ARTICLE

GLOBAL HEALTH

Influence of Prenatal and Postnatal Growth on Intellectual Functioning in School-aged Children

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Objective: To assess the relative influence of size at birth, infant growth, and late postnatal growth on intellectual functioning at 9 years of age.

Design: A follow-up, cross-sectional study.

Setting: Three districts in Khon Kaen province, northeast Thailand.

Participants: A total of 560 children, or 92% of former participants of a trial of iron and/or zinc supplementation during infancy.

Main Exposures: Prenatal (size at birth), early infancy (birth to 4 months), late infancy (4 months to 1 year), and late postnatal (1 to 9 years) growth. Multiple-stage least squares analyses were used to generate uncorrelated residuals of postnatal growth.

Main Outcome Measures: Intellectual functioning was measured at 9 years using the Wechsler Intelligence Scale for Children and the Raven's Colored Progressive Matrices (Pearson). Analyses included adjustment for maternal, household, and school characteristics.

Results: Significant relationships were found between growth and IQ (Wechsler Intelligence Scale for children, third edition, Thai version), but only up to 1 year of age; overall, growth was not related to the Raven's Colored Progressive Matrices. The strongest and most consistent relationships were with length (birth, early infancy, and late infancy); for weight, only early infancy gain was consistently related to IQ. Head circumference at birth was not collected routinely; head circumference at 4 months (but not head circumference growth thereafter) was related to IQ. Late postnatal growth was not associated with any outcome.

Conclusion: Physical growth in early infancy (and, to a lesser extent, physical growth in late infancy and at birth) is associated with IQ at 9 years of age. Early infancy may be a critical window for human development.

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THERE ARE MANY STUDIES ON the relationship between child anthropometry and cognition and schooling.[1] However, few studies have looked at the relative importance of prenatal vs postnatal growth, and even fewer studies have done so using appropriate statistical techniques.[1] A challenge to overcome is that growth is correlated across ages; for example, birth weight influences growth during infancy. To properly assess the relative importance of growth during specific periods and thus identify critical windows for cognitive development, one must generate uncorrelated measures of growth for the analyses. Another problem is that not all studies controlled for confounding using such variables as socioeconomic status and parental education; this is necessary because family characteristics predict deficits in both growth and cognition. After selecting articles with appropriate methods, a recent review[1] concluded that

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> [t]he relative importance of prenatal and postnatal growth is not well understood, but it would appear that the adequacy of growth during the first two years is the critical factor, perhaps even more important than intrauterine growth.

The present study adds to the sparse but important literature by assessing the relative importance of growth at prenatal, early infancy, late infancy, and late postnatal periods on the intellectual functioning of 9-year-old Thai children (n=560) using data from a follow-up study[2] of a micronutrient supplementation trial during infancy. The study's contributions include the

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identification of sensitive windows for development using cohort data, methods that rely on appropriate statistical techniques, and control for confounding.

METHODS

STUDY DESIGN AND PARTICIPANTS

A follow-up study[2] was performed for children who participated in a randomized controlled trial of iron and/or zinc supplementation during infancy in Khon Kaen province in northeast Thailand during the period from 1998 to 1999. Breast-fed infants aged 4 to 6 months were randomly assigned to receive daily oral supplementation of iron, zinc, iron plus zinc, or a placebo for 6 months. Details of the original study are provided elsewhere.[2] Of the 609 infants who completed the trial, 560 (92%) were examined at 9 years. The intervention had no impact on IQ at follow-up.[3] Written informed consent was obtained from parents or caregivers, and verbal assent was obtained from all children. This follow-up study was approved by the institutional review boards of Emory University, Atlanta, Georgia, and the Human Ethics Committee of Mahidol University, Nakhon Pathom, Thailand.

MEASUREMENTS

Intellectual Functioning

Intellectual functioning was assessed by clinical psychologists, using the Wechsler Intelligence Scale for Children (WISC), third edition, Thai version.[4,5] Six verbal subtests (information, similarities, arithmetic, vocabulary, comprehension, and digit span) and 6 performance subtests (picture completion, coding, picture arrangement, block design, object assembly, and symbol search) were administered. Raw scores from each subtest were transformed to the scaled scores and then to the age-adjusted full-scale, verbal, and performance IQ scores according to the Thai norms. The nonverbal Raven's Colored Progressive Matrices (RCPM; Pearson)[6] were also performed; the raw scores for all items were summed, and the total score was used in the analysis. The tests were performed in a quiet environment. All children received a snack and milk before the administration of the test. The WISC and RCPM were used to capture different aspects of intellectual functioning

Anthropometric Measurements

Weight, length, and head circumference (HC) at birth and at the beginning (age range, 3.5-6.5 months; referred to as 4 months) and the end of the trial (age range, 9.3-12.7 months; referred to as 1 year) were obtained from study records. Methods of measurement are given elsewhere.[2] Weight, length, and HC at birth were measured in 560, 462, and 254 newborns, respectively, by health personnel. Head circumference at birth had a very skewed distribution, suggesting poor measurement, and was only available for 42% of the original sample. Thus, only weight and length at birth were used. The *z* scores for age were generated for weight, height, and HC based on the 2006 World Health Organization growth standard for children 0 to 5 years old.[7] Weight, height, and HC at 9 years of age (age range, 8.8-10.1 years) were assessed using standard procedures.[8] Weight-for-age and height-for-age *z* scores were generated using the 2007 World Health Organization growth reference for school-aged children and adolescents.[9]

Sociodemographic Variables

Sociodemographic data (the child's age and sex, the mother's educational level, the availability of the mother at home, household socioeconomic status, and the location of the school) were obtained using a pretested questionnaire. The mother's educational level was categorized as 1 (ie, lower than or equal to grade 6) or 2 (ie, higher than grade 6). The availability of the mother at home, meaning whether she lived at home or not, was coded as present or absent/occasionally present. The location of the school was coded as urban or rural. Standardized household socioeconomic status scores were generated using principal component analysis.[10,11] Characteristics of the home, family assets, and access to services were included in this computation. The mother's height was measured during recruitment (ie, when the child was an infant).

STATISTICAL ANALYSIS

Statistical analyses were performed using SAS for Windows version 9.2 (SAS Institute Inc). The main outcomes were WISC full-scale, verbal, and performance IQ scores and the RCPM score at 9 years of age. An independent *t* test or an analysis of variance with the Tukey post hoc test was used to assess differences in the main outcomes by sociodemographic variables. Ordinary least squares regression analyses were performed to assess associations between growth measures and outcomes, adjusting for sociodemographic variables and maternal height. The growth measures used in the regressions were standard deviation scores, obtained by subtracting individual measurements by the mean of that measurement and then dividing by its standard deviation. Statistical significance was declared at $P < .05$.

Prenatal growth was defined as size at birth. Infancy was partitioned into early infancy growth (from birth to 4 months) and late infancy growth (from 4 months to 1 year). Late postnatal growth was defined as growth from 1 to 9 years. Multiple-stage least squares analyses were used to assess associations between growth and intellectual functioning at 9 years, as done in a study[12] that assessed the relative importance of prenatal and postnatal growth on women's educational achievement. A 4-stage least squares analysis was used to estimate the effect of prenatal growth and the independent effects of early infancy, late infancy, and late postnatal growth. First, size at 4 months was modeled on birth size to estimate predicted size at 4 months. Then, the residual, interpreted to represent early infancy growth (R1), was calculated by subtracting the predicted size from the observed size at 4 months. Then, size at 1 year was modeled on size at birth and the R1 to obtain the predicted size at 1 year of age. As before, the late infancy residual (R2) was calculated by subtracting the predicted size at 1 year from the observed size. Finally, size at 9 years was modeled on birth size, R1, and R2 to generate the predicted size at 9 years. The third residual, R3, was calculated by subtracting the predicted size at 9 years from the observed size. By design, birth size and all residuals were uncorrelated with each other. For length/height and weight, we modeled birth size, R1, R2, and R3 on IQ to assess prenatal, early infancy, late infancy, and late postnatal effects. Only HC measurements at 4 months, 1 year, and 9 years were included in the analysis. Thus, we modeled HC at 4 months, R2 (late infancy), and R3 (late postnatal) on IQ.

RESULTS

DESCRIPTION OF THE PARTICIPANTS

The mean age of the children at follow-up was 9.3 years (**Table 1**). The percentage of boys and the percentage

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of girls were similar. The mean (SD) birth weight was 3.1 (0.4) kg. The mean (SD) weight-for-age *z* scores were –0.4 (0.9) at birth, –0.6 (0.9) at 4 months, –0.9 (0.9) at 1 year, and –0.9 (1.2) at 9 years. The mean (SD) length/height-for-age *z* scores were 0.3 (1.4) at birth, –0.8 (0.9) at 4 months, –1.0 (0.9) at 1 year, and –0.9 (0.9) at 9 years. The mean (SD) HC-for-age *z* scores at 4 months and 1 year were –0.8 (0.9) and –0.9 (0.9), respectively.

BIVARIATE ANALYSIS

Performance IQ and RCPM scores were significantly higher for boys than for girls (**Table 2**). There were no differences in outcomes by supplementation group at infancy. Full-scale and verbal IQ scores were higher for children of better educated mothers, and verbal IQ scores were higher in children whose mothers were available at home, compared with all other children. All outcomes were significantly higher for children of better socioeconomic status and whose schools were located in urban areas.

MULTIVARIATE ANALYSIS

In a 4-stage least squares analysis, a 1 SD gain in early infancy weight was associated with increased scores of 1.3, 0.8, and 1.6 points for full-scale, verbal, and performance IQ, respectively (**Table 3**). Weight at birth was positively associated with performance IQ only. There were no significant associations between gain in weight and IQ from 4 months to 1 year or from 1 to 9 years.

In a 4-stage least squares analysis (Table 3), a 1-SD gain in length from birth to 4 months was associated with increased scores of 1.8, 1.3, and 2.2 points in full-scale, verbal, and performance IQ, respectively. Length at birth was significantly associated with full-scale and performance IQ. Gain in length from 4 months to 1 year was associated with all measures of IQ, whereas gain in length/height from 1 year to 9 years was not associated with any outcome. The largest coefficients were those corresponding to length growth from birth to 4 months.

Head circumference at birth was not included in this analysis. Head circumference at 4 months was significantly associated with IQ in a 3-stage least squares analysis. A 1-SD increase in HC at 4 months was associated with increases of 1.8, 1.5, and 2.0 points, respectively, in full-scale, verbal, and performance IQ (Table 3). Growth in HC from 4 months to 1 year and growth in HC from 1 year to 9 years were not associated with IQ.

None of the measures of weight or HC were associated with RCPM scores (data not shown). Only gain in length from birth to 4 months was associated with an RCPM score.

Table 1. Anthropometric Characteristics of 560 Children Who Were Former Participants of a Trial of Iron and/or Zinc Supplementation During Infancy

Characteristic	Value, Mean (SD)
Age at follow-up, y	9.3 (0.3)
Boys, %	50.7
At birth	
Weight, kg	3.1 (0.4)
Weight-for-age *z* score	–0.4 (0.9)
Length, cm (n=462)	50.3 (2.7)
Length-for-age *z* score	0.3 (1.4)
At 4 mo	
Age, mo	4.5 (0.5)
Weight, kg	6.5 (0.8)
Weight-for-age *z* score	–0.6 (0.9)
Length, cm	62.1 (2.2)
Length-for-age *z* score	–0.8 (0.9)
HC, cm	40.6 (1.2)
HC-for-age *z* score	–0.8 (0.9)
At 1 y	
Age, mo	10.4 (0.6)
Weight, kg	8.1 (0.9)
Weight-for-age *z* score	–0.9 (0.9)
Length, cm	70.6 (2.4)
Length-for-age *z* score	–1.0 (0.9)
HC, cm (n=559)	43.8 (1.3)
HC-for-age *z* score	–0.9 (0.9)
At 9 y	
Age, y	9.4 (0.3)
Weight, kg	26.3 (5.4)
Weight-for-age *z* score (n=558)	–0.9 (1.2)
Height, cm	129.2 (5.9)
Height-for-age *z* score	–0.9 (0.9)
HC, cm	50.7 (1.3)

Abbreviation: HC, head circumference.

COMMENT

Many studies[1,13] find that, compared with children born with normal birth weight, children born with low birth weight have substantially poorer cognitive and schooling outcomes later in life and that children who are small during childhood perform poorly compared with taller children. However, the literature examining the relative importance of prenatal vs postnatal growth for cognitive development is sparse.

Linear growth failure in developing countries occurs during the first 1000 days of life (during the prenatal period and up to 2 years) across developing countries; even in very poor countries, linear growth rates after 2 years of age are similar to those of children in Europe and North America.[14] This window of growth failure coincides with a critical window for brain and neurological development.[15] Growth failure in poor counties is typically a response to the interactive effects of poor nutrient intakes and infection and probably reflects poor nutrient availability at the cellular level, one of several mechanisms for impaired child development and learning. For this reason, it may be important to consider the population characteristics in examining the literature.

Several studies[16-18] from Europe showed inconsistent results regarding the relationship between anthropometric characteristics at birth and IQ measured between 5 and 11 years of age. All these studies[16-18] reported some significant associations with postnatal growth, but the periodicity of measurements during the postnatal period was limited, and the findings themselves inconsistent; thus, the available results do not permit any firm overall conclusion about whether growth during the first

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Table 2. WISC IQ and RCPM Scores at 9 Years of Age, Categorized by Sociodemographic Variables[a]

	Mean (SD)			
	WISC IQ Score			
Variable	Full-Scale	Verbal	Performance	RCPM Score[b]
All children	93.1 (9.8)	94.2 (9.1)	93.4 (11.6)	21.7 (5.4)
Sex				
Boy (n=284)	93.4 (10.0)	93.6 (9.1)	94.5 (12.5)*	20.9 (5.4)*
Girl (n=276)	92.8 (9.6)	94.7 (9.7)	92.3 (10.5)†	21.5 (5.2)†
Supplementation at infancy				
Placebo (n=139)	93.3 (9.9)	93.9 (9.5)	93.9 (12.2)	21.6 (5.3)
Iron (n=147)	93.0 (8.7)	93.7 (8.2)	93.7 (10.8)	21.7 (5.5)
Zinc (n=139)	92.9 (9.9)	94.0 (9.7)	93.0 (11.3)	21.3 (5.4)
Iron and zinc (n=135)	93.4 (10.6)	95.1 (10.2)	92.9 (12.1)	22.3 (5.5)
Education of mother				
Grade 6 or less (n=351)	92.4 (9.9)*	93.4 (9.3)*	92.7 (12.0)	21.4 (5.4)
More than grade 6 (n=206)	94.4 (9.5)†	95.4 (9.5)†	94.5 (10.9)	22.3 (5.3)
Availability of mother at home				
Present (n=486)	93.4 (9.8)	94.5 (9.5)*	93.6 (11.5)	21.7 (5.3)
Absent or occasionally present (n=74)	91.2 (9.7)	91.9 (8.7)†	92.2 (12.0)	21.9 (5.3)
SES tertiles				
Low (n=186)	90.5 (9.9)*	92.0 (9.5)*	90.5 (11.8)*	20.4 (5.3)*
Medium (n=188)	92.8 (9.6)*	94.2 (9.2)*,†	92.8 (11.2)*	21.7 (5.2)†
High (n=186)	96.0 (9.1)†	96.2 (9.1)†	96.9 (11.0)†	23.0 (5.3)‡
School location				
Rural (n=476)	92.2 (9.5)*	93.2 (9.1)*	92.6 (11.3)*	21.3 (5.2)*
Urban (n=84)	98.3 (9.8)†	99.3 (9.3)†	97.8 (12.2)†	23.9 (5.3)†

Abbreviations: RCPM, Raven's Colored Progressive Matrices; SES, socioeconomic status; WISC, Wechsler Intelligence Scale for Children; third edition, Thai version.

[a] Different symbols denote significant difference between categories ($P<.05$).

[b] Adjusted for age.

1 or 2 years of life is more important than later growth in European studies.

The literature from developing countries using uncorrelated measures of growth is equally sparse. A longitudinal study[19] from the 1990s in Guatemala examined associations between birth size and growth between 0 to 6, 6 to 24, and 24 to 36 months with mental and motor scores on the Bayley Scales of Infant Development. Relationships with motor development were stronger and more consistent than with mental development. Birth size and growth in length and weight during the first 24 months were significantly associated with child development, but growth from 24 to 36 months was not; relationships with birth length or weight were of similar magnitude as those found with growth from 0 to 24 months. For HC, birth measures and growth from birth to 6 months were associated with development but not growth after 6 months. Another study[12] from Guatemala examined associations in women between birth size and growth from birth to 2 years and from 2 years to adulthood with educational achievement, a variable summarizing 5 educational tests. Growth from birth to 2 years, but not birth size or growth from 2 years to adulthood, was associated with the summary outcome. Finally, an analysis of data from 5 long-term cohorts[20] in developing countries showed that growth after 2 years is unrelated to highest grade attained and grade failure; on the other hand, growth between birth and 2 years was strongly related to schooling outcomes, whereas birth weight showed weaker associations.[20] The relevant literature from developing countries is limited, with the outcomes measured varying widely in nature and in the timing of their assessment, but overall it suggests that growth in the first 2 years of life is more consistently and more strongly related to psychoeducational outcomes than is birth weight but that growth after 2 years of age is consistently not associated with any outcome.

Our study, although consistent with the literature from developing countries, adds significantly to it. The present study permitted assessment of growth in early and late infancy relative to birth size and growth after infancy. The WISC outcomes were associated with growth, whereas the RCPM scores were not, with the exception of growth in length during early infancy. These contrasting findings were unexpected, and we have no adequate explanation for it, particularly in view of the correlation between the 2 scales ($r=0.60$, $P<.001$). Early infancy was the period during which growth in either weight or length was consistently associated with all intellectual functioning outcomes at 9 years. However, length gain during late infancy was also associated with IQ at 9 years, although to a lesser extent. Birth length and weight were also associated with at least 1 outcome. Growth from 1 to 9 years of age was not associated with intellectual functioning.

These findings are consistent with the pattern of mean changes in z scores in length. The mean z score at birth was 0.3, indicating no growth failure. Thereafter, there was a steep decline of 1.1 z scores by 4 months, a further decrease of 0.2 by 1 year, and an increase of 0.1 z scores by 9 years of age. Clearly, the significant period

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of linear growth failure was early infancy, although there is uncertainty about the measure of birth length. These relationships are modest but perhaps important; for example, the effect sizes for the relationship between 1 SD in length and full-scale IQ (ie, the regression coefficients from Table 3 divided by the standard deviation in IQ from Table 2) were 0.10, 0.18, and 0.14 for analyses at birth, early infancy, and late infancy, respectively.

Our regression models controlled for several confounding variables. Among these, school location and socioeconomic status were the strongest and most consistent predictors of IQ and RCPM scores in multivariate models. Children who attended urban schools and who came from wealthier homes had higher scores than did other children. Availability of the mother at home was also associated with higher IQ scores, but the associations were less consistent. Neither maternal height nor education was associated with IQ scores. Inclusion of experimental treatment group variables did not influence the results (data not shown).

The major strength of our study is that anthropometric data were available at different time points during childhood, allowing us to identify critical windows for development. We used the multiple-stage least squares approach for data analysis, and our analyses controlled for confounding variables. We also were able to follow up with 92% of the participants who completed the measurements during infancy, thus minimizing selection bias.

Our study has limitations. The quality of the HC measurements at birth was uncertain, and they were only available for a subsample; thus, we did not include HC at birth in the analysis. This prevented us from assessing associations with growth in HC during early infancy independent of HC at birth. Weight and length at birth were measured by health personnel, with less precision and accuracy than the measurements taken at older ages by trained personnel. It is possible that birth length may be overestimated, thus masking intrauterine growth failure and exaggerating the decrease in *z* scores between birth and 4 months. On the other hand, the decrease in *z* scores is consistent with poor infant-feeding practices; for example, 41% and 57% of infants were given rice and bananas, respectively, before 4 months of age. Still, growth between birth and 4 months, whether in length or weight, was the variable most consistently and strongly related to IQ; this is in sharp contrast to growth between 1 and 9 years of age, measured at both points by trained personnel, which was consistently unrelated to cognition. We also lacked anthropometric measurements at 2 years of age and were unable to explore whether growth between 1 and 2 years, a period of continuing growth failure in some settings, albeit of lesser importance than prior to 1 year,[14] is also associated with intellectual functioning. Another limitation is that we did not consider gestational age in our models. Information on gestational age was retrieved from the birth record and was usually estimated from recall of the last menstrual period. Some 17% of values on the variable of gestational age were missing. Of 465 children for whom we had information on gestational age, 11% were preterm births, and the birth weight of these children ranged from 1900 to 3500 g. Inclusion of a variable coding for prematurity in the subsample of 465 children with information on gestational age resulted in similar findings as when this variable was not included (data not shown).

Table 3. Association Between Birth Size and Postnatal Growth Measures and WISC IQ in 4-SLS (Weight and Length/Height) or 3-SLS (Head Circumference) Analyses

Variable	SD Score,[a] β (SE)		
	Full-Scale IQ	Verbal IQ	Performance IQ
Weight (n=551)			
Birth	0.6 (0.4)	0.2 (0.4)	1.0[b] (0.5)
Early infancy growth, birth to 4 mo	1.3[b] (0.4)	0.8[b] (0.4)	1.6[b] (0.5)
Late infancy growth, 4 mo to 1 y	0.6 (0.4)	0.4 (0.4)	0.5 (0.5)
Late postnatal growth, 1-9 y	–0.1 (0.4)	0.5 (0.4)	–0.8 (0.5)
Length/height (n=453)			
Birth	1.0[b] (0.4)	0.3 (0.4)	1.6[b] (0.5)
Early infancy growth, birth to 4 mo	1.8[b] (0.5)	1.3[b] (0.5)	2.2[b] (0.6)
Late infancy growth, 4 mo to 1 y	1.4[b] (0.4)	0.9[b] (0.4)	1.7[b] (0.5)
Late postnatal growth, 1-9 y	0.4 (0.4)	0.7 (0.4)	–0.1 (0.5)
Head circumference (n=550)			
Early infancy growth, 4 mo	1.8[b] (0.5)	1.5[b] (0.4)	2.0[b] (0.5)
Late infancy growth, 4 mo to 1 y	0.5 (0.4)	0.6 (0.4)	0.3 (0.5)
Late postnatal growth, 1-9 y	–0.2 (0.4)	–0.1 (0.4)	–0.3 (0.5)

Abbreviations: WISC, Wechsler Intelligence Scale for Children, third edition, Thai version; 3-SLS, 3-stage least squares; 4-SLS, 4-stage least squares.

[a] Weight at birth, 1 SD=0.4 kg; early infancy growth in weight, 1 SD=0.7 kg; late infancy growth in weight, 1 SD=0.5 kg; and late postnatal growth in weight, 1 SD=4.9 kg. Adjusted for sex, maternal height, mother's education, availability of mother at home, socioeconomic status, and school location.

[b] $P<.05$.

In conclusion, our study suggests that faster growth in early infancy leads to better intellectual functioning at school age. Thus, strategies to provide support for exclusive breast feeding, for nurturing mother-child interactions, for guidance on appropriate and timely complementary feeding, and for controlling diarrheal diseases and other infections should be emphasized to ensure optimal growth and cognitive development among children in Thailand and other developing countries.

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