Associations of head circumference trajectories and growth-sensitive periods during the first two years of life with adolescent cognitive, emotional and behavioral health: A birth cohort in rural western China

Zhonghai Zhu
Xi'an Jiaotong University
Jiali Shen
Xi'an Jiaotong University
Yingze Zhu (zhuyingze@stu.xjtu.edu.cn)
Xi'an Jiaotong University https://orcid.org/0000-0001-5571-704X
Liang Wang
Xi'an Jiaotong University
Qi Qi
Xi'an Jiaotong University
Xueyao Wang
Xi'an Jiaotong University
Chao Li
Xi'an Jiaotong University
Amanuel Kidane Andegiorgish
Xi'an Jiaotong University
Mohamed Elhoumed
Xi'an Jiaotong University
Yue Cheng
Xi'an Jiaotong University
Michael J Dibley
The University of Sydney School of Public Health
Lingxia Zeng
Xi'an Jiaotong University

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Abstract

Purpose

The associations of early-life head circumference (HC) with child cognition and emotional and behavioral health among generally healthy population remain unclear. We aimed to examine the associations of early-life HC trajectories with adolescent neurodevelopmental and mental health and to identify HC growth-sensitive period.

Methods

We conducted a prospective, community-based birth cohort in rural western China, and 745 adolescents aged 10-14 years were followed between June to December 2016. We repeatedly assessed child HC for eight times during the first two years of life, and adolescent cognitive and emotional and behavioral outcomes using Wechsler Intelligence Scale for Children and Youth Self-Report, respectively. We applied group-based trajectory modeling to identify HC trajectories and used conditional growth to derive sensitive periods.

Results

We identified five distinct HC trajectories characterized as Start below average-then decrease (7.8% of the sample), Start below average-then increase (6.8%), Start average-then decrease (33.4%), Consistently average (37.9%), and Consistently above average (14.1%). Infants in the trajectory of consistently above average had higher cognitive scores at early adolescence as compared to those from suboptimal trajectories, with adjusted mean differences ranging from -2.84 to -8.99 points. The conditional gains show that the sensitive HC growth period appeared to be between 0-6 months. While we found null associations between HC measures and adolescent emotional and behavioral health.

Conclusions

Routine HC measurements especially during the first 6 months were recommended for monitoring child cognition but for mental health. Integrated prenatal and postnatal interventions should be pursued to promote child development.

What Is Known

Postnatal head circumference (HC) has been shown to be associated with cognitive development in infants who were born prematurity and/or fetal growth restriction, while inconsistent associations were reported among generally healthy population especially in low- and middle- income countries, challenging its utility in public health practices.

What is new

We identified five distinct HC trajectories during the first two years of life, and only 6.8% of the sample showed HC growth improvement to the average after prenatal growth restriction.

Adolescents in HC growth trajectory of consistently above average had higher cognitive scores at adolescence as compared to those in other suboptimal trajectories. However, null findings were observed for adolescent emotional and behavioral health.

Routine HC measurements especially during the first 6 months were recommended for monitoring child cognition but for mental health.

Introduction

Globally, most adolescents are characterized by suboptimal cognitive, emotional, and behavioral health that impair their potential to thrive in adulthood.[1] Measures of cognitive function and mental health are of great importance for implementing programs of promoting early childhood development, but these outcomes are difficult to assess in general population. Anthropometric measurements may serve as a surrogate for suboptimal developmental outcomes, thereby signaling timely interventions. Postnatal head circumference (HC) was associated with cognitive development in infants who were born prematurity and/or fetal growth restriction.[2-4] However, inconsistent results between HC and developmental outcomes were documented in generally healthy infants and young children,[5,6] which used summary measures at a single-time point rather assessed the dynamic changes of HC growth, challenging its utility as a surrogate in public health practices.

Kirkegaard and colleagues reported that a higher HC *z*-score between 12 months and 5 years of age was associated with increased scores of cognitive tests at age 5 in Denmark.[7] Similar positive associations of HC growth at two-time points with child neurodevelopment were reported in other developed settings.[8,9] While, Dupont and colleagues reported a null association between HC growth in birth-12 months and cognitive functions at age 24 months in Canada.[10] Trajectory analysis using repeated HC measures may shed light on this link. Few studies from low- and middle- income countries (LMIC) assessed HC growth and reported its association with long-term developmental outcomes. [11] In addition, the association of early life HC growth with adolescent emotional and behavioral health was much less studied with inconsistent results.[12,13] Therefore, given the limited health resources especially in LMICs, it is meaningful to further clarify the link between early-life HC and child cognitive and mental outcomes and identify the HC growth sensitive periods for optimizing population monitoring.

In this paper, we used data from a birth cohort in rural western China that repeatedly assessed the HC for eight times since birth during the first two years of life. We aimed to examine the associations of HC trajectories from birth to two years of age with cognitive, emotional and behavioral outcomes at early adolescence aged 10-14, and to identify HC growth-sensitive periods.

Methods

Study design and participants

We analyzed data from a prospective birth cohort of children born to mothers who participated in a double-blind, cluster-randomized controlled trial in rural western China, which has been described in detail elsewhere.[14] Briefly, pregnant women from every village in two counties were randomized to daily consume a capsule of folic acid, iron/folic acid, or multiple micronutrients between 1st August 2002 and 28th February 2006. 1400 singleton births from the parent trial after 2004 were enrolled for long-term follow-up, and 1388 were followed during the first two years of age. Among them, 745 were followed at early adolescence aged 10-14 years between 1st June and 31st December 2016 (see Supplementary online material: Figure S1). Data analyses took place from 1st October 2020 to 30th April 2021. The trial and follow-up evaluation protocols were approved by the Ethics Committee in Xi'an Jiaotong University Health Science Center. Written informed consent was obtained from the biological parents or caregivers, while verbal consent was obtained from all the participants depending on their age.

Measurements

Anthropometric measurements

We measured HC in maximum frontooccipital circumference at birth, 1, 3, 6, 9, 12, 18, and 24 months of age. Field workers from public health graduates implemented all these measurements using a flexible tape by standardized procedures. We standardized all these measures into z-scores using the INTERGRROWTH-21st and WHO growth standard for birth and postnatal HCs, respectively.[15,16]

Cognitive development and emotional and behavioral health assessments

We administered the scale of Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV) among adolescents in a school meeting room. We derived the age-standardized full-scale intelligence quotient (FSIQ) to represent adolescent general cognitive ability and verbal comprehension (VCI), perceptual reasoning (PRI), working memory (WMI), and processing speed index (PSI) to assess other aspects of cognitive development.[17] At the same day, we applied the Youth Self-Report (YSR-2001) of the Achenbach System of Empirically Based Assessment (ASEBA) to assess the emotional and behavioral outcome which was completed by adolescents themselves after uniform instructions.[18] Eight narrow-band scales or syndromes i.e., Anxious/Depressed, Withdrawn, Somatic Complaints, Social Problems, Thought Problems, Attention Problems, Delinquent/Rule-Breaking Behavior and Aggressive Behavior, and three broad-band scales i.e., scores of Internalizing Behavior Problems (constituting by Anxious/Depressed, Withdrawn and Somatic Complaints), Externalizing Behavior Problems (constituting by Delinquent/Rule-Breaking Behavior and Aggressive Behavior) and Total Behavior Problems, were derived. All these scales were localized and qualified in Chinese norms with satisfying reliability.

Covariates

The following covariates were potentially included in the present study. Socioeconomic characteristics at enrollment included parent age, education, occupation and household wealth. The wealth index was constructed by principal component analysis using the 16 household assets or facilities, and then categorized into low-, medium-, and high-income households. Antenatal randomized regimens with durations were classified into folic acid or folic acid plus iron <180 days, folic acid plus iron ≥180 days, multiple micronutrients <180 days, and multiple micronutrients ≥180 days. Maternal reproductive history was indicated by parity. Birth outcomes mainly included birth weight-for-gestational age and sex z-score calculated by INTERGRWOTH, preterm birth (<37 gestational weeks), low birth weight (<2500 g), small-for-gestational age (SGA, <10th by INTERGROWTH)[15] and sex. All the information obtained from the parent trial by face-to-face interview, and/or standard procedures were detailed elsewhere.[14]

Statistical analyses

To identify infant HC *z*-score trajectories across birth, 1, 3, 6, 9, 12, 18, and 24 months of age, we conducted a group-based trajectory modelling that could efficiently segment the sample into mutually exclusive and exhaustive subgroups of individuals with similar growth patterns.[19] We decided the final trajectories by comprehensively accounting for the following principles as well as parsimoniously summarizing the data features: i) statistically significant tests of parameter estimates for linear, quadratic, cubic or quartic terms, ii) lower Bayesian and Akaike information criterion values, ii) average of the posterior probabilities of group membership for individuals assigned to each group >0.7, and iv) odds of correct classification based on the posterior probabilities of group membership >5.

We then compared the characteristics among the trajectory groups using Chi-squared tests or analysis of variance. Further, the multivariable multinomial logistic regressions were used to examine the predictors of HC trajectories. In addition, we performed generalized estimating equations to estimate the associations of HC trajectories with adolescent cognitive development and emotional and behavioral health. For general interests, we examined the associations of HC *z*-score at single-time point with adolescent developmental outcomes.

To help identify the sensitive periods of HC growth, we calculated the conditional growth of HC in the following periods: 0-1, 1-3, 3-6, 6-12, 12-18, 18-24, 0-3, 0-6, 0-12, 0-24 and 12-24 months,[20] and then examined their associations with adolescent developmental outcomes using generalized estimating equations.

We took the FSIQ and scores of total behavior problems, internalizing and externalizing behavioral problems as primary outcomes, and the other aspects of cognitive development and mental health as secondary outcomes, respectively. All statistical analyses were conducted by using Stata 15.0 (Stata Corp, College Station, Texas, USA). A two-sided *P* value < 0.05 was considered statistical significance.

Results

Background characteristics of participants

Table 1 presents the background characteristics of 745 children who were followed through infancy into early adolescence. Most mothers had education of secondary (54.4%), and 83.7% of mothers lived on farming. At early adolescence, the mean age was 11.3±0.6 years, and 60.4% were male. The mean scores of adolescent FISQ and total behavioral problem were 98.1 (±12.5) and 47.0 (±23.9) points, respectively. In addition, supplementary online material (Table S1) shows the balance of background characteristics between adolescents followed and those lost to follow-up.

HC growth trajectories during the first two years of life

Five distinct HC growth trajectories

We identified five distinct HC growth trajectories (Figure 1) which were labeled as “Subgroup 1: Start below average-then decrease” (7.8%), “Subgroup 2: Start below average-then increase” (6.8%), “Subgroup 3: Start average-then decrease” (33.4%), “Subgroup 4: Consistently average” (37.9%), and “Subgroup 5: Consistently above average” (14.1%). Supplementary online material (Table S2) presents the criteria of model selections.

Factors associated with HC growth trajectories

We then examined the factors associated with infant HC growth trajectories (supplementary online material Table S3 and Table S4). We observed that infants born to mothers who had higher education level were less likely to be in the trajectories of small HC. While, female sex, preterm birth and SGA were statistically significantly associated with increased likelihood of being in the lower HC trajectories. Besides, infants who were born small had reduced odds of being in the trajectory of Start below average-then increase.

Predictive role of HC trajectories

Table 2 presents the associations of early life HC growth trajectories with adolescent FSIQ and scores of total behavioral, internalizing and externalizing behavior problems. We found that the mean scores of adolescent FSIQ increased from low to high HC growth trajectories, while, this pattern was not observed in emotional and behavioral outcomes. The adjusted FSIQ differences were -8.99 (95% CI -13.69, -4.28) points for Subgroup 1, -5.80 (95% CI -9.79, -1.82) points for Subgroup 2, -5.22 (95% CI -8.13, -2.31) points for Subgroup 3, and -2.84 (95% CI -4.93, -0.75) points for Subgroup 4 as compared with the highest HC growth trajectory (Subgroup 5), respectively. We also observed that adolescents from Subgroup 1 (Start below average-then decrease) had statistically significantly lower scores of FSIQ than those in Subgroup 2 (Start below average-then increase; -6.72 points, 95% CI -12.24, -1.19), while we found insignificant differences of FSIQ between adolescents in Subgroup 2 (Start below average-then increase) and those in Subgroup 4 (Consistently average).

In addition, we found inconsistent associations of HC growth trajectories with other aspects of adolescent cognitive and emotional and behavioral outcomes in supplementary online material (Table S5 and Table S6).

Sensitive periods of HC growth for adolescent cognitive, emotional and behavioral outcomes

As shown in Figure 2, we observed that per standardized residual of conditional HC growth between birth and 3 months, and between birth and 6 months of age were associated with 0.44 (95% CI -0.04, 0.93) and 0.72 (95% CI 0.24, 1.19) higher points of adolescent FSIQ, respectively. Yet, we did not observe associations between conditional HC growth and adolescent emotional and behavioral outcomes. Results for other aspects of adolescent cognitive and emotional and behavioral outcomes (supplementary online material: Table S7 and Table S8) generally agreed with the results for primary outcomes above. In addition, supplementary online material (Table S9) in the supplement presents the inconsistent associations of HC *z*-score at sing-time point with adolescent cognitive, emotional and behavioral outcomes.

Discussions

We identified five distinct head circumference growth trajectories during the first two years of life which were associated with socioeconomic factors and birth outcomes. Only a small subsample showed head circumference growth improvement to the average. Further, these trajectories could robustly predict adolescent cognitive test scores but not emotional and behavioral outcomes. In addition, the sensitive window of head circumference growth within the first two years for cognitive development appears to be the period of birth to 6 months of age.

To the best of our knowledge, our study is the first to apply group-based trajectory modelling to draw HC trajectory within the critical window of first two years of life which accounts for the heterogeneity of HC growth within a population and its non-linear relationship with developmental outcomes.[5,7] Half of the sample in the Consistently average and Consistently above average had determined HC growth trajectory since birth, suggesting the potentially permanent influences of birth outcomes on postnatal HC growth.[21] The remaining three trajectories indicate the modifiable impacts of postnatal factors on early HC growth. Of note, only a small subsample (6.8%) after experiencing prenatal deficits could catch up to the average and still was below the optimal Subgroup 5, i.e., growth consistently above average. This finding is accordance with a review that postnatal interventions and dramatic improvements of the caring environment may lead to some growth catch-up but not complete recovery from the consequences of prenatal undernourishment.[22] Consequently, given that the HC trajectories could predict adolescent cognitive test scores in the present study, our findings suggest that prenatal deprivations may have potentially permanent influences on HC growth and further on adolescent developmental outcomes. Also, preventing maternal malnutrition and other risk exposures during preconception and pregnancy seems to be more practical for improving child development.

Regarding the influencing factors of HC trajectories, our results contribute to the evidence that higher maternal education and better birth outcomes were associated with lower risk of being in the lower HC growth trajectory. Although the underlying pathways behind these associations remain clear, together with other similar results,[23-25] this evidence suggests that the socioeconomic inequalities in HC growth emerge early and may continue to persist. Thus, further support for lower socioeconomic subpopulations from public health programs is needed. In agreement with other studies,[26] we also observed that male infants were more likely to have larger HC as compared with their female counterparts, indicating the utility of sex-specific infant growth patterns. This phenomenon was replicated in the fetus period which might be explained by the differences in placentation, sex-steroids, and its interactions with various genetic and environmental determinants.[26,27] In addition, we did not observe significant associations between antenatal micronutrient supplementation and larger size of HC trajectory, which may be due to the small sample size,[28,29] but we found that preterm birth, lower birth weight-for-gestational and sex *z*-score and SGA were statistically associated with lower HC trajectory. Pooling evidence of randomized trials shows antenatal micronutrient supplementation reduces the risk of preterm birth and SGA and improves birth outcomes.[30] Therefore, mediation of the relationship between antenatal micronutrient supplementation and HC growth by birth outcomes could be pursued in the future.

In the present study, we found that HC trajectories during the first two years could robustly predict adolescent developmental outcomes. This finding was in line with the results from other cohorts in LMICs,[6,11] and may extend to adulthood and older adults with benefits on reducing the risk of age-related cognitive dysfunction.[8] Further, the benefits could confer to school performance and academic achievements.[31,32] HC growth has been shown as a validated estimate of grey and white matter volume and their maturation in infants.[33,34] Besides, Lee and colleagues applied the principles of Mendelian randomization and found significant causal estimates of intracranial volume on human education years and intelligence.[35] Given the correlations between HC and linear growth, a well-known proxy for child well-being, another explanation may be due to the common causes of HC growth and child development, i.e., factors increasing HC growth also improving cognitive development, such as low parental education, short maternal stature, comprised birth outcomes and malnutrition in infancy.[36] Nevertheless, null findings between HC growth and cognitive development were reported in some studies, which might be due to the differences in the study setting, sample sizes, measuring methods, times of assessment and time periods, and ages at outcome assessment.[5,10,11] Using the HC *z*-score at a single-time point, we also found inconsistent associations between HC growth and cognitive development and relatively weaker estimates as compared with those using the trajectories which assessed the cumulative impacts of HC growth during the first two years of life.

In addition, the HC trajectories show that the dynamic changes of HC growth mainly occurred during the first six months after birth, which agreed well with the results of conditional HC growth in the present study. Based on the MAL-ED cohort from eight LMICs, Scharf and colleagues calculated the summative growth of HC, i.e., areas between child's growth curve and the WHO growth curve by 6-month intervals during the first two years of life. They found the strength of point estimates for cognitive development at 24 months increased by age and reached statistical significance up to 18 months of age.[11] This inconsistency may be partly explained by the residual correlations between different periods which was similar to our results using the sing-time assessment of HC growth. Sammallahti and colleagues applied a similar method of conditional growth to account for the correlations of growth among periods, and observed significant associations between HC conditional growth during 0-5 months and later intelligence quotients and academic grades.[13] Similar findings were found in another cohort in Copenhagen.[8] Therefore, these results suggest that routine HC measures during the first six months were meaningful for monitoring developmental outcomes and should be prioritized.

Emotional and behavioral problems manifest among adolescents which are becoming increasingly prevalent and have substantial impacts on the individual, family and society.[37] Our study was one of the few studies conducted in LMICs to explore the early life proxy of adolescent mental health, although we found inconsistent associations between HC growth and adolescent emotional and behavioral outcomes. This finding was similar to studies in developed setting and China.[38,39] Yet, some studies conducted among participants born with prematurity or fetal growth restriction reported that small head size was associated with a higher risk of internalizing, or attention difficulty problems among older children and young adults.[40,41] We hypothesize that the HC growth measure may be a useful proxy for mental health in a clinic context but not in a generally healthy population. For example, infants who have HC z-score < -2 SD may be the high-risk subpopulation of occurring suboptimal mental development. That said, we observed that infants in the lowest HC trajectory had statistically lower scores of total behavioral problems, internalizing and externalizing behavioral tests. This finding was in contrast to a path analysis reporting that neurological abnormalities characterized by higher Apgar score, lower head circumference, and birth weight increased the likelihood of children's antisocial behavior through comprising the intelligent quotient. Consequently, these results contribute to the confusion of the relationships among early-life anthropometric indicators and mental health outcomes later in life which warrants further studies shedding light on sex differences, broad measures, and particular aspects of mental health.[42]

Despite the strengths as commented above, our study has several limitations to acknowledge. As with other birth cohorts with long-term follow-up, attrition or lost to-follow up close to 46% may lead to bias, although the differences of background characteristics between adolescents followed and those lost to follow were negligible. Secondly, we adjusted for potential confounders from multiple domains, residual or uncontrolled confounding is always a concern in observational studies. In addition, we could not provide evidence for the underlying mechanisms or influencing pathways of these associations. Besides, we are unable to confirm the causal link given the nature of observational design.

Conclusions

We identified distinct head circumferences growth trajectories during the first two years of life which could robustly predict adolescent cognitive test scores but not emotional and behavioral outcomes. These HC growth trajectories were largely determined by prenatal programming but also with growth improvement to some extent during the postnatal period, suggesting the importance of improving development and thriving population in a life-course manner. Routine HC measurements especially during the first 6 months were recommended for monitoring adolescent cognitive development.

Abbreviations

CI, confidence interval; FSIQ, full-scale intelligence quotient; LMICs, low- and middle-income counties; MUAC, mid upper arm circumference; PRI, perceptual reasoning index; PSI, processing speed index; SD, standard deviation; SGA, small for gestational age; VCI, verbal Comprehension index; WHO, world health organization; WISC-IV, Wechsler intelligence scale for children, Fourth Edition; and WMI, working memory index.

Declarations

Funding

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Competing interests

The authors declare to have no competing interests.

Availability of data and materials

Individual data are available from the corresponding author on reasonable request.

Authors' contributions

ZZ, YC, MJD and LZ designed the study; ZZ, JS, YZ, LW, XW, LC, QQ, AKA, and ME conducted the study; ZZ and JS analyzed data and interpreted results; ZZ wrote the paper; LZ had primary responsibility for final content; and all authors reviewed, revised and approved the final paper. ZZ and JS contributed equally to this paper.

Code availability

Not applicable.

Ethics approval

The trial and follow-up evaluation protocols were approved by the Ethics Committee in Xi'an Jiaotong University Health Science Center.

Consent to participate

Written informed consent was obtained from the biological parents or caregivers, while verbal consent was obtained from all the participants depending on their age.

Consent to publication

Not applicable.

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Tables

Table 1 Background characteristics of participants (N=745)

Factors	No. (%)	Factors	No. (%)
Maternal age years/Mean (SD)	24.5(4.5)	Randomized regimens	
15-19	70(9.4)	Folic acid or folic acid plus iron <180 days	385(51.7)
20-24	365(49.0)	Folic acid plus iron ≥180 days	120(16.1)
25-29	178(23.9)	Multiple micronutrient <180 days	134(18.0)
30-34	116(15.6)	Multiple micronutrient ≥180 days	106(14.2)
35+	16(2.2)	Household wealth at enrollment	
Maternal education		Low	180(24.2)
< 3 years	30(4.0)	Medium	294(39.5)
Primary	192(25.8)	High	271(36.4)
Secondary	404(54.4)	Child sex	
High school and above	117(15.8)	Male	450(60.4)
Maternal occupation		Female	295(39.6)
Farmer	622(83.7)	Birth weight (gram) /Mean (SD)	3197(400)
Others	121(16.3)	Birth weight-for-gestational- age and sex Z score/Mean (SD)	-0.27(1.0)
Paternal age (years)/Mean (SD)	27.7(4.2)	Preterm	19(2.6)
15-19	0(0.0)	Low birth weight	25(3.4)
20-24	197(26.4)	Small-for-gestational age	105(14.5)
25-29	307(41.2)	Age at adolescence (years)/Mean (SD)	11.3(0.6)
30-34	183(24.6)	Cognition at early adolescence/Mean (SD)	
35+	58(7.8)	FSIQ	98.1(12.5)
Paternal education		Verbal comprehension index	102.9(15.6)
< 3 years	9(1.2)	Working memory index	94.5(11.0)
Primary	80(10.8)	Perceptual reasoning index	96.0(12.5)
Secondary	472(63.6)	Processing speed index	100.0(13.7)
High school and above	181(24.4)	Scores of emotional and behavioral problems at early adolescence/Mean(SD)	
Paternal occupation		Total problems	47.0(23.86)

Farmer	555(74.7)	Internalizing	10.8(7.7)
Others	188(25.3)	Externalizing	7.9(6.9)
Parity at enrollment		Anxious	4.6(3.6)
0	508(68.2)	Withdrawn	3.2(2.5)
≥1	237(31.8)	Somatic complaints	3.1(3.0)
Maternal MUAC (cm)		Social problems	3.8(3.1)
<21.5	107(14.5)	Thought problems	2.6(2.9)
≥21.5	631(85.5)	Attention problems	4.0(2.8)
		Rule breaking	2.5(2.9)
		Aggressive behavior	5.4(4.6)

[a]Data are missing for maternal age (n=1), maternal education (n=2), maternal occupation (n=2), paternal age (n=1), paternal education (n=3), paternal occupation (n=2), maternal MUAC (n=7), birth weight (n=23), low birth weight (n=9), small-for-gestational age (n=23), cognitive test scores (n=10), emotional and behavioral test scores (n=79).

Table 2 Associations of identified head circumference trajectories in the first two years of life with cognitive and metal outcomes at early adolescence

Trajectories	FSIQ (*n*=735)	Scores of emotional and behavioral outcomes (*n*=666)		
		Total problems	Internalizing	Externalizing
Subgroup 1: Start below average-then decrease /Mean (SD)	91.7(13.4)	37.7(18.5)	8.26(6.67)	5.36(5.43)
Subgroup 2: Start below average-then increase /Mean (SD)	96.2(12.00)	50.6(30.4)	11.94(10.02)	8.76(9.37)
Subgroup 3: Start average-then decrease /Mean (SD)	97.3(12.6)	47.2(23.4)	11.09(7.33)	7.54(6.71)
Subgroup 4: Consistently average /Mean (SD)	99.1(12.1)	47.7(24.0)	10.97(7.85)	8.17(6.79)
Subgroup 5: Consistently above average /Mean (SD)	101.0(12.4)	48.1(23.9)	10.62(7.81)	8.96(7.16)
Adjusted mean differences (95% CI)[a]				
Subgroup 1 vs Subgroup 5 as reference	-8.99(-13.69, -4.28)	-7.60(-16.85, 1.65)	-1.97(-5.05, 1.10)	-2.14(-4.72, 0.43)
Subgroup 2 vs Subgroup 5 as reference	-5.80(-9.79, -1.82)	5.54(-6.03, 17.11)	2.12(-1.70, 5.95)	0.65(-3.08, 4.38)
Subgroup 3 vs Subgroup 5 as reference	-5.22(-8.13, -2.31)	3.37(-3.45, 10.19)	1.42(-0.81, 3.65)	0.12(-1.91, 2.16)
Subgroup 4 vs Subgroup 5 as reference	-2.84(-4.93, -0.75)	1.12(-4.91,7.14)	0.85(-1.14, 2.83)	-0.17(-1.94, 1.60)
Subgroup 1 vs Subgroup 4 as reference	-6.62(-10.67, -2.57)	-8.43(-16.21, -0.65)	-2.70(-5.24, -0.16)	-2.00(-4.11, 0.12)
Subgroup 2 vs Subgroup 4 as reference	-3.01(-6.17, 0.15)	4.18(-6.51, 14.88)	1.19(-2.30, 4.68)	0.76(-2.60, 4.12)
Subgroup 3 vs Subgroup 4 as reference	-2.61(-4.70, -0.52)	2.25(-2.30, 6.80)	0.58(-0.82, 1.98)	0.26(-1.12, 1.65)
Subgroup 1 vs Subgroup 2 as reference	-6.72(-12.24, -1.19)	-15.63(-35.54, 4.27)	-4.18(-10.94, 1.32)	-4.70(-10.19, 0.78)
Subgroup 2 vs Subgroup 3 as reference	-0.81(-3.83, 2.20)	-0.20(-10.93, 10.52)	0.23(-3.20, 3.66)	-0.01(-3.36, 3.34)
Subgroup 1 vs Subgroup 3 as reference	-3.89(-7.57, -0.22)	-9.45(-16.22, -2.69)	-2.85(-5.18, -0.53)	-1.96(-3.86, -0.07)

[a]Adjusted for assessors and potential confounding factors including parental age, job and education at enrollment, household wealth at enrollment, maternal MUAC at enrollment, maternal parity, randomized regimen by durations, type of delivery, small-for-gestational age, and sex in general estimating equation

linear models. FSIQ, representing the general cognitive ability. Emotional and behavioral outcomes i.e., scores of internalizing (constituting by Anxious/Depressed, Withdrawn and Somatic Complaints), externalizing (constituting by Delinquent/Rule-Breaking Behavior and Aggressive Behavior) and total behavior problems were derived from Youth Self-Report.

Abbreviations: CI, confidence interval; FSIQ, full-scale intelligence quotient derived; SD, standard deviation.

Figures

Figure 1

Head circumference growth trajectories from birth to two years of age in rural western China. Lines show for each trajectory the predicated means of z-score and 95% confidence intervals. Size (%) of each trajectory estimated by the model is presented below the x-axis. The Subgroups 1, 2, 3, 4 and 5 were labeled “Start below average-then decrease”, “Start below average-then increase”, “Start average-then decrease”, “Consistently average”, and “Consistently above average”, respectively.

Figure 2

Associations of conditional growth of head circumference among different periods in the first two years of life with cognitive, emotional and behavioral outcomes at early adolescence. We adjusted for confounding factors including parental age, job and education at enrollment, household wealth at enrollment, maternal MUAC at enrollment, maternal parity, randomized regimen by durations, type of delivery, small-for-gestational age, and sex in general estimating equation linear models. FSIQ, representing the general cognitive ability. Emotional and behavioral outcomes i.e., scores of internalizing (constituting by Anxious/Depressed, Withdrawn and Somatic Complaints), externalizing (constituting by Delinquent/Rule-Breaking Behavior and Aggressive Behavior) and total behavior problems were derived from Youth Self-Report (YSR-2001). Abbreviations: CI, confidence interval; FSIQ, full-scale intelligence quotient derived.

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