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Cognition and behavioural development in early childhood: the role of birth weight and postnatal growth

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Background We evaluate the relative importance of birth weight and postnatal growth for cognition and behavioural development in 8389 Chinese children, 4–7 years of age.

Method Weight was the only size measure available at birth. Weight, height, head circumference and intelligence quotient (IQ) were measured between 4 and 7 years of age. Z-scores of birth weight and postnatal conditional weight gain to 4–7 years, as well as height and head circumference at 4–7 years of age, were the exposure variables. Z-scores of weight at 4–7 years were regressed on birth weight Z-scores, and the residual was used as the measure of postnatal conditional weight gain. The outcomes were child's IQ, measured by the Chinese Wechsler Young Children Scale of Intelligence, as well as internalizing behavioural problems, externalizing behavioural problems and other behavioural problems, evaluated by the Child Behaviour Checklist 4–18. Multivariate regressions were conducted to investigate the relationship of birth weight and postnatal growth variables with the outcomes, separately for preterm children and term children.

Results Both birth weight and postnatal weight gain were associated with IQ among term children; 1 unit increment in Z-score of birth weight (∼450 g) was associated with an increase of 1.60 [Confidence interval (CI): 1.18–2.02; $P < 0.001$] points in IQ, and 1 unit increment in conditional postnatal weight was associated with an increase of 0.46 (CI: 0.06–0.86; $P = 0.02$) points in IQ, after adjustment for confounders; similar patterns were observed when Z-scores of postnatal height and head circumference at age 4–7 years were used as alternative measurements of postnatal growth. Effect sizes of relationships with IQ were smaller than 0.1 of a standard deviation in all cases. Neither birth weight nor postnatal growth indicators were associated with behavioural outcomes among term children. In preterm children, neither birth weight nor postnatal growth measures were associated with IQ or behavioural outcomes.

Conclusions Both birth weight and postnatal growth were associated with IQ but not behavioural outcomes for Chinese term children aged 4–7 years, but the effect sizes were small. No relation between either birth weight or postnatal growth and cognition or behavioural outcomes was observed among preterm children aged 4–7 years.

Keywords Cognition, internalizing behavioural problems, externalizing behavioural problems, birth weight, postnatal weight gain

Introduction

Nutrition is vital to brain development.[1] The evidence suggests that undernutrition during 'critical' or 'sensitive' periods, predominantly during pregnancy and the early postnatal period, may have profound effects on cognition and behaviour throughout life.[2,3] For example, as an indicator of prenatal malnutrition, low birth weight (birth weight <2500 g) is associated with lower cognition,[4–6] poor school performance,[5,7,8] and behavioural disorders.[4,8–11] Positive relation of birth weight with intelligence quotient (IQ) was also observed across the normal range of birth weights,[12–16] but inconsistently so at very high values of birth weight.[16,17] The relations are shown to be robust to adjustment for confounders including family socioeconomic status (SES) and other familial confounding in sibship studies.[14,18,19] Postnatal growth matters as well. Consistent evidence from many countries shows that early stunting, defined as height-for-age below −2 standard deviation (SD) of reference values, predicts lower cognition and educational achievement.[20,21] Failure to thrive in infancy and childhood has been reported to be associated with behavioural abnormalities.[22]

What remains unclear is the relative importance of prenatal compared with postnatal growth on cognitive function and behavioural development, and evidence from the few relevant studies is inconclusive.[22–29] For example, a study in the UK found an association of cognitive function with both birth weight and weight gain in infancy, birth weight having a relatively stronger impact.[30] Another study in Guatemala found that early postnatal growth (0–2 years), but not prenatal or late postnatal growth, predicts women's later educational achievement.[24] Findings from the Newcastle Thousand Families Study suggested that height at the ages of 9 and 13 years, but not birth weight, predict childhood IQ at age 11 years.[31] The inconsistency may be due to the use of different indicators of growth and human development across the studies, different time points when postnatal growth was measured, random error due to small sample size, and lack of control for some important confounders.[24,28] In addition, major flaws existed in some previous studies. For example, including birth weight and postnatal weight directly in the same regression may confront problems of multicollinearity because growth is correlated across time.[32,33] Only a few studies have taken into account the correlation between prenatal and postnatal growths, using appropriate analytic strategies including multi-stage least square estimation,[23,24,34] and structural equation modeling.[28]

In the present study, we explored the relative importance of birth weight and postnatal growth in early childhood for a broad measure of cognitive and behavioural development, using a large sample ($n = 8389$) of Chinese children aged 4–7 years. We employed a two-stage least square estimation to address methodological issues caused by correlations among measures of weight at different ages. We were also interested in whether the findings were different between preterm children and term children.

Materials and Methods

Study sample

The data were from a China–US collaborative project designed to prevent neural tube birth defects with periconceptual folic acid supplementation during the period 1993–1996, which was approved and conducted by the U.S. Centers for Diseases Control and Prevention (CDC) and Peking University Health Science Center (PUHSC).[35,36] The program enrolled more than 247 000 women who were preparing for marriage from Hebei, Zhejiang and Jiangsu provinces in China. Upon enrollment, extensive information from the participants, including basic demographics, education, occupation, other family, SES and general health conditions was obtained by well-trained medical staff, and the pregnancy/birth outcomes were tracked by the maternal and child health hospital-based monitoring system.[35] In 2001, a random sample of 9100 children aged 4–7 years was selected from the children born to these women, and extensive data were collected concerning growth, cognition and behavioural development.[37,38]

We limited our sample to 8919 singleton live births, and we further excluded cases with missing data on child's sex, birth order, birth weight, gestational age, mother's age at delivery, maternal pre-pregnancy weight, mother taking folic acid during pregnancy, maternal height, maternal education, father's occupation and mother's IQ, as well as child's height, weight, head circumference, IQ and behavioural problems at 4–7 years old. Our final sample included 8389 (94% of the 8919) children aged 4–7 years: 4424 boys and 3965 girls.

Measurements

Assessment of cognitive ability

The assessments of cognitive ability among the mothers and children were conducted at county maternal and children's hospitals or designated township hospitals by well-trained neurological pediatricians, and interview appointments were arranged at the convenience of the mothers to administer the Chinese Wechsler Young Children Scale of Intelligence (C-WYCSI) for their children and the Wechsler Adult Intelligence Scale-Revised in China for themselves (WAIS-RC).[38]

Maternal cognitive ability. The children's biologic mothers' IQ was assessed using the WAIS-RC, which is based on the WAIS with specific questions adapted to the Chinese setting. The WAIS-RC exhibited satisfactory reliability and validity similar to those of the WAIS.[39,40]

Child cognitive ability. The C-WYCSI was employed to measure intelligence of the children. C-WYCSI is based on the Wechsler Preschool and Primary Scale of Intelligence (WPPSI), but was adapted to the Chinese setting. Satisfactory validity and reliability of WPPSI have been confirmed by previous studies.[41,42] The C-WYCSI retains five subsets of the original WPPSI, namely knowledge, arithmetic comprehension, picture completion mazes, block design and geometric design. The remaining three subsets (vocabulary, similarities and animal house) were substituted with picture vocabulary, picture summary and animal peg, respectively. C-WYCSI also includes an additional subset (pattern match). Like the WPPSI, the C-WYCSI adjusts for age and sex. Two standardized versions of the C-WYCSI, slightly differing in the numbers of items for each subset, were administered to children in rural and urban areas taking into account the marked cultural, educational and economic disparities between the areas.[43] Studies show similar psychometric characteristics for the C-WYCSI in urban children and rural children, and the C-WYCSI could be validly and equally applied to the two groups.[41] A raw score was first obtained on each subset and then converted to an age-scaled score of IQ according to a nationally standardized norm of China; a detailed description of the C-WYCSI is given elsewhere.[41,44]

Child behavioural problems

The assessment was based on the Child Behaviour Checklist (CBCL) 4–18, a widely used tool designed to evaluate children's competencies and problem behaviours.[45] The CBCL scale scores from societies with different cultures and languages were very comparable.[46] CBCL was translated into Chinese in the 1980s and has been widely used since then, and the construct validity of the CBCL has been established.[47–51] Comparison of children's behavioural and emotional problems reported by parents in Chinese and American samples suggested that cross-cultural differences were generally modest in magnitude.[52] In this survey, parents of the children were invited to administer the CBCL at county maternal and children's hospitals or designated township hospitals. Under the instructions of two interviewers, who were well-trained neurological pediatricians, informants (in most cases, the children's mothers) rated the children using a three-point scale (0 = not true; 1 = somewhat or sometimes true; and 2 = very true or often true) for each of 118 problem behaviour items.[37] These items capture several broad scales classified as internalizing syndromes (withdrawal, somatic complaints and anxiety/depression), externalizing problems (delinquency and aggressive behaviour) and other problems (social problems, thought problems and attention problems).[45]

Birth weight and postnatal growth. Birth weight was measured within 24 h after delivery. Postnatal growth, including height, weight and head circumference, was measured in 2001, when the children were 4–7 years of age, at the same time as the neurodevelopment assessments, by well-trained medical professionals.[37]

Family SES. SES indicators include maternal education (high school and above, junior high school, elementary school and less), paternal occupation (agricultural worker, industrial worker, governmental employee/office worker and other).

Other variables. Other variables in the analysis were gestational age, sex and birth order of the child (firstborn vs higher-order births), mother's age at childbirth (years) and pre-pregnancy maternal weight (kg) and height (cm). We also included whether the mother took a folic acid supplement during pregnancy for its observed effect on cognitive development,[53] and urban residence to control for potential effects of urban/rural inequalities in socioeconomic, infrastructural and public health characteristics.[43]

Statistical analysis

Two-stage least square (2-SLS) modeling

We applied the 2-SLS approach to address potential problems that may be caused by the correlation between birth weight and postnatal weight at later time points. In the first stage, we created 'conditional postnatal weight gain' to substitute for the measured postnatal weight gain. This stage involves the prediction of postnatal weight from birth weight and the calculation of residual as 'conditional postnatal weight gain'. In the second stage, birth weight and the residual ('conditional postnatal weight gain') were used as independent variables for assessing the relative importance of prenatal vs postnatal effects in regression models. The 2-SLS approach removes bias due to the correlation between growths at different time points; it also addresses the problem of multicollinearity and complicated interpretation of regression coefficients when compared with results from models in which initial size and subsequent size are simultaneously entered.[32,33] We used Z-scores rather than raw scores in the weight variables, as weight-for-age Z-scores capture how far a weight deviates from the mean weight of children of the same age and sex, according to the World Health Organization's 2006 standard.[54] Z-scores are more appropriate than raw score in this analysis because the postnatal measures of weight were obtained from children at different ages, ranging from 4 to 7 years.

Preterm children and term children may follow different growth patterns in the early years of life,[55] and they may also differ in cognitive and behavioural development. For example, preterm births may have higher risks for cognitive and behavioural problems as a result of the reduction in gestational duration or obstetric complications.[56] We therefore analysed the data separately for preterm children and term children. For each sample, we tested the crude associations of birth weight (Z-score) and 'postnatal conditional weight gain Z-scores' with cognitive and behavioural outcomes: general IQ, internalizing behavioural problems, externalizing behavioural problems and other behavioural problems, with each outcome in a single model. In these crude analyses, we controlled for child's age, in addition to child's sex, to adjust for potential residual age effect on the age-standardized outcomes. We then tested whether these associations were robust to adjustment for a broad array of confounders including gestational age of the child, birth order of the child (firstborn vs higher-order births), mother's age at childbirth, pre-pregnancy maternal weight and height, urban residence, father's occupation (agricultural worker, industrial worker, government employee/office worker and other), mother's education (high school and above, junior high school, and elementary school and below), whether mother took folic acid supplement during pregnancy and mother's IQ. In all the models, we estimated cluster-robust standard error because the samples are clustered by residential areas.

We also conducted similar analysis with postnatal height and head circumference as alternative indicators of postnatal growth. We chose not to include postnatal weight and postnatal height simultaneously in the models because of their high correlation ($r = 0.62$), which may cause multicollinearity problems when including both in the regressions. All analyses were conducted using the Statistical Analysis System (SAS version 8.2).

Effect size analysis

To compare the relative magnitude of associations between growth variables (predictors) and the outcome variables, we also conducted effect-size analysis on any association with a P-value less than 0.05. The effect size is calculated as the absolute change in SD units in the outcome variable per 1-SD change in the predictor; effect sizes of magnitude 0.1, 0.3 and 0.5 are considered small, medium and large, respectively.[57]

Results

Descriptive information

Table 1 presents descriptive information by term status and sex of children. Approximately 8.5% of births were preterm (born before 37 weeks of gestation), and the average gestational age was 255 days (range: 175–265 days) for both preterm boys and preterm girls. Although the preterm children exhibited lower birth weight compared with term children (−0.67 vs 0.10 in Z-score of birth weight for boys; −0.57 vs 0.10 in Z-score of birth weight for girls), their postnatal growth, indicated by Z-scores of postnatal weight and height, was similar to that of term children. Term children and preterm children exhibited no difference in IQ or in behavioural problems. For both preterm children and term children, boys exhibited higher IQ than girls (Table 1). Boys performed better than girls on most of the subsets of the test, except for animal pegs and picture matching (two subsets measuring performance IQ) on which boys and girls obtained similar scores (results not shown). Similar boys' advantages on IQ tests was found in the samples used for the standardization of the WISC-R in the US and Scotland, where boys outperformed girls on full-scale, verbal and performance IQ, and obtained higher scores on almost all subsets except for coding and digit span, which are considered to be tests of short-term memory.[58] In addition, compared with girls, boys also had more externalizing behavioural problems but similar internalizing behavioural problems and other behavioural problems, which is similar to the gender patterns observed among preschool children across societies.[59] All these differences were significant at the 0.05 level.

Relationships of birth weight and postnatal weight gain with cognition and behavioural problems

Among preterm children (Table 2, top panel), birth weight was not associated with full-scale IQ, controlling for sex; postnatal weight gain was positively associated with full-scale IQ at 4–7 years of age ($P < 0.01$), and a 1-unit increment of Z-score in postnatal weight gain was associated with a 1.94-point (95% CI: 0.44–3.44) increase in full-scale IQ, with an effect size of 0.1. Adjustment for confounders

Table 1 Characteristics of Chinese children by sex [mean (standard deviation) or percentage]

Characteristics	Preterm children		Term children	
	Boys (N = 388)	Girls (N = 266)	Boys (N = 4036)	Girls (N = 3699)
Birth weight (kg)	3.05 (0.48)	2.99 (0.47)	3.41 (0.39)	3.29 (0.38)
Birth weight<2.5 kg (%)	10.5	11.3	0.7	1.2
Birth weight for age Z-score	−0.67 (1.06)	−0.57 (1.09)	0.10 (0.78)	0.10 (0.82)
Postnatal weight for age Z-score	−1.21 (0.81)	−1.20 (0.86)	−1.17 (0.85)	−1.23 (0.79)
Underweight (%)	16.5	15.4	14.1	15.1
Postnatal height for age Z-score	−2.00 (0.93)	−1.93 (0.86)	−1.95 (0.94)	−1.93 (0.91)
Postnatal head circumference	51.1 (1.6)	50.3 (1.6)	50.8 (1.4)	50.1 (1.4)
Taking folic acid during pregnancy (%)	48.7	51.1	51.5	51.1
First born (%)	54.6	56.8	54.3	55.1
Age of child (months)	69.0 (7.4)	69.0 (7.0)	68.4 (7.4)	68.3 (7.4)
Mother's age at child's birth (years)	25.8 (3.6)	25.3 (3.3)	25.6 (3.1)	25.6 (3.1)
Gestational age (days)	254.9 (13.1)	254.9 (12.6)	281.4 (8.3)	282.3 (8.4)
Pre-pregnancy maternal weight (kg)	62.3 (7.6)	62.2 (6.6)	64.2 (7.3)	63.8 (7.1)
Maternal height (cm)	159.4 (4.3)	158.9 (4.5)	159.1 (4.5)	159.1 (4.3)
Mother's education (%)				
High school and above	18.6	19.6	20.9	20.9
Junior high school	63.7	63.2	61.4	60.2
Elementary school and below	17.8	17.3	17.8	18.9
Maternal IQ	93.9 (17.0)	94.3 (15.8)	94.8 (16.4)	94.5 (16.5)
Father's occupation (%)				
Agricultural worker	45.1	45.1	48.2	48.0
Industrial worker	39.2	38.7	36.5	36.4
Government employee/office worker	8.5	7.9	8.6	8.5
Other	7.2	8.3	6.6	7.1
Urban residency (%)	41.2	33.1	38.2	38.3
Child's general IQ	100.1 (15.6)	97.9 (15.6)	100.2 (16.3)	98.2 (16.4)
Externalizing behavioural problems	8.9 (6.1)	7.1 (5.6)	9.0 (6.4)	7.5 (5.7)
Internalizing behavioural problems	5.0 (4.9)	4.9 (4.5)	4.7 (4.8)	5.0 (4.9)
Other behavioural problems	9.2 (7.0)	8.5 (7.0)	8.9 (7.0)	8.6 (6.9)

Source: China-U.S. Collaborative Project for Neural Tube Defect Prevention.

including birth order, gestational age, pre-pregnancy maternal height and weight, mother taking folic acid supplement, mother's education, father's occupation, urban/rural residence and mother's IQ substantially attenuated the association toward the null (0.90; 95% CI: −0.45 to −2.25; $P = 0.18$). In addition, the R-square values suggested that birth weight, postnatal weight gain and sex of child explained 12.5% of the variance in IQ; with the addition of potential confounders, a total of 32.0% of variance in IQ was explained.

Regarding the behavioural outcomes, postnatal weight gain, rather than birth weight, is negatively associated with internalizing behavioural problems when controlling for sex of child, and an increment of 1 point in postnatal weight gain was associated with a 0.48-point (95% CI: 0.02–0.94; $P = 0.04$) decrease in child's internalizing behavioural problems, but this association was no longer significant ($P = 0.06$) after adjusting for confounders. Neither birth weight nor postnatal weight gain was associated with externalizing behavioural problems or other behavioural problems.

The lower panel (Table 2) presents the results for term children. Both birth weight and postnatal weight gain were positively associated with full-scale IQ of the child when controlling for sex of the child. A 1-unit increment of Z-score in birth weight was associated with a 1.91-point (95% CI: 1.48–2.34; $P < 0.001$) increase in IQ, with an effect size of 0.09; and an increment of 1 point in postnatal weight gain was associated with a 0.87-point (95% CI: 0.43–1.30;

Table 2 Coefficient estimates (95% CI) of relationships of birth weight and postnatal weight gain with IQ and behavioural problems among Chinese children 4–7 years of age

Sample	Variable	IQ		Internalizing behavioural problems		Externalizing behavioural problems		Other behavioural problems	
		Adjusted for sex	Adjusted for other factors[a]	Adjusted for sex	Adjusted for other factors[a]	Adjusted for sex	Adjusted for other factors[a]	Adjusted for sex	Adjusted for other factors[a]
Preterm children	Z-score of birth weight	0.20 (−0.90, 1.29)	0.02 (−1.02,1.07)	−0.11 (−0.45,0.23)	0.02 (−0.34,0.38)	−0.06 (−0.49,0.35)	−0.01 (−0.46, 0.43)	−0.04 (−0.53,0.44)	0.04 (−0.48, 0.57)
	Postnatal weight gain	1.94 (0.44,3.44)	0.90 (−0.45, 2.25)	−0.48 (−0.94,−0.02)	−0.45 (−0.92, 0.02)	−0.19 (−0.76,0.38)	−0.28 (−0.86, 0.29)	−0.29 (−0.95, 0.38)	−0.29 (−0.97, 0.39)
	R-square	**0.125**	**0.320**	**0.106**	**0.118**	**0.140**	**0.178**	**0.137**	**0.158**
Term children	Z-score of birth weight	1.91 (1.48,2.34)	1.60 (1.18, 2.02)	−0.09 (−0.22,0.05)	−0.03 (−0.17, 0.11)	−0.10 (−0.26, 0.06)	−0.14 (−0.31, 0.04)	−0.15 (−0.34,0.03)	−0.13 (−0.33, 0.07)
	Postnatal weight gain	0.87 (0.43, 1.30)	0.46 (0.06, 0.86)	−0.09 (−0.23, 0.04)	−0.09 (−0.23, 0.04)	0.05 (−0.11, 0.22)	−0.00 (−0.17, 0.17)	0.04 (−0.14, 0.23)	0.03 (−0.16, 0.22)
	R-square	**0.134**	**0.281**	**0.063**	**0.070**	**0.086**	**0.101**	**0.098**	**0.109**

[a]Other factors include birth order and gestational age of child, pre-pregnancy maternal height and weight, mother taking folic acid supplement during pregnancy, mother's education and IQ, father's occupation and urban residency.
Source: China-U.S. Collaborative Project for Neural Tube Defect Prevention.

p < 0.001) increase in IQ, with an effect size of 0.04. After adjusting for confounders, the magnitude of the association between birth weight and IQ was reduced to 1.60 (95% CI: 1.18–2.02; $P < 0.001$) and that between postnatal weight gain and IQ to 0.46 (95% CI: 0.06–0.86; $P = 0.02$).

Regarding the behavioural outcomes, none of internalizing behavioural problems, externalizing behavioural problems or other behavioural problems was associated with Z-score of birth weight or conditional postnatal weight gain among term children.

Relationships of birth weight and alternative postnatal growth indicators with cognition and behavioural problems

Table 3 presents the relative importance of birth weight and postnatal growth to cognition and behavioural problems when the Z-score of height at age 4–7 years was used as an indicator of postnatal growth.

Among preterm children (upper panel, Table 3), postnatal height, rather than birth weight, was positively associated with IQ ($P = 0.03$), controlling for sex; a 1-unit increase in Z-score of postnatal height was associated with a 1.59-point (95% CI: 0.18–3.01) increase in child's IQ, with an effect size of 0.1. After adjusting for confounders, the magnitude of the association was attenuated by about 60% to 0.68 (95% CI: −0.59 to 1.94; $P = 0.29$).

The lower panel (Table 3) presents results among term children. Both birth weight and postnatal height were positively associated with IQ of child, controlling for sex ($P < 0.001$). A 1-unit increment of Z-score in birth weight was associated with a 1.66-point (95% CI: 1.23–2.09) increase in IQ, with an effect size of 0.08; and a 1-unit increment of Z-score in postnatal height was associated with a 1.49-point (95% CI: 1.07–1.92) increase in IQ, with an effect size of 0.08. After adjusting for confounders, the association of IQ with postnatal height was reduced to 0.82 (95% CI: 0.46–1.17; $P < 0.001$) and that with birth weight was reduced slightly to 1.49 (95% CI: 1.07–1.92; $P < 0.001$).

Table 3 also shows that for both preterm children (upper panel) and term children (lower panel), neither birth weight nor postnatal height was associated with any of the behavioural outcomes including internalizing behavioural problems, externalizing behavioural problems or other behavioural problems.

As shown in Table 4, results using head circumference at age 4–7 years as an alternative indicator of postnatal growth were very similar to those using height at age 4–7 years as an indicator of postnatal growth (Table 3).

Results from additional analyses

For easier interpretation of the results, linear regression models were employed in the main analysis above, which assume that every 1-unit change in growth variables results in the same change in

Table 3 Coefficient estimates (95% CI) of relationships of birth weight and postnatal height with IQ and behavioural problems among Chinese children 4–7 years of age

		IQ		Internalizing behavioural problems		Externalizing behavioural problems		Other behavioural problems	
Sample	**Variable**	Adjusted for sex	Adjusted for other factors[a]	Adjusted for sex	Adjusted for other factors[a]	Adjusted for sex	Adjusted for other factors[a]	Adjusted for sex	Adjusted for other factors[a]
Preterm children	Z-score of birth weight	−0.05 (−1.16, 1.06)	−0.08 (−1.13, 0.97)	−0.06 (−0.40, 0.28)	0.07 (−0.30, 0.43)	−0.05 (−0.47, 0.37)	0.03 (−0.41, 0.48)	0.01 (−0.48, 0.50)	0.13 (−0.40, 0.65)
	Postnatal height	1.59 (0.18, 3.01)	0.68 (−0.59, 1.94)	−0.34 (−0.77, 0.10)	−0.31 (−0.75, 0.12)	−0.11 (−0.65, 0.42)	−0.16 (−0.70, 0.37)	−0.36 (−0.98, 0.27)	−0.35 (−0.98, 0.28)
	R-square	**0.123**	**0.319**	**0.103**	**0.115**	**0.140**	**0.166**	**0.138**	**0.151**
Term children	Z-score of birth weight	1.66 (1.23,2.09)	1.49 (1.07, 1.92)	−0.08 (−0.21, 0.06)	−0.02 (−0.16, 0.13)	−0.11 (−0.27, 0.06)	−0.12 (−0.30, 0.05)	−0.17 (−0.35, 0.02)	−0.13 (−0.33, 0.07)
	Postnatal height	1.49 (1.10, 1.89)	0.82 (0.46, 1.17)	−0.07 (−0.19, 0.05)	−0.07 (−0.20, 0.05)	0.02 (−0.13, 0.17)	−0.05 (−0.20, 0.10)	0.08 (−0.09, 0.25)	0.05 (−0.12, 0.22)
	R-square	**0.138**	**0.296**	**0.063**	**0.067**	**0.086**	**0.099**	**0.098**	**0.106**

[a]Other factors include birth order and gestational age of child, pre-pregnancy maternal height and weight, mother taking folic acid supplement during pregnancy, mother's education and IQ, father's occupation and urban residency.
Source: China-U.S. Collaborative Project for Neural Tube Defect Prevention.

Table 4 Coefficient estimates (95% CI) of relationships of birth weight and postnatal head circumference with IQ and behavioural problems among Chinese children 4–7 years of age

		IQ		Internalizing behavioural problems		Externalizing behavioural problems		Other behavioural problems	
Sample	**Variable**	Adjusted for sex	Adjusted for other factors[a]	Adjusted for sex	Adjusted for other factors[a]	Adjusted for sex	Adjusted for other factors[a]	Adjusted for sex	Adjusted for other factors[a]
Preterm children	Z-score of birth weight	−0.12 (−1.23, 0.99)	−0.05 (−1.08, 0.98)	−0.10 (−0.45, 0.24)	0.01 (−0.35, 0.37)	−0.12 (−0.54, 0.30)	−0.03 (−0.47, 0.41)	−0.05 (−0.54, 0.44)	0.09 (−0.42, 0.61)
	Postnatal head circumference	1.10 (0.31, 1.89)	0.30 (−0.42, 1.02)	0.03 (−0.21, 0.28)	0.05 (−0.20, 0.29)	0.25 (−0.05, 0.55)	0.20 (−0.10, 0.50)	0.05 (−0.30, 0.40)	0.07 (−0.29, 0.43)
	R-square	**0.126**	**0.319**	**0.100**	**0.111**	**0.143**	**0.168**	**0.136**	**0.150**
Term children	Z-score of birth weight	1.46 (1.03, 1.90)	1.24 (0.82, 1.66)	−0.09 (−0.22, 0.05)	−0.03 (−0.17, 0.12)	−0.12 (−0.29, 0.05)	−0.13 (−0.31, 0.05)	−0.13 (−0.32, 0.06)	−0.09 (−0.29, 0.12)
	Postnatal head circumference	1.49 (1.22, 1.76)	1.05 (0.80, 1.29)	−0.00 (−0.08, 0.08)	−0.01 (−0.09, 0.08)	0.07 (−0.03, 0.17)	0.02 (−0.08, 0.12)	−0.08 (−0.19, 0.04)	−0.10 (−0.22, 0.02)
	R-square	**0.146**	**0.301**	**0.063**	**0.067**	**0.086**	**0.099**	**0.098**	**0.107**

[a]Other factors include birth order and gestational age of child, pre-pregnancy maternal height and weight, mother taking folic acid supplement during pregnancy, mother's education and IQ, father's occupation and urban residency.
Source: China-U.S. Collaborative Project for Neural Tube Defect Prevention.

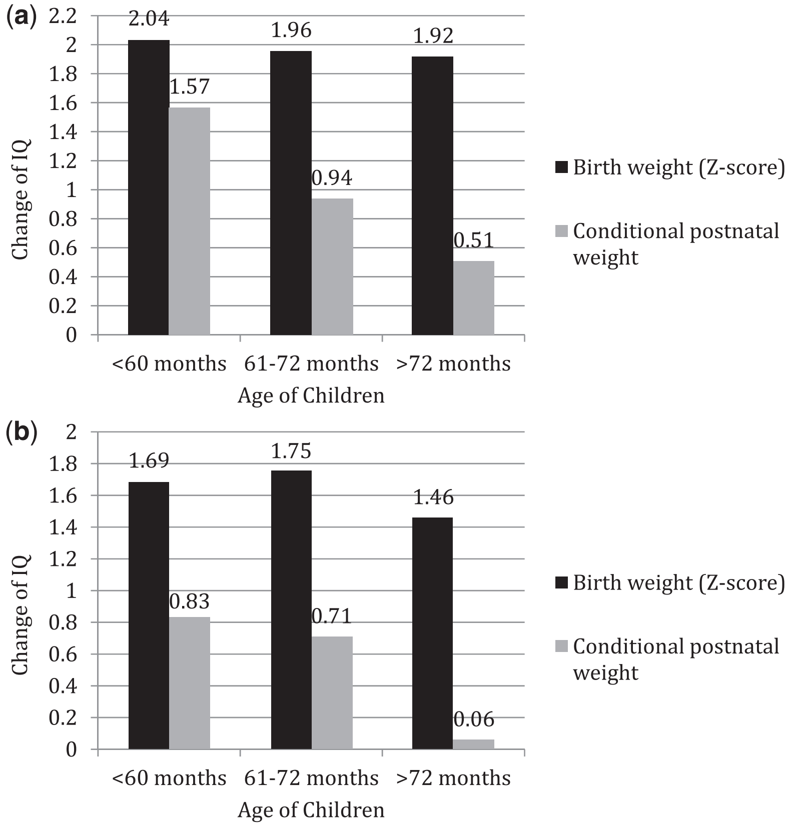

Figure 1 Estimated changes of children's IQ for one unit change in Z-score of birth weight and conditional postnatal weight by age of children (**a**) controlling for sex; (**b**) controlling for confounders

outcome variables across the entire distribution of the exposure variables. The alternative analyses in which intelligence score is modeled as a nonlinear function of birth weight Z-score and the square of birth weight Z-score, plus other variables, showed slightly improved prediction compared with linear regression without square term of birth weight Z-score. Results from non-linear regression suggested that the effect of birth weight on intelligence score is greater when birth weight is lower than that at higher values of birth weight, until birth weight reaches approximately 4.1 kg (1.9 SD above the mean of the Z-score of birth weight in this sample), beyond which point birth weight starts to be negatively associated with intelligence. The pattern is consistent with the quadratic shape of the relation between birth weight and IQ observed in other studies.[18,19]

To test whether the impacts of birth weight and postnatal growth on IQ decline with age, further analyses were also conducted with subsamples divided by age. As shown in Figure 1, the relation between birth weight and IQ is consistent across ages, whereas postnatal weight has greater effect on IQ at younger age than older age. For children aged 48-60 months, a 1-unit increment in Z-score of postnatal weight is associated with a 1.57-point (95% CI: 0.11–3.02; $P = 0.03$) increment in IQ controlling for sex, whereas the association decreases to 0.94 (95% CI: 0.31–1.57; $P = 0.003$) for children aged 61–72 months, and toward the null (0.51; 95 CI: −0.14, 1.16; $P = 0.12$) for children aged 72 months and above. Similar patterns were observed with other postnatal growth variables.

In our sample, the distributions of both externalizing behavioural problems and other behavioural problems were right skewed, and internalizing behavioural problems were not normally distributed either. We also tested whether findings from the main analyses based on normal distribution assumption were robust. In alternative analyses with externalizing behavioural problems and other behavioural problems as outcome variables, we regressed the natural logarithm of the value of outcome variables (we added 0.1 to the value of outcome variables for all the cases to avoid taking the natural logarithm of zero) on birth weight and postnatal growth. In the alternative analysis with internalizing behavioural problems as the outcome variable, we first classified internalizing behavioural problems into five ordered categories by degrees of severity, and then used cumulative logit models to estimate the relative importance of birth weight and postnatal growth. These alternative analyses yielded similar findings regarding the relative importance of birth weight and postnatal growth on behavioural outcomes (results available upon request).

Finally, to test whether these results regarding the relative importance of birth weight and postnatal growth (Tables 2–4) were different between urban children and rural children, we added interaction terms between the growth indicators and urban/rural residence. All the P-values for these interactions were smaller than 0.05, which suggests that the relationships of prenatal growth and postnatal growth on cognition and behavioural problems were very similar for rural children and urban children.

Discussion

We investigated the relative importance of birth weight and postnatal growth in cognitive and behavioural outcomes in a large longitudinal cohort aged 4–7 years among both preterm children and term children in China.

Among preterm children, we found no association between birth weight and any outcome variable including IQ, internalizing behavioural problems, externalizing behavioural problems and other behavioural problems, whereas postnatal weight gain was positively associated with IQ and negatively associated with internalizing behavioural problems. Previous studies report similar findings and conclude that postnatal catch-up growth is crucial for development of pre-term children, especially for their cognitive functioning and neurodevelopment.[60–64] However, this beneficial effect of catch-up growth was not robust to adjustment for confounders including family SES and mother's IQ in our results, which may suggest an alternative mechanism underlying this association. For example, better family SES and higher mother's IQ may improve both postnatal catch-up growth and cognitive development for preterm children. These findings regarding relative importance of birth weight and postnatal growth among preterm children were primarily based on 'late preterm' children who had an average gestational age of 36.4 weeks and showed successful postnatal catch-up growth in terms of weight, height and head circumference at ages 4–7 years; and whether these findings are applicable to children born very preterm merits further research. Previous studies found that the smaller the birth weight, the longer compensatory growth toward normal continues,[55] and lack of 'catch-up' growth primarily occurs among small for gestational age (SGA) preterm children.[65]

Among term children, neither birth weight nor postnatal growth predicted any behavioural outcome, whereas both birth weight and postnatal growth were associated with child's IQ at age 4–7 years, independently of a wide array of potential confounding variables. It is worth noting that all these associations were very small in terms of effect sizes. For example, the effect size for association with IQ is 0.09 for birth weight and 0.05 for postnatal weight gain, i.e. an increment of one SD in birth weight is associated with about 1.6 IQ points and an increment of one SD in postnatal weight is associated with about 0.8 IQ points. Such small effect sizes were also observed in other studies.[11,13] For example, a study on 11899 Canadian children aged 6.5 years found that 1 SD in birth weight was associated with 0.82 IQ points (95% CI: 0.54–1.10) after adjusting for confounders, with an effect size of 0.05. For postnatal weight gain trajectories, 1 SD faster weight gain during 0–3 months, 3–12 months and 1–5 years was associated with an increase of 0.77 (95% CI: 0.42–1.11) IQ points (effect size = 0.05), 0.30 (95% CI: 0.02–0.58) IQ points (effect size = 0.02) and 0.40 (95% CI: 0.04–0.76) IQ points (effect size = 0.03), respectively, controlling for confounders and earlier growth. Sizes of the effects observed in studies that relied on neurobehavioural endpoints are often small.[66] Such a small effect may not be clinically important for individual children, but should not be considered inconsequential at the population level,[14,27] as 'a large number of people at a small risk may give rise to more cases of disease than the small number who are at a high risk'.[67] Therefore, nutritional interventions targeting underweight children in developing countries such as India, where 47% of children under 3 years old were underweight and 18% were severely underweight,[68] may present a good strategy to avoid the considerable loss of IQ and developmental potentials in children in these countries.[69]

Several mechanisms may explain the significant, albeit weak, relationships between growth and cognition. First, proper nutrition during the critical first 1000 days (pregnancy and first 2 years) is vital for both normal growth and brain development, and nutritional deficits have long-term implications for cognitive function, school success and human capital.[20,70,71] For example, iodine deficiency during pregnancy is associated with both impaired foetal growth and delayed brain development.[72] A meta-analysis suggested that iodine deficiency was associated with a fall of 12 IQ points.[73] Malnutrition during the first 1000 days may also reduce the numbers of neurons and synapses, dendritic arborization, and myelination, and consequently result in decreased brain size;[74] it may cause changes in the structure or biochemistry of the brain and impair the functioning of the central nervous system.[71]

Another potential mechanism for the association between IQ and body size may be related to insulin-like growth factor (IGF) and growth hormone (GH).[75] IGF and GH play a critical role in determining somatic growth and are also located in key regions of the brain responsible for learning and memory. Increasing evidence suggests IGF may impact on cognitive brain function.[76] In children born small for gestational age, GH therapy led to catch-up growth as well as improvements in IQ scores.[77]

In addition, environmental factors, such as diet and childhood illness, may mediate the association between growth and cognitive development. More subtle mechanisms are also possible. Malnourished children are stunted and thus appear younger which may hamper positive interaction with others, particularly adults; stunted children may be less likely to be challenged to explore and expand their capability by parents and teachers, which may negatively impact on cognitive and behavioural development.[33] 'Functional isolation' may also contribute, whereby malnourished infants are less active or attentive and seek less stimulation from their physical and social environments.[78]

Caution should be exercised in interpreting findings from this study. First, although we adjusted for a rich set of confounding factors, including maternal IQ, we cannot exclude the possibility that these observed associations were due to residual confounding by other factors. For example, households that provide better care to pregnant women may also provide more cognitively stimulating growth environments later for the newborn, which may improve children's IQ.[79] Previous sibling studies and twin studies that rule out genetic and shared environmental factors/confounders suggest that such familial confounding is less likely to be important.[18,19,80] Second, postnatal growth in our study was measured at a single point at age 4–7 years, and the results cannot speak as to whether the earlier postnatal period may have a greater effect on cognition and behavioural development.[81] There is evidence that adverse effects of postnatal growth failure on intellectual development may decline over time,[25] which is consistent with our finding that postnatal growth has a larger association with IQ among younger children and that the association is toward the null among children aged 6 years and above. Third, because birth length and head circumference were measured very imprecisely, we used only birth weight as the proxy for prenatal growth,[27] which prevented us from assessing associations with growth in height/head circumference during childhood independently of birth length/head circumference at birth. Fourth, the relatively small sample size of preterm children and the lesser statistical power may not allow detection of potential associations between birth weight and IQ and behavioural outcomes among preterm children, if these associations are small. Finally, our sample may not necessarily represent other developing countries. Although underweight and stunting are prevalent among Chinese children,[82] China has a very low prevalence of low birth weight, lower than most developing countries and some developed countries,[83] which is possibly due to its cultural practices and universal access to basic health and education.[84]

Despite these limitations, our study contributes to a better understanding of early growth and child development with several strengths. First, it benefited from its longitudinal nature and the large sample with careful measurements by well-trained professionals on key variables such as cognitive and behavioural development of a child. Second, we adjusted for gestational age, which makes birth weight a more accurate proxy of foetal growth. Third, we investigated both cognitive development and behavioural problems, whereas most previous studies focused on either cognition or behavioural dimensions. Finally, we applied rigorous methods to address methodological issues caused by the correlation between birth weight and postnatal weight.

Findings from our study and others confirm links between child growth and cognitive development, although mechanisms underlying these links remain unclear and merit further investigation. Future studies should improve measurements of growth including weight, height/length, head circumference at birth and multiple postnatal time points, and include populations with more severe malnutrition and prenatal and postnatal growth failure. When data become available, a sibling study or twins study design would be highly desirable.[19]

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