into 3 categories based on the days of hyperglycemia, consisting of 0 days, 1-4 days, and ≥5 days.

The infants were followed daily, while inpatient, by the neonatal nutrition support service. Nutritional data were recorded by the neonatal dieticians, including daily calorie and protein intake. First week intake was defined by the total number of kcal/kg/d and g/kg/d of protein received on days of life (DOL) 2-8. Cumulative weekly energy (kcal/kg/d) and protein (g/kg/d) deficits were calculated based on daily goals of 120 kcal/kg/d and 4 g/kg/d protein. Clinical and nutritional management were jointly agreed on by the neonatologist and the nutrition support service. Illness severity scores on DOL 1-2 were assessed using the Score for Neonatal Acute Physiology-II (SNAP-II).[18,19] The presence or absence of IVH grade 2 or greater was recorded.

Body composition (fat mass, fat free mass, and % fat mass) was measured using air-displacement plethysmography (PEA POD; COSMED, Ltd, Concord, California)[20] at hospital discharge and 4 months' PMA. Infants were eligible for body composition measurement if they were able to remain on room air for approximately 5 minutes. The discharge measurement was defined as each infant's measurement closest to 40 weeks' PMA and between 34 and 42 weeks' PMA.

The BSID-III (Pearson Education, San Antonio, Texas) was administered at 12 months' PMA by a single experienced pediatric neuropsychologist during the neonatal intensive care unit follow-up clinic visit at the University of Minnesota Masonic Children's Hospital.

### Statistical Analyses

Descriptive statistical values were calculated (mean, SD, median, minimum and maximum values). Logistic regression analysis was performed to test for associations between days of hyperglycemia and body composition measurements (fat mass, fat free mass, and % fat mass) at discharge and 4 months' PMA, as well as BSID-III scores at 12 months' PMA. Model 1 was adjusted for gestational age at birth only for associations with body composition, and for gestational age at birth, head circumference z score at discharge, and IVH for associations with neurodevelopment.

To assess the influence of early nutritional provision and illness on the aforementioned associations, first-week protein and calorie deficits were added to model 2 and SNAP-II score on DOL 1-2 to model 3. Analysis was conducted using SAS, version 9.4 (SAS Institute, Cary, North Carolina).

## Results

Subject recruitment is documented in the **Figure** (available at www.jpeds.com). During the recruitment period, a total of 476 infants with VLBW were admitted to the neonatal intensive care unit. Consent was obtained for 120 infants, and 97 had complete data collected. There was loss to follow-up resulting in 78% with body composition at 4 months' PMA and 68% with neurodevelopmental scores at 12 months' PMA.

Subject characteristics are documented in **Table I**. Hyperglycemia occurred in 48.5% of infants; 27% had 1-4 days of hyperglycemia and 21% had 5 or more days of hyperglycemia; 83 subjects (86% of the cohort) had a body composition measurement between 34 and 42 weeks' PMA (discharge measurement; remaining infants were unable to maintain saturations on room air for 5 minutes at this gestational age) and 76 patients (78% of the cohort) had body composition measurements at 4 months' PMA. Sixty-six subjects (68% of the cohort) had BSID-III scores at 12 months' PMA. The subset of patients followed through 12 months' PMA were slightly less mature at birth compared with those lost to follow-up (27.5 weeks vs 28.5 weeks) ($P = .04$) but were similar with regards to sex, birth weight, birth weight z score, and days of inpatient hyperglycemia ($P \geq .2$ for all).

Comparison of characteristics between infants who were hyperglycemic and infants were not hyperglycemic are shown in **Table II** (available at www.jpeds.com). Infants with

**Table I. Patient cohort characteristics**

| Variables | n | % | Mean | SD | Min | Max |
|---|---|---|---|---|---|---|
| Sex | | | | | | |
| Female | 47 | 48.5 | | | | |
| Male | 50 | 51.5 | | | | |
| Gestational age at birth, wk | 97 | | 27.79 | 2.39 | 22.10 | 32.40 |
| IVH, grade 2 or greater | | | | | | |
| No | 79 | 81.4 | | | | |
| Yes | 18 | 18.6 | | | | |
| SNAP-II score, day 1-2 | | | | | | |
| 0 | 18 | 18.6 | | | | |
| 1-13 | 44 | 45.4 | | | | |
| 14-40 | 35 | 36.1 | | | | |
| Glucose level ≥150 mg/dL, d | | | | | | |
| 0 | 50 | 51.5 | | | | |
| 1-4 d | 26 | 26.8 | | | | |
| ≥5 d | 21 | 21.6 | | | | |
| PMA, discharge, wk | 83 | | 37.57 | 2.21 | 34.00 | 41.90 |
| Fat mass z score, discharge | 83 | | 1.73 | 1.18 | −0.49 | 5.00 |
| Fat free mass z score, discharge | 83 | | −1.44 | 1.21 | −5.02 | 1.43 |
| % fat mass z score, discharge | 83 | | 2.24 | 1.11 | −0.13 | 4.66 |
| PMA, wk, 4-mo CA visit | 76 | | 57.66 | 1.72 | 54.00 | 63.00 |
| Fat mass z score, 4-mo PMA | 76 | | −1.08 | 1.25 | −4.56 | 1.96 |
| Fat free mass z score, 4-mo PMA | 76 | | 0.06 | 1.52 | −3.39 | 3.50 |
| % fat mass z score, 4-mo PMA | 76 | | −1.16 | 1.25 | −4.59 | 1.37 |
| Bayley Cognition, 12-mo PMA | 66 | | 100.7 | 14.33 | 60.00 | 135.0 |
| Bayley Language, 12-mo PMA | 65 | | 86.97 | 13.73 | 50.00 | 121.0 |
| Bayley Motor, 12-mo PMA | 66 | | 90.38 | 14.46 | 58.00 | 124.0 |

*PMA*, Postmenstrual age.

hyperglycemia were born earlier, had lower birth weights, and greater numbers of postnatal steroid days than their nonhyperglycemic counterparts. In contrast, there were no significant differences in birth length and head circumference z scores, as well as antenatal steroid exposure between the groups.

Associations between inpatient hyperglycemia days and fat mass z scores, fat free mass z scores, and % fat mass z scores are shown in **Table III**. Hyperglycemia for ≥5 days was negatively associated with both fat mass ($P = .007$) and fat free mass ($P = .003$) z scores at discharge, and only fat free mass ($P = .017$) z score was negatively associated at 4 months' PMA. Similar associations were identified after we controlled for early illness using SNAP-II scores (model 3). However, when first-week nutrient intake (protein and caloric deficits) was added to the model, the associations were significantly diminished for all measurements (all $P > .05$) (model 2). Additional models (data not shown) accounting for average weekly kilocalorie and protein deficit, days on positive pressure, days on steroids, and days on antibiotics did not show substantial change in $P$ values or beta coefficients.

Associations of BSID-III scores in cognition, language, and motor domains at 12 months' PMA with inpatient hyperglycemia days are shown in **Table IV**. Hyperglycemia for ≥5 days was negatively associated with scores on the BSID-III at 12 months in cognition ($P < .02$), language ($P < .02$), and motor ($P < .01$) areas. Addition of severity of illness measured by SNAP-II scores largely did not alter the associations; all remained significant. However, when first-week nutrient intake (protein and caloric) was added, the previously noted association was diminished (all $P > .05$). Additional models, as described previously for body composition analysis, did not show substantial change in $P$ values or beta coefficients.

## Discussion

Early hyperglycemia occurred in nearly one-half of our cohort and at a similar rate to other published reports.[1,2,21] Hyperglycemia (>150 mg/dL) for ≥5 days during hospitalization in infants with VLBW <32 weeks was associated with decreased fat free mass, fat mass, and % fat mass at hospital discharge, and the association with decreased fat free mass persisted at 4 months' PMA. Those infants with hyperglycemia for ≥5 days also had lower neurodevelopmental scores at 12 months' PMA when compared with infants without hyperglycemia. This relationship appears to be driven by decreased nutrient intake during the first week of life. These findings add

**Table III. Association of body composition compartments z scores at discharge and 4 months CGA with inpatient hyperglycemia**

| | | | Model 1* | | Model 2† | | Model 3‡ | |
|---|---|---|---|---|---|---|---|---|
| Measures | n | Hyperglycemia days | β (SE) | P value | β (SE) | P value | ßβ (SE) | P value |
| Fat mass z score, discharge | 83 | 1-4 days vs 0 | −0.14 (0.30) | .642 | −0.09 (0.31) | .750 | −0.22 (0.31) | .479 |
| | | 5+ days vs 0 | −1.41 (0.51) | .007 | −1.14 (0.56) | .048 | −1.52 (0.51) | .004 |
| Fat free mass z score, discharge | 83 | 1-4 days vs 0 | −0.14 (0.32) | .663 | −0.03 (0.30) | .903 | −0.18 (0.31) | .558 |
| | | 5+ days vs 0 | −1.61 (0.53) | .003 | −0.96 (0.56) | .090 | −1.72 (0.52) | .001 |
| % fat mass z score, discharge | 83 | 1-4 days vs 0 | −0.17 (0.29) | .560 | −0.14 (0.29) | .618 | −0.24 (0.29) | .419 |
| | | 5+ days vs 0 | −0.96 (0.48) | .048 | −0.81 (0.53) | .133 | −1.05 (0.49) | .035 |
| Fat mass z score, 4-mo CGA | 76 | 1-4 days vs 0 | −0.14 (0.38) | .710 | −0.08 (0.38) | .834 | −0.07 (0.38) | .848 |
| | | 5+ days vs 0 | −1.09 (0.63) | .089 | −1.07 (0.73) | .144 | −0.97 (0.63) | .130 |
| Fat free mass z score, 4-mo CGA | 76 | 1-4 days vs 0 | −0.38 (0.43) | .379 | −0.20 (0.43) | .643 | −0.39 (0.44) | .377 |
| | | 5+ days vs 0 | −1.77 (0.73) | .017 | −1.06 (0.82) | .203 | −1.79 (0.74) | .019 |
| % fat mass z score, 4-mo CGA | 76 | 1-4 days vs 0 | −0.008 (0.39) | .982 | −0.001 (0.39) | .998 | 0.06 (0.38) | .860 |
| | | 5+ days vs 0 | −0.55 (0.65) | .394 | −0.74 (0.75) | .324 | −0.42 (0.65) | .515 |

*Model 1 adjusted for gestational age at birth.
†Model 2 adjusted for gestational age at birth, average first week kilocalorie deficit, and average first-week protein deficit.
‡Model 3 adjusted for gestational age at birth, day of life 1-2 SNAP-II score (0, 1-13, 14+ days).

**Table IV. Association of Bayley Scores at 12 months' CGA with inpatient hyperglycemia**

| | | | Model 1* | | Model 2† | | Model 3‡ | |
|---|---|---|---|---|---|---|---|---|
| Measures | N | Hyperglycemia days | β (SE) | P value | β (SE) | P value | β(SE) | P value |
| Bayley Cognition, 12-mo CGA | 66 | 1-4 days vs 0 | −3.09 (4.30) | .474 | −2.07 (4.51) | .648 | −3.22 (3.99) | .423 |
| | | 5+ days vs 0 | −15.92 (6.97) | .026 | −11.08 (8.14) | .178 | −17.75 (6.58) | .009 |
| Bayley Language, 12-mo CGA | 65 | 1-4 days vs 0 | −7.89 (4.11) | .059 | −6.19 (4.41) | .166 | −7.81 (4.17) | .066 |
| | | 5+ days vs 0 | −15.68 (6.56) | .020 | −10.73 (7.79) | .174 | −15.83 (6.80) | .023 |
| Bayley Motor, 12-mo CGA | 66 | 1-4 days vs 0 | −2.42 (4.00) | .548 | −3.29 (4.15) | .430 | −2.27 (3.99) | .571 |
| | | 5+ days vs 0 | −16.22 (6.49) | .015 | −16.30 (7.48) | .033 | −16.71 (6.57) | .013 |

*Model 1 adjusted for gestational age at birth, IVH (grade 2+, <2), head circumference z score at discharge.
†Model 2 adjusted for gestational age at birth, IVH (grade 2+, <2), head circumference z score at discharge, average first-week kilocalorie deficit, and average first-week protein deficit.
‡Model 3 adjusted for gestational age at birth, IVH (grade 2+, <2), head circumference z score at discharge, day of life 1-2 SNAP-II score (0, 1-13, 14+ days).

to the limited literature relating days of hyperglycemia with diminished growth and altered body composition measurements in infancy[10] and early childhood.[9]

Our findings indicate that decreased nutrient provision in the first week of life is largely responsible for the relationship between hyperglycemia and poor infancy growth. One common management strategy for hyperglycemia is to decrease the GIR.[22] Previous studies have shown that this may not be an effective strategy, as the relationship between dextrose provision, GIR and hyperglycemia is not well characterized. For example, studies by Beardsall et al and Pertierra-Cortada et al were not able to link episodes of hyperglycemia with carbohydrate intake or dextrose infusions, respectively.[21,23] Given this previous information in combination with our study findings, decreased nutrient provision may actually lead to poorer long-term outcomes of decreased growth and poorer neurodevelopmental outcomes without the benefit of reducing the incidence of hyperglycemia.

The relationship between hyperglycemia and its long-term consequences on neurodevelopment has been studied in a limited fashion in infants born preterm with VLBW. In a study by Van der Lugt et al, a cohort of patients born very preterm was followed out to 2 years' corrected age.[4] They found that infants born preterm who experienced hyperglycemia had a greater incidence of abnormal neurologic and behavioral outcomes, evaluated by way of limited neurologic assessment and parent self-reporting through the Pediatric Symptom Checklist. Similar relationships have been seen in children with type 1 diabetes, who have poorer neurodevelopment compared with their healthy counterparts, including impaired cognitive development, compromised learning, consolidation, and organizational abilities.[24,25] In a cohort of infants <1500 g or <30 weeks, those with hyperglycemia during the first week were less likely to survive without neurodevelopmental impairment (68% vs 84% in normoglycemic) at 2 years of age.[13] However, this association was primarily mediated by gestational age, birth weight z score, and socioeconomic status. Our study demonstrates an association between early persistent hyperglycemia and scores on the BSID-III, a standardized developmental test for infants and children. Compared with infants with no hyperglycemia, those who experienced ≥5 days of hyperglycemia had scores of up to 15 points lower on all 3 subscales even after we adjusted for the presence of IVH and head circumference z scores at discharge. We also found that nutrient intake in the first week largely drove the relationship between early persistent hyperglycemia and later neurodevelopment. This association between first-week nutrient intake and improved neurodevelopment has been shown in other studies as well.[15] Limiting nutrient intake may not eliminate hyperglycemia but could contribute to the poorer outcomes in this population. In addition to decreased nutrient provision, an influence of inflammation on the growth hormone/insulin-like growth hormone axis or insulin deficiency may have played a role in the growth and neurodevelopmental effects,[26,27] but these were not tested in our cohort.

Glycemic control of infants with VLBW remains controversial. Previous studies by Tottman et al and Alsweiler et al have addressed the use of insulin to maintain tight glycemic control in patients with long-term follow-up to 36 months' and 7 years' corrected age.[12,28] Although Tottman et al described no differences in survival without neurodevelopmental impairment in patients with tighter glucose control, they did show poorer linear growth that persisted to 7 years of age. The mechanisms involved in these outcomes are still not clear; however, undernutrition during critical times of illness might be a significant factor to consider in this relationship. The benefits of using insulin preferentially over decreasing nutritional support shortly after birth requires further investigation. Zamir et al demonstrated decreased mortality in patients who received insulin treatment for hyperglycemia.[1]

There is no current gold-standard strategy for management of hyperglycemia among infants with VLBW, and management typically includes a combination of GIR reduction and/or insulin administration.[22] The importance of optimized early nutrition to support long-term outcomes[29,30] may need to be balanced by the risk of hypoglycemia associated with tight glucose control with insulin.[1,28,31,32] Further investigation, including randomized trials, is needed to identify the strategy that will optimize early glucose control and achieve the best growth and neurodevelopmental outcomes.

Important limitations of our study include a relatively small sample size and recruitment from a single institution. The number of glucose measurements recorded on each enrolled patient varied according to clinical discretion, which could underestimate the true hyperglycemic state of each patient. The follow-up rate of 68% at 12 months' corrected age may make the results less representative of the original

sample of patients recruited; however, the groups were largely similar with regards to birth weight, sex, and days of hyperglycemia. Finally, the observational nature of the study limits the ability to determine causality.

In summary, 5 or more days of hyperglycemia was associated with alterations in body composition (fat mass, fat free mass, and % fat mass) at hospital discharge in our cohort of infants with VLBW, with persistent associations between hyperglycemia and fat free mass at 4 months' corrected age. Persistent hyperglycemia also was associated with impaired neurodevelopment at 12 months' corrected age. These relationships appear to be mediated by decreased nutrient intake during the first week of life rather than the severity of illness. Randomized trials of insulin therapy combined with nutritional adjustments are needed to determine the optimal strategy to improve long-term growth and neurodevelopmental outcomes. ■

Submitted for publication Jan 3, 2020; last revision received Mar 12, 2020; accepted Apr 15, 2020.

Reprint requests: Juan David Gonzalez Villamizar, MD, 2450 Riverside Ave, East Building MB630, Minneapolis, MN 55454. E-mail: gonz0241@umn.edu

## References


1. Zamir I, Tornevi A, Abrahamsson T, Ahlsson F, Engström E, Hallberg B, et al. Hyperglycemia in Extremely Preterm Infants—Insulin Treatment, Mortality and Nutrient Intakes. J Pediatr 2018;200:104-10.e1.
2. Mohammad Kazem S, Seyed Abolfazl A, Marjan S, Parinaz A, Ahmad Reza S, Fatemeh E. Hyperglycemia in VLBW infants; incidence, risk factors, and outcome. Arch Iran Med 2014;17:429-34.
3. Beardsall K, Vanhaesebrouck S, Frystyk J, Ogilvy-Stuart AL, Vanhole C, Van Weissenbruch M, et al. Relationship between insulin-like growth factor i levels, early insulin treatment, and clinical outcomes of very low birth weight infants. J Pediatr 2014;164:1038-44.
4. Van der Lugt NM, Smits-Wintjens V, Van Zwieten P, Walther F. Short and long term outcome of neonatal hyperglycemia in very preterm infants: a retrospective follow-up study. BMC Pediatr 2010;10:52.
5. Kao LS, Morris BH, Lally KP, Stewart CD, Huseby V, Kennedy KA. Hyperglycemia and morbidity and mortality in extremely low birth weight infants. J Perinatol 2006;26:730-6.
6. Mohamed S, Murray JC, Dagle JM, Colaizy T. Hyperglycemia as a risk factor for the development of retinopathy of prematurity. BMC Pediatr 2013;13:78.
7. Hall NJ, Peters M, Eaton S, Pierro A. Hyperglycemia is associated with increased morbidity and mortality rates in neonates with necrotizing enterocolitis. J Pediatr Surg 2004;39:898-901.
8. Auerbach A, Eventov-Friedman S, Arad I, Peleg O, Bdolah-Abram T, Bar-Oz B, et al. Long duration of hyperglycemia in the first 96 hours of life is associated with severe intraventricular hemorrhage in preterm infants. J Pediatr 2013;163:388-93.
9. Ramel SE, Long JD, Gray H, Durrwachter-Erno K, Demerath EW, Rao R. Neonatal hyperglycemia and diminished long-term growth in very low birth weight preterm infants. J Perinatol 2013;33:882-6.
10. Scheurer JM, Gray HL, Demerath EW, Rao R, Ramel SE. Diminished growth and lower adiposity in hyperglycemic very low birth weight neonates at 4 months corrected age. J Perinatol 2015;36:145.
11. Alexandrou G, Skiöld B, Karlén J, Tessma MK, Norman M, Ådén U, et al. Early hyperglycemia is a risk factor for death and white matter reduction in preterm infants. Pediatrics 2010;125:e584-91.
12. Tottman AC, Alsweiler JM, Bloomfield FH, Gamble G, Jiang Y, Leung M, et al. Long-term outcomes of hyperglycemic preterm infants randomized to tight glycemic control. J Pediatr 2018;193:68-75.e1.
13. Tottman AC, Alsweiler JM, Bloomfield FH, Pan M, Harding JE. Relationship between measures of neonatal glycemia, neonatal illness, and 2-year outcomes in very preterm infants. J Pediatr 2017;188:115-21.
14. Greenwood S, Abdel-Latif ME, Bajuk B, Lui K. Can the early condition at admission of a high-risk infant aid in the prediction of mortality and poor neurodevelopmental outcome? A population study in Australia. J Paediatr Child Health 2012;48:588-95.
15. Stephens BE, Walden RV, Gargus RA, Tucker R, McKinley L, Mance M, et al. First-week protein and energy intakes are associated with 18-month developmental outcomes in extremely low birth weight infants. Pediatrics 2009;123:1337-43.
16. Ramel SE, Gray HL, Christiansen E, Boys C, Georgieff MK, Demerath EW. Greater early gains in fat-free mass, but not fat mass, are associated with improved neurodevelopment at 1 year corrected age for prematurity in very low birth weight preterm infants. J Pediatr 2016;173:108-15.
17. Fenton TR, Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. BMC Pediatr 2013;13:59.
18. Richardson DK, Corcoran JD, Escobar GJ, Lee SK. SNAP-II and SNAPPE-II: simplified newborn illness severity and mortality risk scores. J Pediatr 2001;138:92-100.
19. Richardson DK, Gray JE, McCormick MC, Workman K, Goldmann DA. Score for Neonatal Acute Physiology: a physiologic severity index for neonatal intensive care. Pediatrics 1993;91:617-23.
20. Ellis KJ, Shypailo RJ, Wong WW, Heird WC, Yao M, Urlando A. Body-composition assessment in infancy: air-displacement plethysmography compared with a reference 4-compartment model. Am J Clin Nutr 2007;85:90-5.
21. Beardsall K, Vanhaesebrouck S, Ogilvy-Stuart AL, Vanhole C, Palmer CR, Ong K, et al. Prevalence and determinants of hyperglycemia in very low birth weight infants: cohort analyses of the NIRTURE study. J Pediatr 2010;157:715-9.e3.
22. Ramel S, Rao R. Hyperglycemia in extremely preterm infants. Neoreviews 2020;21:e89-97.
23. Pertierra-Cortada Á, Ramon-Krauel M, Iriondo-Sanz M, Iglesias-Platas I. Instability of glucose values in very preterm babies at term postmenstrual age. J Pediatr 2014;165:1146-53.e2.
24. Perantie DC, Lim A, Wu J, Weaver P, Warren SL, Sadler M, et al. Effects of prior hypoglycemia and hyperglycemia on cognition in children with type 1 diabetes mellitus. Pediatr Diabetes 2008;9:87-95.
25. Northam EA, Anderson PJ, Werther GA, Warne GL, Andrewes D. Predictors of change in the neuropsychological profiles of children with type 1 diabetes 2 years after disease onset. Diabetes Care 1999;22:1438-44.
26. AboElAsrar MA, Elbarbary NS, Elshennawy DE, Omar AM. Insulin-like growth factor-1 cytokines cross-talk in type 1 diabetes mellitus: relationship to microvascular complications and bone mineral density. Cytokine 2012;59:86-93.
27. Ogilvy-Stuart AL, Beardsall K. Management of hyperglycaemia in the preterm infant. Arch Dis Child Fetal Neonatal Ed 2010;95:126-31.
28. Alsweiler JM, Harding JE, Bloomfield FH. Tight glycemic control with insulin in hyperglycemic preterm babies: a randomized controlled trial. Pediatrics 2012;129:639-47.
29. Lithoxopoulou M, Rallis D, Christou H, Goutsiou E, Varaklioti A, Karagianni P, et al. Early caloric deprivation in preterm infants affects Bayley-III scales performance at 18-24 months of corrected age. Res Dev Disabil 2019;91:103429.
30. Georgieff MK, Ramel SE, Cusick SE. Nutritional influences on brain development. Acta Paediatr 2018;107:1310-21.
31. Chen L, Li T, Fang F, Zhang Y, Faramand A. Tight glycemic control in critically ill pediatric patients: a systematic review and meta-analysis. Crit Care 2018;22:1-11.
32. Lipsky LM, Gee B, Liu A, Nansel TR. Glycemic control and variability in association with body mass index and body composition over 18 months in youth with type 1 diabetes. Diabetes Res Clin Pract 2016;120:97-103.

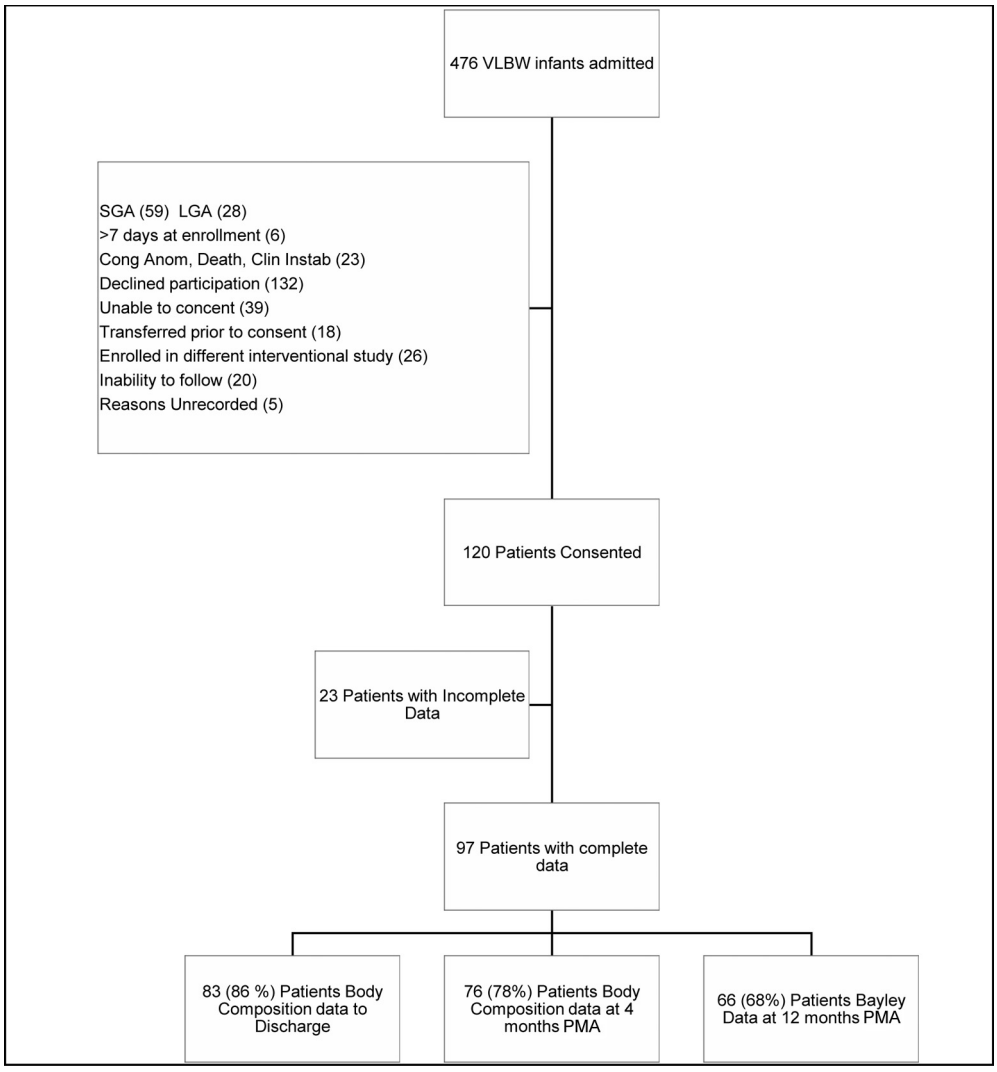


**Figure.** Flowchart with patient recruitment description. *LGA*, Large for gestational age; *PMA*, postmentrual age; *SGA*, small for gestational age.

**Table II. Characteristics of hyperglycemic vs nonhyperglycemic groups**

| | | Hyperglycemia days | | | |
|---|---|---|---|---|---|
| | Overall | 0 days | 1-4 days | 5+ days | |
| Characteristics | n (97) | n (50) | n (26) | n (21) | *P* value |
| Sex | | | | | |
| Female | 47 | 25 | 12 | 10 | .9471 |
| Male | 50 | 25 | 14 | 11 | |
| Gestational age at birth, wk | | | | | |
| Mean ± SD | 27.8 ± 2.4 | 29.3 ± 1.3 | 27.5 ± 1.8 | 24.5 ± 1.6 | <.0001 |
| 95% CI | 27.3-28.3 | 28.9-29.7 | 26.8-28.3 | 23.8-25.3 | |
| [Min, max] | [22, 32] | [26, 32] | [24, 31] | [22, 29] | |
| Birth weight, g | | | | | |
| Mean ± SD | 1059.0 ± 300.4 | 1233.1 ± 180.6 | 1039.1 ± 276.2 | 669.0 ± 148.3 | <.0001 |
| 95% CI | 998.4-1119.5 | 1181.8-1284.4 | 927.5-1150.7 | 601.5-736.5 | |
| [Min, max] | [408, 1730] | [910, 1590] | [470, 1730] | [408, 1010] | |
| Birth weight z score | | | | | |
| Mean ± SD | −0.10 ± 0.70 | −0.10 ± 0.64 | −0.06 ± 0.81 | −0.15 ± 0.71 | .9024 |
| 95% CI | −0.24, 0.04 | −0.28, 0.09 | −0.39, 0.27 | −0.48, 0.17 | |
| [Min, max] | [–2, 1] | [–1, 1] | [–2, 1] | [–1, 1] | |
| Birth length z score | | | | | |
| Mean ± SD | −0.27 ± 0.79 | −0.26 ± 0.79 | −0.13 ± 0.80 | −0.48 ± 0.79 | .3372 |
| 95% CI | −0.43, −0.11 | −0.48, −0.03 | −0.46, 0.19 | −0.84, −0.12 | |
| [Min, max] | [–2, 2] | [-2, 2] | [-2, 1] | [-2, 1] | |
| Birth head circumference z score | | | | | |
| Mean ± SD | −0.24 ± 0.71 | −0.20 ± 0.72 | −0.26 ± 0.73 | −0.31 ± 0.70 | .8411 |
| 95% CI | −0.39, −0.10 | −0.41, −0.00 | −0.56, 0.03 | −0.63, 0.01 | |
| [Min, max] | [–2, 2] | [–2, 2] | [–1, 2] | [–2, 2] | |
| Total postnatal steroid days at 35 wk | | | | | |
| Mean ± SD | 7.5 ± 14.9 | 0.46 ± 1.79 | 5.5 ± 11.3 | 26.7 ± 19.6 | <.0001 |
| 95% CI | 4.5-10.5 | −0.05, 0.97 | 0.9-10.0 | 17.8-35.6 | |
| [Min, max] | [0, 74] | [0, 11] | [0, 50] | [0, 74] | |
| Antenatal steroids | | | | | |
| 1 dose | 14 (15) | 5 (10) | 4 (16) | 5 (25) | .2560 |
| 2 doses | 67 (72) | 34 (71) | 20 (80) | 13 (65) | |
| >2 doses | 12 (13) | 9 (19) | 1 (4) | 2 (10) | |