Head growth during neonatal intensive care unit stay is related to neurodevelopmental outcome in preterm infants born small for gestational age

Hannah Cho
Korea University Anam Hospital
Ee-Kyung Kim (kimek@snu.ac.kr)
https://orcid.org/0000-0002-7063-168X
In Gyu Song
Yonsei University College of Medicine
Ju Sun Heo
Korea University Anam Hospital
Seung Han Shin
Seoul National University College of Medicine
Han-Suk Kim
Seoul National University College of Medicine

Research article

Keywords: Small for gestational age, Preterm infants, Catch-up growth, Neurodevelopment

Posted Date: July 14th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-41321/v1

Version of Record: A version of this preprint was published at Pediatrics & Neonatology on June 1st, 2021. See the published version at https://doi.org/10.1016/j.pedneo.2021.05.023.

Abstract

Background: To investigate postnatal growth patterns and their relationship with neurodevelopment in preterm infants born small for gestational age (SGA).

Methods: This study analyzed 90 infants born SGA with birth weight <1,500 g or gestational age <32 weeks. Length, weight, and head circumference (HC) were recorded at birth, 35 weeks postmenstrual age (PMA), 40 weeks PMA, and at 4, 9, and 18 months corrected age (CA). Neurodevelopmental outcomes were assessed using the Bayley-III scales at 18 months CA.

Results: Z-score of HC in SGA infants increased from birth to 40 weeks PMA. Failure of head growth catch-up to 10^{th} percentile by 4 months CA and all three parameters by 9 months CA and onwards were associated with worse neurodevelopmental outcomes. Z-score changes in head growth between birth and 35 weeks PMA were significantly associated with neurodevelopmental outcome (p=0.006, adjusted odds ratio 6.964, 95% confidence interval: 1.763-27.506).

Conclusions: Head growth during neonatal intensive care unit stay were associated with neurodevelopmental outcomes in preterm SGA infants. Preterm SGA infants are predicted to have optimal neurodevelopment at 18 months CA, if the head growth catch-up is achieved by 4 months CA and length and weight by 9 months CA.

Background

Postnatal growth in length, weight, and head circumference (HC) is associated with later neurodevelopmental outcome in preterm infants [1–8]. However, preterm infants born small for gestational age (SGA) comprised a small proportion of the study population or were occasionally excluded from those studies, which explored the relationship between postnatal growth and development. Considering the heightened risk in development [9, 10], increased neonatal morbidities [11, 12] and possible different growth patterns of SGA preterm infants compared to appropriate for gestational age (AGA) infants, there is a need to separately analyze the relationship between growth and development, according to being SGA or AGA. Head growth from 1 week to term and weight and length growth from term to 4 months corrected age (CA) were associated with better motor development in preterm AGA infants; however, none of them was true for SGA infants (< 10th percentile) [8]. In the study which examined the 5-year intelligence quotient observed that head circumference growth from birth to 6 time points within 2 years of age was associated with a better outcome in preterm AGA infants. However, only optimal HC growth around term age was beneficial for SGA infants (<-2 standard deviation, SD) [2]. Similarly, a previous study demonstrated a correlation of the growth parameters and changes in the interval with neurodevelopment in AGA infants; however, this association was not meaningful in SGA infants (<-2SD) [13]. Studies that focused on the growth patterns and neurodevelopmental outcomes of preterm SGA infants are limited [1, 2, 14–16], and all but one study analyzed the preterm population born before the 1990s. For this reason, while catch-up growth is one of the main goals in following-up the preterm SGA infants, a controversy remains over the required time frame of occurrence in this population. Therefore, we aimed to investigate the postnatal growth patterns and the effect of timing of catch-up growth on the neurodevelopment of preterm SGA infants in a patient population born between 2006 and 2016.

Methods

Study design

We conducted a retrospective study of infants born SGA who were admitted to the neonatal intensive care unit (NICU) of Seoul National University Children's Hospital with birth weight <1,500 g or gestational age <32 weeks between September 2006 and December 2016. Among them, infants who underwent assessment with the *Bayley Scales of Infant and Toddler Development, Third Edition* (Bayley-III) at 18-24 months corrected age (CA) were included. Infants whose growth measurement data were not applicable or who were diagnosed with a congenital anomaly or cerebral palsy were excluded. Data were collected from the infant's hospital records. Trained nurses measured the infants in the NICU and at the follow-up clinic. After birth, weight was measured daily, and the crown–heel length and HC were measured once a week until discharge. The baby laid supine during height measurement, and HC was measured by a soft tapeline. Length, weight, and HC were recorded at birth, at 35 weeks postmenstrual age (PMA) near discharge, 40 weeks PMA at first clinic visit after discharge and at 4, 9, and 18 months CA. Z-scores for length, weight, and HC were calculated using reference data, which included the Fenton Preterm Growth Chart until 40 weeks PMA and World Health Organization measurements at 4, 9, and 18 months CA. Clinical characteristics, including treated patent ductus arteriosus (PDA), bronchopulmonary dysplasia (BPD), periventricular leukomalacia (PVL), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), and retinopathy of prematurity (ROP) operation, were similarly reviewed. To characterize the growth patterns of SGA infants, growth data of 1:1 gestational age-matched AGA infants who were admitted during the same period were collected.

Definitions

SGA was defined as a birth weight <10th percentile for gestational age at birth [17]. Catch-up growth was defined as each parameter attaining ≥10th percentile at that time point [15, 18]. Growth failure was defined as the change in Z-score of each growth parameter <-1 at the period from birth to 40 weeks PMA and <0 at the period from a 40 weeks PMA to 18 months CA [6, 19]. The neurodevelopmental outcome was assessed using the Bayley-III scales at 18-24 months CA [20]. Neurodevelopmental impairment (NDI) was defined as any of the following: cognitive and language score <85 [21] or motor score <85. Treated PDA included medical or surgical treatment. BPD was diagnosed according to the National Institute of Child Health and Human Development (NICHD) definition (moderate to severe BPD) [22]. IVH was classified according to Papile et al. [23]. NEC was diagnosed according to the modified Bell's criteria (≥stage 2) [24]

Statistical Analysis

The analysis was performed with the SPSS statistical package 19.0 (IBM Corp. Armonk, NY, USA). Differences between categorical variables were analyzed using the chi-square test or Fisher's exact test. On the contrary, differences between continuous variables were tested using an independent sample t-test. Multivariate logistic regression analysis was conducted to determine the risk factors for NDI in the study population. Values of $p<0.05$ were considered statistically significant.

Ethics statement

Ethical exemption was granted by the Institutional Review Board of Seoul National University Hospital (Seoul, Korea) because of the retrospective study design. (IRB No. 1906-112-1041).

Results

During the study period, 1591 infants were admitted to the NICU of Seoul National University Children's Hospital with a birth weight <1,500 g or gestational age <32 weeks. There were 252 SGA infants (15.8%); of these, 90 infants with Bayley-III data were reviewed (Figure 1).

The growth patterns of SGA infants were compared with 1:1 matched AGA infants (Figure 2). While the Z-scores of all growth parameters in AGA infants and those of length and weight in SGA infants decreased from birth to 40 weeks PMA, the Z-score of HC in SGA infants increased from birth to 40 weeks PMA (Z-score change, SGA vs. AGA; 0.33 vs. -0.58; $P<0.001$).

The clinical characteristics of SGA infants with or without NDI were compared. Infants with NDI had a smaller weight at birth and higher rates of IVH, ROP, and NEC (Table 1). Therefore, the study population was adjusted for gestational age, birth weight, IVH, ROP, and NEC in further analyses on neurodevelopment.

The relationship between growth failure and NDI was analyzed at each time point. Growth failure of HC from birth to 35 weeks PMA was associated with higher incidence of NDI (p=0.006, adjusted odds ratio 6.964, 95% confidence interval: 1.763-27.506). From 35 weeks to 40 weeks PMA, growth failure in length was associated with higher incidence of NDI (Table 2).

The rates of failed catch-up growth for each parameter by 18 months CA were as follows: length 38.9%, weight 44.4%, and HC 31.1%. Head sparing at birth was not associated with better neurodevelopment. As from 9 months CA, further length and weight catch-up growths rarely occurred until the 18 months CA; however, the HC catch-up was still occurring at a lower rate. Failed catch-up growth of HC by 4 months CA was significantly associated with NDI (p =0.004, adjusted odds ratio 9.600, 95% confidence interval: 2.049-44.974). Failed catch-up growth of any growth parameter by 9 and 18 months CA was associated with NDI (Table 3).

We explored the clinical factors during the NICU stay, which was associated with subsequent head growth. Longer duration of antibiotics usage and longer time to full enteral feeding were significantly associated with failed catch-up growth of HC at CAs of 4, 9, and 18 months (Table 4).

Discussion

Head growth spurt in SGA infants started earlier than in AGA infants. Head growth from birth to 35 weeks PMA was associated with the neurodevelopmental outcomes. Similarly, the catch-up growth of HC at 4 months CA was significantly associated with better neurodevelopmental outcomes. Failed catch-up growth of any of the three growth parameters at 9 and 18 months CA showed worse neurodevelopmental outcomes. Antibiotics usage and feeding tolerance were significantly associated with subsequent head growth.

This study revealed different growth patterns between SGA and AGA infants from birth to 18 months CA(Fig. 2). Compared to AGA infants, the degree of postnatal HC Z score drop was less in SGA infants; additionally, Z-score of HC at 40 weeks PMA reached that at birth in SGA infants while it remained decreased in AGA infants. This suggests that there is an earlier spurt of head growth in SGA infants than in AGA infants, which was consistent with the study findings of Brandt et al. showing a sensitive period for catch-up growth of HC only during the phase of rapid growth in SGA preterm infants [14]. In the analysis of the relationship between growth failure and NDI at each time point, head growth failure from birth to PMA of 35 weeks was associated with more NDI. It can be interpreted that the characteristic early head growth observed in preterm SGA infants (Fig. 2) was related to subsequent neurodevelopment [19]. While head growth between birth and 35 weeks PMA exhibited overall downward growth, the trajectory was of relevance to neurodevelopment.

There have been debates on the significant timing of head growth, which affects neurodevelopment in SGA infants. Belfort et al. explored the associations of growth from 1 week of age to term, term to 4 months, and 4 to 12 months with Bayley Scales of Infant Development (2nd edition) at 18 months. Unlike our results, poor head growth had no effect on NDI at any time point in their SGA subgroup [8]. The SGA definition and the time point of neurodevelopmental assessment in their study were similar to those of our study; however, they used the previous version of Bayley Scales and included 50 SGA infants. Leppänen et al. observed that among seven periods within 2 years of age, only optimal head growth around term age was beneficial for SGA infants, which is similar to our results [2].

Similarly, the relationship between growth and development was analyzed regarding the attainment of the 10th percentile at a particular time point. By 4 months CA, only head growth that did not reach the 10th percentile was associated with worse neurodevelopmental outcomes (Table 3). By 9 months CA and onwards, failed catch-up growths in length, weight, and HC were all associated with poor outcomes. This information can aid the establishment of growth goals and the definition of the population with poor developmental prognosis by clinicians in the course of following up preterm SGA infants. It was difficult to compare the study results with those of previous studies because of variations in the definition of SGA, time points of growth assessment, and outcome. Frisk et al. observed that SGA infants with optimal postnatal head growth until 9 months CA demonstrated better cognitive development at 7–9 years [15]. Nine months CA was the first time point of growth assessment after term age, and the definition of SGA was less than 2SD. Brandt et al. showed that optimal head catch-up growth until 1 year showed benefits to the intelligence scores in SGA infants [14]. They explored longer-term cognitive outcomes; however, only 46 SGA infants were enrolled (< 10th percentile), and growth parameters before 1 year were not examined.

Because failed head growth catch-up was shown as a consistent risk factor for NDI after 4 months CA, the clinical factors during NICU stay, which were related to poor head growth by these time points, were sought. Days of antibiotics usage and days to full enteral feeding were associated with head growth (Table 4). Days of antibiotics usage may reflect the period during which the infants experienced inflammation. Inflammation is considered one of the important risk factors of growth restriction in the perinatal period. The growth rate was observed to be negatively correlated with C-reactive protein, erythrocyte sedimentation rate, and Interleukin (IL)-6. In a mice study, a decrease in insulin-like growth factor-1 (the synthesis of which is stimulated by growth hormones) was observed in transgenic IL-6 overproducing mice [25]. Similarly, inflammation is related to head growth. Elevated concentrations of inflammation-related proteins in early postnatal blood specimen provided information about an increased risk of microcephaly 2 years after [26] and impaired mental and motor development at 2 years of age in extremely preterm infants [27]. Days to full enteral feeding may indicate the general clinical complexities as well as the nutritional status of an infant. The duration (in days) of antibiotics usage and days to full enteral feeding could be potential targets for improving neurodevelopment in preterm SGA infants; however, a causal relationship between them cannot be concluded from this study.

The strengths of this study are as follows: we focused on the growth and development of preterm SGA infants; the growth was analyzed using both an absolute criterion, the attainment of 10th percentile and a relative criterion, Z-score changes. The growth parameters were examined at multiple time points before 1 year CA and information was provided on the contemporary preterm SGA population. On the contrary, the limitations of our study include its retrospective design, which led to the exclusion of many infants because of missing Bayley-III data. However, Bayley scales were recommended for preterm infants with gestational age < 32 weeks or birth weight < 1500 g in our follow-up clinic without any medical or social consideration.

Conclusion

In conclusion, the acceleration of head growth begins earlier in preterm SGA infants than in preterm AGA infants and reaches the birth percentile by 40 weeks PMA. This early brain growth in NICU was associated with neurodevelopmental outcomes. If head growth catch-up is achieved by 4 months CA, optimal neurodevelopment is more likely to be attained at 18 months CA. These data guide the follow-up care and may help improve the neurodevelopment outcomes of preterm SGA infants.

Declarations

Ethics approval and consent to participate

Ethical exemption was granted by the Institutional Review Board of Seoul National University Hospital (Seoul, Korea) because of the retrospective study design. (IRB No. 1906-112-1041).

Consent for publication

Not applicable

Availability of data and materials

The datasets used or analyzed during the current study are available from the corresponding author on reasonable request

Competing interests

The authors have no conflicts of interest to declare.

Funding

This study was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (NRF-2017R1D1A1B04030931)

Author's contributions

HC had primary responsibility for protocol development, patient screening, formal analysis, data interpretation and writing the manuscript. EKK supervised the design and protocol development, performed the final data analyses and contributed to the writing of the manuscript. IGS and JSH participated in the writing and editing. SHS contributed to analysis for the study and participated in the wrighting. HSK contributed to the wrighting and editing. All authors have read read and approved the final manuscript.

Acknowledgements

The authors would like to acknowledge the Division of Neonatology at Seoul National University Children's Hospital for their support.

References

1. Latal-Hajnal B, von Siebenthal K, Kovari H, Bucher HU, Largo RH: **Postnatal growth in VLBW infants: significant association with neurodevelopmental outcome**. *J Pediatr* 2003, **143**(2):163-170.
2. Leppanen M, Lapinleimu H, Lind A, Matomaki J, Lehtonen L, Haataja L, Rautava P, Group PS: **Antenatal and postnatal growth and 5-year cognitive outcome in very preterm infants**. *Pediatrics*

2014, **133**(1):63-70.

3. Neubauer V, Fuchs T, Griesmaier E, Kager K, Pupp-Peglow U, Kiechl-Kohlendorfer U: **Poor postdischarge head growth is related to a 10% lower intelligence quotient in very preterm infants at the chronological age of five years**. *Acta Paediatr* 2016, **105**(5):501-507.
4. Ramel SE, Demerath EW, Gray HL, Younge N, Boys C, Georgieff MK: **The relationship of poor linear growth velocity with neonatal illness and two-year neurodevelopment in preterm infants**. *Neonatology* 2012, **102**(1):19-24.
5. Wright CM, Emond A: **Head growth and neurocognitive outcomes**. *Pediatrics* 2015, **135**(6):e1393-1398.
6. Raghuram K, Yang J, Church PT, Cieslak Z, Synnes A, Mukerji A, Shah PS, Canadian Neonatal N, Canadian Neonatal Follow-Up Network I: **Head Growth Trajectory and Neurodevelopmental Outcomes in Preterm Neonates**. *Pediatrics* 2017, **140**(1).
7. Neubauer V, Griesmaier E, Pehbock-Walser N, Pupp-Peglow U, Kiechl-Kohlendorfer U: **Poor postnatal head growth in very preterm infants is associated with impaired neurodevelopment outcome**. *Acta Paediatr* 2013, **102**(9):883-888.
8. Belfort MB, Rifas-Shiman SL, Sullivan T, Collins CT, McPhee AJ, Ryan P, Kleinman KP, Gillman MW, Gibson RA, Makrides M: **Infant growth before and after term: effects on neurodevelopment in preterm infants**. *Pediatrics* 2011, **128**(4):e899-906.
9. Sung IK, Vohr B, Oh W: **Growth and neurodevelopmental outcome of very low birth weight infants with intrauterine growth retardation: comparison with control subjects matched by birth weight and gestational age**. *J Pediatr* 1993, **123**(4):618-624.
10. Guellec I, Lapillonne A, Renolleau S, Charlaluk ML, Roze JC, Marret S, Vieux R, Monique K, Ancel PY, Group ES: **Neurologic outcomes at school age in very preterm infants born with severe or mild growth restriction**. *Pediatrics* 2011, **127**(4):e883-891.
11. Bernstein IM, Horbar JD, Badger GJ, Ohlsson A, Golan A: **Morbidity and mortality among very-low-birth-weight neonates with intrauterine growth restriction. The Vermont Oxford Network**. *Am J Obstet Gynecol* 2000, **182**(1 Pt 1):198-206.
12. Simchen MJ, Beiner ME, Strauss-Liviathan N, Dulitzky M, Kuint J, Mashiach S, Schiff E: **Neonatal outcome in growth-restricted versus appropriately grown preterm infants**. *Am J Perinatol* 2000, **17**(4):187-192.
13. Song IG, Kim EK, Cho H, Shin SH, Sohn JA, Kim HS: **Differential Effect of Growth on Development between AGA and SGA Preterm Infants**. *Int J Environ Res Public Health* 2020, **17**(9).
14. Brandt I, Sticker EJ, Lentze MJ: **Catch-up growth of head circumference of very low birth weight, small for gestational age preterm infants and mental development to adulthood**. *J Pediatr* 2003, **142**(5):463-468.
15. Frisk V, Amsel R, Whyte HE: **The importance of head growth patterns in predicting the cognitive abilities and literacy skills of small-for-gestational-age children**. *Dev Neuropsychol* 2002, **22**(3):565-593.

16. Casey PH, Whiteside-Mansell L, Barrett K, Bradley RH, Gargus R: **Impact of prenatal and/or postnatal growth problems in low birth weight preterm infants on school-age outcomes: an 8-year longitudinal evaluation**. *Pediatrics* 2006, **118**(3):1078-1086.
17. **Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee**. *World Health Organ Tech Rep Ser* 1995, **854**:1-452.
18. Lundgren M, Cnattingius S, Jonsson B, Tuvemo T: **Intellectual performance in young adult males born small for gestational age**. *Growth Horm IGF Res* 2004, **14 Suppl A**:S7-8.
19. Cooke RJ: **Postnatal growth and development in the preterm and small for gestational age infant**. *Nestle Nutr Workshop Ser Pediatr Program* 2010, **65**:85-95; discussion 96-88.
20. Albers CA, Grieve AJ: **Bayley scales of infant and toddler development, third edition.***J Psychoeduc Assess* 2007, **25**(2):180-190.
21. Johnson S, Moore T, Marlow N: **Using the Bayley-III to assess neurodevelopmental delay: which cut-off should be used?***Pediatr Res* 2014, **75**(5):670-674.
22. Jobe AH, Bancalari E: **Bronchopulmonary dysplasia**. *Am J Respir Crit Care Med* 2001, **163**(7):1723-1729.
23. Papile LA, Burstein J, Burstein R, Koffler H: **Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm**. *J Pediatr* 1978, **92**(4):529-534.
24. Bell MJ: **Perforation of the gastrointestinal tract and peritonitis in the neonate**. *Surg Gynecol Obstet* 1985, **160**(1):20-26.
25. De Benedetti F: **The impact of chronic inflammation on the growing skeleton: lessons from interleukin-6 transgenic mice**. *Horm Res* 2009, **72 Suppl 1**:26-29.
26. Leviton A, Kuban KC, Allred EN, Fichorova RN, O'Shea TM, Paneth N, Investigators ES: **Early postnatal blood concentrations of inflammation-related proteins and microcephaly two years later in infants born before the 28th post-menstrual week**. *Early Hum Dev* 2011, **87**(5):325-330.
27. O'Shea TM, Allred EN, Kuban KC, Dammann O, Paneth N, Fichorova R, Hirtz D, Leviton A, Extremely Low Gestational Age Newborn Study I: **Elevated concentrations of inflammation-related proteins in postnatal blood predict severe developmental delay at 2 years of age in extremely preterm infants**. *J Pediatr* 2012, **160**(3):395-401 e394.

Tables

Table 1. Demographic and clinical characteristics of the study population

	NDI (+) (n=16)	NDI (-) (n=74)	*p* value
Gestational age, week	$29^{+4} \pm 3^{+4}$	$31^{+2} \pm 2^{+4}$	0.095
Birth weight, g	758.8 ± 325.9	973.8 ± 289.8	0.01*
Female	7(43.8)	30(40.5)	1
Multiple	8(50)	31(43.1)	0.782
Cesarean section	11(68.8)	62(83.8)	0.173
Treated PDA	8(50)	22(29.7)	0.147
BPD	8(50)	18(24.3)	0.065
IVH ≥grade III	2(12.5)	0(0)	0.03*
PVL	0(0)	3(4.1)	1
ROP	5(31.3)	4(5.4)	0.008*
NEC ≥stage II	4(25)	3(4.1)	0.017*
Sepsis	2(12.5)	3(4.1)	0.215
Gestational diabetes mellitus	1(6.3)	1(1.4)	0.329
Preeclampsia	5(31.3)	32(43.8)	0.412
Chorioamnionitis	6(37.5)	22(29.7)	0.561

Data are presented as n(%) or the mean ± 2SD. * $p < 0.05$. NDI, neurodevelopmental impairment; PDA, patent ductus arteriosus; BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity; NEC, necrotizing enterocolitis

Table 2. Growth failure and risk of neurodevelopmental impairment

Time period	Parameter of growth failure	Neurodevelopmental impairment		
		p value	aOR†	95%CI
Birth to 35 weeks PMA	Length	0.222	3.134	0.502-19.573
	Weight	0.086	3.54	0.836-14.999
	Head circumference	0.006*	6.964	1.763-27.506
35 weeks PMA to 40 weeks PMA	Length	0.008*	10.658	1.872-60.681
	Weight	0.998	1.003	0.087-11.536
	Head circumference	0.584	2.921	0.063-135.408
40 weeks PMA to 4 months CA	Length	0.999	-	-
	Weight	0.520	2.456	0.159-37.926
	Head circumference	0.067	6.591	0.876-49.6
4 months to 9 months CA	Length	0.118	0.12	0.008-1.710
	Weight	0.986	0.987	0.028-4.677
	Head circumference	0.907	1.105	0.207-5.884
9 months to 18 months CA	Length	0.202	2.753	0.581-13.037
	Weight	0.759	1.243	0.310-4.985
	Head circumference	0.454	0.592	0.15-2.334

*$p < 0.05$. †Adjusted for infant's gestational age, birth weight, intraventricular hemorrhage, necrotizing enterocolitis, and retinopathy of prematurity. PMA, postmenstrual age; CA, corrected age; aOR, adjusted odds ratio; CI, confidence interval

Table 3. Proportion of failure to catch-up and risk of neurodevelopmental impairment

Time point	Growth parameters	Failure to catch-up (%)	Neurodevelopmental impairment		
			P value	aOR†	95%CI
Birth	Length	77.8	0.704	0.721	0.133-3.900
	Head circumference	71.1	0.367	2.350	0.366-15.076
35 weeks PMA	Length	98.9	1	-‡	-
	Weight	98.9	1	-‡	-
	Head circumference	91.1	0.078	0.159	0.021-1.233
40 weeks PMA	Length	94.4	0.999	-‡	-
	Weight	93.3	0.999	-‡	-
	Head circumference	55.6	0.281	2.765	0.434-17.598
4 months CA	Length	53.3	0.544	1.656	0.325-8.43
	Weight	51.1	0.621	1.554	0.271-8.893
	Head circumference	43.3	0.004*	9.600	2.049-44.974
9 months CA	Length	36.7	0.027*	4.128	1.175-14.497
	Weight	44.4	0.012*	6.086	1.135-31.879
	Head circumference	37.8	< 0.001*	20.25	4.099-100.051
18 months CA	Length	38.9	0.029*	4.229	1.158-15.443
	Weight	44.4	0.004*	14.015	2.290-85.762
	Head circumference	31.1	0.010*	5.256	1.479-18.68

*$p < 0.05$. †Adjusted for infant's gestational age, birth weight, intraventricular hemorrhage, necrotizing enterocolitis, and retinopathy of prematurity. ‡Not enough case to calculate. PMA, postmenstrual age; CA, corrected age; aOR, adjusted odds ratio; CI, confidence interval

Table 4. Clinical factors that affected the failure to catch-up growth of HC at 4, 9, and 18 months corrected age.

Failure to catch-up growth of HC	4 months CA	9 months CA	18 months CA
	p	*p*	*p*
Days of O_2 therapy	0.247	0.119	0.107
Days of antibiotics usage	0.01*	0.009*	0.013*
Days to full enteral feedings	0.002*	0.002*	0.001*
Days of steroid usage	0.239	0.162	0.33

* $p < 0.05$. Adjusted for infant's gestational age, birth weight. HC, head circumference; NDI, neurodevelopmental impairment; CA, corrected age; aOR, adjusted odds ratio

Figures

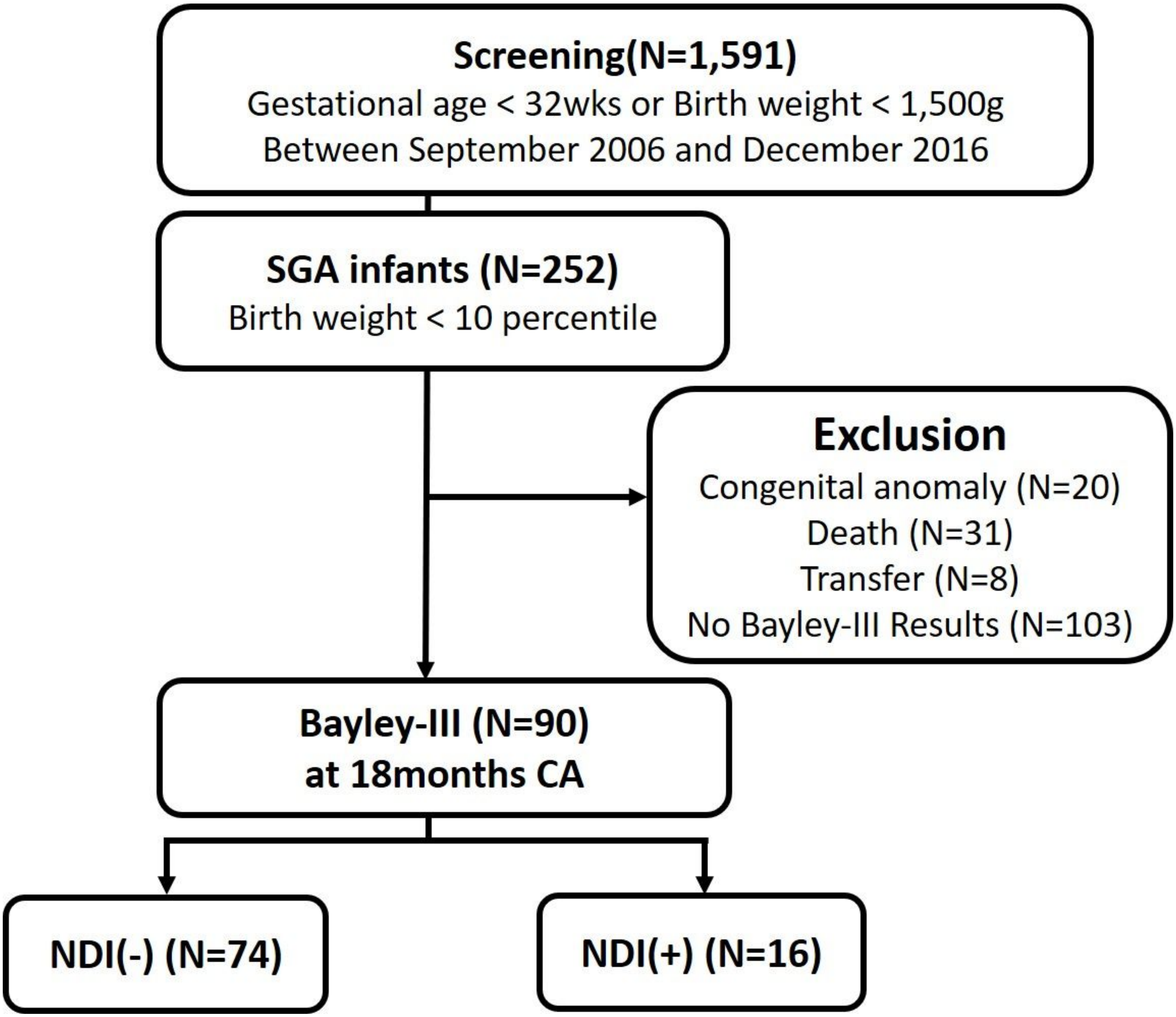

Figure 1

A flow diagram of the study population

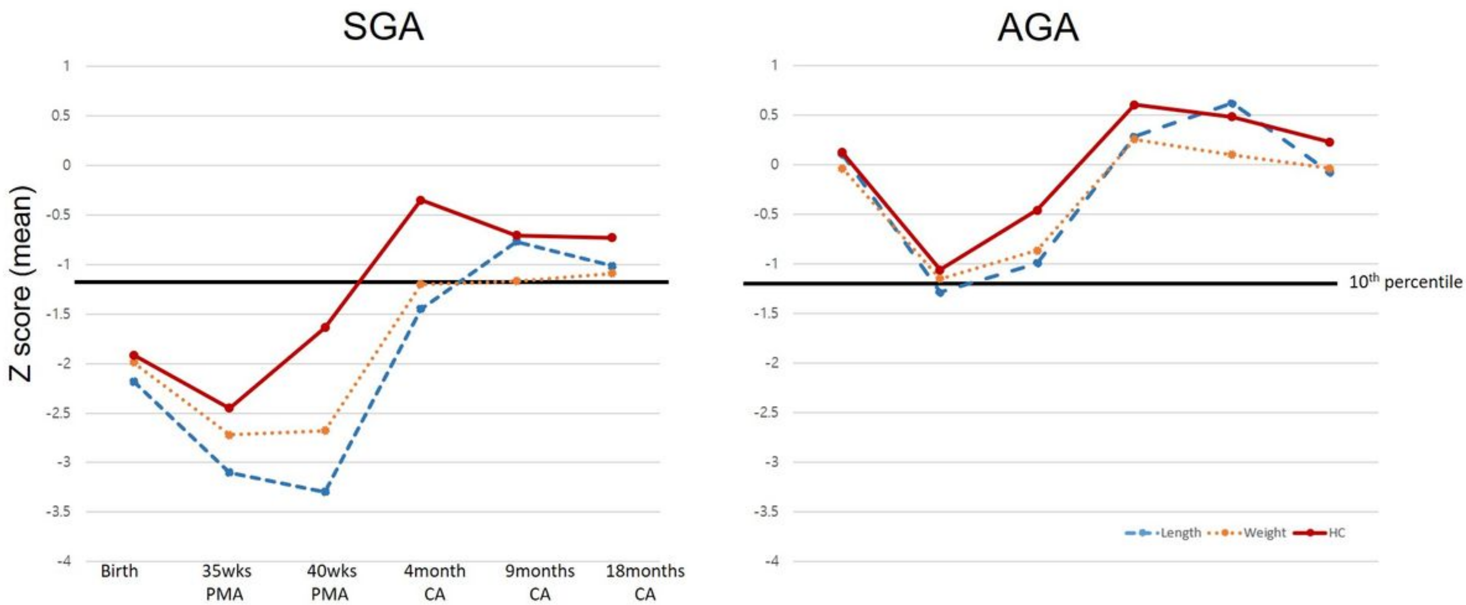

Figure 2

Differences in the growth patterns between small for gestational age (SGA) and appropriate for gestational age (AGA) infants from birth to 18 months corrected age (CA)