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Early growth patterns are associated with intelligence quotient scores in children born small-for-gestational age

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ABSTRACT

Objective: To assess whether patterns of growth trajectory during infancy are associated with intelligence quotient (IQ) scores at 4 years of age in children born small-for-gestational age (SGA).
Methods: Children in the Collaborative Perinatal Project born SGA were eligible for analysis. The primary outcome was the Stanford–Binet IQ score at 4 years of age. Growth patterns were defined based on changes in weight-for-age *z*-scores from birth to 4 months and 4 to 12 months of age and consisted of steady, early catch-up, late catch-up, constant catch-up, early catch-down, late catch-down, constant catch-down, early catch-up & late catch-down, and early catch-down & late catch-up. Multivariate linear regression was used to assess associations between patterns of growth and IQ.
Results: We evaluated patterns of growth and IQ in 5640 children. Compared with children with steady growth, IQ scores were 2.9 [standard deviation (SD) = 0.54], 1.5 (SD = 0.63), and 2.2 (SD = 0.9) higher in children with early catch-up, early catch-up and later catch-down, and constant catch-up growth patterns, respectively, and 4.4 (SD = 1.4) and 3.9 (SD = 1.5) lower in children with early catch-down & late catch-up, and early catch-down growth patterns, respectively.
Conclusions: Patterns in weight gain before 4 months of age were associated with differences in IQ scores at 4 years of age, with children with early catch-up having slightly higher IQ scores than children with steady growth and children with early catch-down having slightly lower IQ scores. These findings have implications for early infant nutrition in children born SGA.

1. Introduction

Approximately 400,000 newborns are born small-for-gestational age (SGA) in the United States yearly [1]. SGA refers to newborns with birth weight below a threshold (e.g., below the 10th percentile) [2]. While SGA term is often used as a proxy for intrauterine growth restriction, in truth, it is composed of a combination of pathologically growth restricted fetuses and constitutionally small but otherwise normal newborns [3]. Consequently, methods were proposed to improve identification of the pathologically small newborns, including adjustment for the maternal constitutional determinants (e.g., growth potential) [4]. Yet, SGA newborns are associated with adverse consequences in the short and long-term [5–8], including decreased levels of intelligence and cognition [9] compared to children born appropriate-for-gestational age.

Most SGA infants develop compensatory accelerated catch-up growth [10,11]. Catch-up growth in SGA children has been associated with both beneficial and adverse health consequences. SGA children who developed catch-up growth were shown to have completed successfully higher school grades and higher mean IQ scores compared to those who fail to develop catch-up growth [12–15]. These associations were robust after adjustment for socio-economic variables, parental education, family income, and household assets index [13]. However, SGA children with catch-up growth may have an increased risk of cardiovascular and metabolic diseases during adulthood compared to those without catch-up growth [16–20].

Little is known about trajectories of growth during infancy in SGA children, particularly whether different trajectories of growth have health implications. Specifically, no data exist on whether catch-up growth after 6 months of age impacts cognition compared to early catch-up growth. Given the potential early benefits but later detrimental effects of catch-up growth, a more detailed description of the association between growth trajectories and cognition early in the childhood is needed to elucidate whether or not catch-up growth should be encouraged in SGA children and potentially aid to identify whether there is critical period in the first year of life for catch-up growth that would have a long-term beneficial health impact. In that context, we used data from a large cohort of children born in the United States from the

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National Collaborative Perinatal Project to assess whether growth trajectories in the first year of life were associated with intelligence quotient (IQ) scores at 4 years of age.

2. Methods

2.1. Study cohort

Data were obtained from the National Collaborative Perinatal Project (NCPP). The NCPP enrolled about 59,000 pregnant women from 12 medical centers in the United States between 1959 and 1965, aiming primarily to evaluate prenatal and perinatal risk factors for adverse neurodevelopmental outcomes. Their offspring were followed for 8 years with multiple questionnaires regarding medical and social history and neuropsychological testing were completed. A comprehensive study description was published previously [21,22].

Verbal consent was obtained from participant's parents or legal guardians at enrollment. The NCPP data file has no personal identifiers and is in the public domain.

SGA was defined as age-, sex-, and singleton-specific birth weights below the 10th percentile according to curves established by the California Department of Health Services [23]. As these curves describe percentiles for newborns with gestational ages ranging from 22 to 48 weeks, only newborns within this range of gestational age were included. Children with malformations and syndromes, and those with missing weight at 4 and 12 months of age were excluded. Gestational age was based on the last menstrual period (LMP). In participants of the Johns Hopkins Center of the NCPP, estimation of gestational age using LMP was considered accurate compared to clinical assessments [24].

2.2. Intelligence quotient

IQ was measured at 4 years of age as a continuous variable based on the Stanford–Binet intelligence scale, form L-M [25]. IQ scores at 4 years of age were less commonly explored and potentially might be influenced differently by factors such as parental education and schooling as compared IQ measured at older ages [26,27]. The Stanford–Binet test IQ scores have a population mean of 100 and standard deviation of 15 and were based on ratings by NCPP-trained examiners. Detailed description of the methods is available elsewhere [28]. The Stanford–Binet form L-M test is considered highly reliable (correlation coefficient of 0.75 to 0.85) compared to the Wechsler Intelligence Scale for Children (WISC) [29,30].

2.3. Growth trajectories

Growth trajectories were defined based on weight-for-age z-scores at birth, 4, and 12 months of age. Weight-for-age at 8 months was missing for 58% of the sample and thus, not used in the study. Weight measurements were converted to z-scores using the NCHS 2000 population as reference [31]. Weight z-scores at 4 months were compared to weight z-scores at birth and 12 months and were classified as equal (difference within ± 0.66), smaller (difference greater than -0.66), or greater (difference greater than $+0.66$). The cut-off of 0.66 was based on the fact that a 0.66 weight z-score corresponds approximately to a percentile band width in the growth nomograms [32]. Nine trajectories were created: steady (z-score at 4 months equal to the z-score at birth and 12 months); early catch-up (z-score at 4 months greater than z-score at birth and equal to the z-score at 12 months); early catch-up & late catch-down (z-score at 4 months greater than z-score at birth and 12 months); late catch-up (z-score at 4 months equal to the z-score at birth but smaller than the z-score at 12 months); constant catch-up (z-score at 4 months greater than z-score at birth and smaller than the z-score at 12 months); early catch-down (z-score at 4 months smaller than the z-score at birth and equal to the z-score at 12 months); early catch-down & late catch-up (z-score at 4 months smaller than the z-score at birth and 12 months); late catch-down (z-score at 4 months equal to the z-score at birth, but greater than the z-score at 12 months); and constant catch-down (z-score at 4 months smaller than the z-score at birth and greater than the z-score at 12 months).

2.4. Additional variables

Potential confounders evaluated included variables related to the antenatal period (maternal height and parity, and prior history of abortion, stillbirth, preterm birth, and history of diabetes, eclampsia or pre-eclampsia, anemia, and infection in the index pregnancy, gestational age when prenatal care started, and number of prenatal care visits), parental demographic and socio-economic indicators (race, age, marital and work status, income, education, center of enrollment), birth (anthropometric measurements, gestational age, preterm status, and 5 min Apgar score), and early life (hyaline membrane disease and use of antibiotics before nursery discharge).

3. Statistical methods

Mean IQ scores were compared among the trajectories of growth using ANOVA with pairwise comparisons using the Bonferroni method to assess statistical significance. Independent associations were tested using multivariate linear regression. Potential confounders included those consistently described in the literature (e.g., maternal education) as well as those associated with both the outcome and exposure with a p-value less than 0.1 in the univariate analyses. Different models were tested using manual stepwise inclusion of covariates. Statistical significance was considered for p-values < 0.05 for a two-tailed test. Stata software (release 10.0 StataCorp, College Station, Texas, USA) was used for analyses [33].

4. Results

4.1. Study participants

The NCPP included 56,990 children. Of those, 17% ($n = 9903$) were SGA. After exclusion of children with malformations or syndromes ($n = 774$) and those missing weight at 4 or 12 months of age ($n = 2222$), 5640 children were included in the analysis.

The characteristics of the 5640 SGA children included were similar to the complete NCPP cohort, with few exceptions (Table 1). Of the children included in this analysis, the median maternal age was 22 years [inter-quartile range (IQR) = 19–27]. Most mothers of the study children were African-American (59%) and married (70%), and the median years of education was 11 (IQR = 9–12). Most children had families with low income (45% with income between $2000 and $3999 and 22% between $4000 and 5999 dollars). The median paternal age and years of education were respectively 27 (IQR = 23–32) and 11 (IQR = 9–12) years. The median number of prenatal visits was 9 (IQR = 6–12). Lastly, half of the study newborns were male and the median gestational age was 40 weeks (IQR = 39–41).

SGA children for whom IQ information was missing were more likely to have mothers who were slightly younger, Puerto Rican or other races, and primigravidas; were more likely to have fathers slightly more educated and younger; and were more likely preterm and to have received antibiotics before nursery discharge compared to those SGA children included for analysis (Table 1).

4.2. Growth trajectories and IQ

The median age at the time of the IQ test was 4 years (IQR: 3.9–4.1 years). Children with early catch-up, constant catch-up, and early catch-up & later catch-down growth patterns had the highest median IQ scores. The lowest mean IQ scores were in children with early