Early life cognitive development trajectories and intelligence quotient in middle childhood and early adolescence in rural western China

Zhonghai Zhu1,2,8, Suying Chang3,8, Yue Cheng4, Qi Qi1, Shaoru Li1, Mohamed Elhoumed1, Hong Yan1,5,6, Michael J. Dibley7, Wafaie W. Fawzi2, Lingxia Zeng1,6* & Christopher R. Sudfeld2

The relationship of cognitive developmental trajectories during the dynamic first years with later life development outcomes remains unclear in low- and middle-income countries. 1388 Children born to women who participated in a randomized trial of antenatal micronutrient supplementation in rural China were prospectively followed. Cognitive development was assessed six times between 3 and 30 months of age using Bayley Scales of Infant Development, and then in mid-childhood (7–9 years) and early adolescence (10–12 years) using Wechsler Intelligence Scale for Children. We identified four distinct infant cognitive development trajectory subgroups using group-based trajectory modeling: (i) consistently above average, (ii) consistently average, (iii) started below average and then improved, and (iv) started below average and then declined. LBW infants (<2500 g) were 10.60 times (95% CI 3.57, 31.49) more likely to be in the trajectory group that started below average and then declined, while each grade increase in maternal education decreased the risk of being in this group by 73% (95% CI 54%, 84%). Infants who performed consistently above average had 8.02 (95% CI 1.46, 14.59) points higher IQ in adolescence versus the declining trajectory group. These findings suggest that interventions to improve early child development trajectories may produce long-term human capital benefits.

An estimated 250 million children under five years living in low- and middle-income countries (LMICs) failed to reach their full developmental potential1. Adversities and risk factors during the first 1000 days of life lay the foundation for development and have long-term consequences across the lifecourse1–4. Studies have shown that suboptimal childhood cognitive development is associated with higher risk of coronary heart disease, reduced human capital, and increased risk of mortality and poor health outcomes later in life5–8.

A number of modifiable risk factors for suboptimal development have been identified including poverty-related factors, inadequate stimulation, environmental and nutritional factors9,10. Nevertheless, a limitation of studies that examined early life determinants of cognitive development typically only assess children at a single time-point, which does not capture the dynamic process of child development. In fact, only a few studies from high-income countries focused on preterm infants have assessed cognitive development trajectories in early childhood. One cohort study from UK and Ireland among 315 extremely preterm births found that impaired cognitive trajectory in infancy persisted into early adulthood and there was no evidence of catch-up11. In contrast,
a study in the US reported catch-up language trajectory from 3 to 12 years among very preterm infants. To the best of our knowledge, no studies have examined the relationship of early child development trajectories with later life development outcomes among the general population in LMICs.

In this study, we used data from a rural Chinese birth cohort, in which the cognitive development was assessed at 3, 6, 12, 18, and 24 months during the first two years of life and then at 30 months, middle childhood (7–9 years) and in adolescence (10–12 years). The main aims of our analysis were to (1) identify distinct trajectories of cognitive development during the first two years of life, (2) examine predictors associated with these trajectories, and (3) assess whether these trajectories were associated with long-term cognitive outcomes in middle childhood and early adolescence.

Table 1. Background characteristics of infants included in group-based trajectory analysis in a Chinese birth cohort study (N = 1388). *Data are missing for maternal age (n = 2), maternal education (n = 3), maternal occupation (n = 6), paternal age (n = 2), paternal education (n = 6), paternal occupation (n = 2), maternal MUAC (n = 10), birth weight (n = 21), preterm (n = 21), and SGA (n = 51). Abbreviation: VCI, verbal comprehension index; FSIQ, full-scale intelligence quotient derived from WISC-IV, Wechsler Intelligence Scale for Children-Fourth Edition; MDI, mental development index; MUAC, mid-upper arm circumference; PRI, perceptual reasoning index; PSI, processing speed index; SD, standard deviation; SGA, small for gestational age; WMI, working memory index.

Results

A total of 1388 children were included in group-based trajectory modelling (GBTM) analyses. Baseline characteristics of these participants are presented in Table 1. A total of 669 and 735 of these participants were followed at middle childhood (7–9 years) and early adolescence (10–12 years), respectively (Supplementary Fig. S1). The mean age at middle childhood and adolescence were 7.8 years (SD ± 0.6) and 11.3 (SD ± 0.6) years, respectively. Most background characteristics were similar between individuals who completed the middle childhood and early adolescence assessments and those who were lost to follow-up (Supplementary Table S1).
Identification of child development trajectories during the first two years of life. GBTM identified four trajectory subgroups: (1) “Subgroup 1: Start below average-then decrease” (3.2% of all participants), (2) “Subgroup 2: Start below average-then increase” (10.2%), (3) “Subgroup 3: Consistently average” (40.3%), (4) “Subgroup 4: Consistently above average” (46.3%). The fit indexes are presented in Supplementary Table S2 and Fig. 1 graphically presents the final trajectories of cognitive test z scores during the first two years of life.

Predictors of child development trajectory group. We then compared the distribution of socioeconomic, pregnancy and birth outcome characteristics between the trajectory groups (Supplementary Table S3 and Table 2). We determined that children born to mothers with increasing educational level were less likely to be in the groups that started below average and then declined (RR 0.27, 95% CI 0.16, 0.46), started below average and then improved (RR 0.59, 95% CI 0.41, 0.85) and that performed consistently average (RR 0.76, 95% CI 0.61, 0.94) than being in the group that performed consistently above average. Greater than 180 days of multiple micronutrients supplementation was associated with being in the consistently above average group (RR 0.14, 95% CI 0.02, 1.07).

Table 2. Multivariate multinomial logistic regression analyses identifying predictors for being in the consistently above average group versus the other development trajectory groups. “Subgroup 4: Consistently above average” was the comparison group. Variables were included in the multinomial logistic regression analyses for their p values in the one-way analysis of variance or Chi-Square tests (Supplementary Table S3) less than 0.10. Maternal and paternal education were categorized as <3 years, Primary, Secondary and High school +, respectively. Household wealth was categorized as low, medium and high, respectively. All the variables were then treated as continuous variables in the multinomial logistic regression analyses. The results for low birth weight were adjusted for the variables in the main model but excluding preterm and small for gestational age. Abbreviations: RR, relative risk; CI, confidence interval.
### Table 3. Associations of identified cognitive development trajectories in the first two years of life with cognitive outcomes at 30 months of age, middle childhood and early adolescence. *Adjusted for assessors and potential confounding factors including parental age, job and education at pregnancy enrollment, household wealth at pregnancy enrollment, maternal MUAC at pregnancy enrollment, maternal parity, randomized regimen, birth outcome (SGA), and sex in general estimating equation linear models. Abbreviations: CI, confidence interval; FSIQ, full-scale intelligence quotient derived from WISC-IV, Wechsler Intelligence Scale for Children-Fourth Edition; SD, standard deviation; SGA, small for gestational age; MUAC, mid upper arm circumference.

| Subgroup | MDI at 30 months (N = 1099) | FSIQ at middle childhood (N = 669) | FSIQ at early adolescence (N = 735) |
|----------|-----------------------------|----------------------------------|----------------------------------|
| Subgroup 1: Start below average-then decrease | Mean (SD) 55.1 (27.2) | 76.8 (12.8) | 88.0 (15.0) |
| Subgroup 2: Start below average-then increase | Mean (SD) 81.5 (16.2) | 91.3 (12.9) | 97.0 (12.0) |
| Subgroup 3: Consistently average | Mean (SD) 80.0 (17.5) | 87.0 (11.4) | 96.0 (12.0) |
| Subgroup 4: Consistently above average | Mean (SD) 94.7 (15.0) | 91.9 (12.7) | 100.0 (12.0) |

**Unadjusted mean differences (95% CI)**

| Subgroup 1 vs Subgroup 2 as reference | $-39.59 (-50.15, -29.04)$ | $-15.11 (-20.32, -9.91)$ | $-12.01 (-18.08, -5.94)$ |
| Subgroup 2 vs Subgroup 3 as reference | $-13.24 (-16.97, -9.51)$ | $-0.62 (-4.55, 3.31)$ | $-3.94 (-6.13, -1.75)$ |
| Subgroup 3 vs Subgroup 4 as reference | $-14.67 (-16.71, -12.64)$ | $-4.97 (-6.77, -3.18)$ | $-4.72 (-6.69, -2.75)$ |
| Subgroup 2 vs Subgroup 3 as reference | $1.43 (-2.58, 5.44)$ | $4.36 (0.20, 8.51)$ | $0.78 (-2.30, 3.87)$ |
| Subgroup 1 vs Subgroup 2 as reference | $-26.35 (-37.47, -15.23)$ | $-14.50 (-20.38, -8.61)$ | $-8.07 (-14.56, -1.58)$ |

**Adjusted mean differences (95% CI)**

| Subgroup 1 vs Subgroup 2 as reference | $-35.52 (-45.38, -25.66)$ | $-10.20 (-14.41, -5.99)$ | $-8.02 (-14.59, -1.46)$ |
| Subgroup 2 vs Subgroup 3 as reference | $-10.93 (-14.80, -7.06)$ | $1.75 (-2.97, 6.48)$ | $-2.58 (-4.88, -0.28)$ |
| Subgroup 3 vs Subgroup 4 as reference | $-12.76 (-14.86, -10.65)$ | $-2.92 (-4.31, -1.52)$ | $-2.52 (-4.41, -0.62)$ |
| Subgroup 2 vs Subgroup 3 as reference | $2.34 (-1.52, 6.20)$ | $3.59 (-1.20, 8.38)$ | $0.61 (-2.67, 3.90)$ |
| Subgroup 1 vs Subgroup 2 as reference | $-25.16 (-35.13, -15.19)$ | $-11.43 (-19.69, -3.18)$ | $-6.98 (-13.47, -0.49)$ |

### Relationships of development trajectory group with middle childhood and adolescent developmental outcomes.

As shown in Table 3, the children who performed consistently above average during the first 2 years of life had persistently higher test scores in middle childhood and early adolescence. Infants that were consistently above average during the first two years had 8.02 (95% CI 1.46, 14.59) and 2.52 (95% CI 0.62, 4.41) points higher cognitive test scores in adolescence as compared to those who started below average and then declined or those who were consistently average, respectively.

In the adjusted analyses (Table 3), infants in the trajectory group that started below average and then improved and the group that were consistently average did not differ in cognitive outcomes in middle childhood or adolescence. However, the cognitive deficits of trajectory group that started below average and then declined relative to group that started below average and then improved persisted into adolescence with an adjusted mean FSIQ differences of $-6.98$ (95% CI $-13.47$, $-0.49$).

We conducted a sensitivity analysis using IPW to account for potential bias due to outcome censoring (loss to follow-up) and found there were no qualitative differences in our findings (Supplemental Table S4).
We also examined components of the FSIQ score and found similar associations within the VCI, WMI, PRI and PSI scores (Supplementary Tables S6 and Table S7).

Relationships of single-time point BSID-II scores at 12 and 24 months with middle childhood and adolescent development outcomes. We observed statistically significant, but weaker correlations magnitude of association, between BSID-II tertiles and development outcomes in middle childhood and early adolescence (Supplementary Table S8). Young children in the highest tertile of development scores at 12 and 24 months had 2.57 (95% CI: 0.31, 4.82) and 4.67 (95% CI: 2.01, 7.33) points higher scores in early adolescence as compared to those in the lowest tertile, respectively.

Discussion

We identified four distinct trajectories of infant cognitive development during the first two years of life in rural China: (1) children who started below average and then declined, (2) children who started below average and then improved, (3) children who were consistently average and (4) children who performed consistently above average. Higher maternal education and supplementing antenatal multiple micronutrients beyond 180 days were associated with reduced risk of being in suboptimal development trajectories; while, SGA and low birth weight birth increased the risk of being in the suboptimal groups. The developmental advantages of Subgroup 4 (consistently above average) over the other three trajectory groups persisted through middle childhood into early adolescence. Although, this finding and another from interventions. As described by the early nutrition programming (Supplementary Table S3). Hence, these findings highlight the programs that aim to reduce the risk of adverse birth outcomes before and during pregnancy.

There remains debate as to the long-term functional outcomes of cognitive tests in infancy in LMIC settings. After using structural equation model to account for measurement error with 3 repeated measures among...
130 infants, one longitudinal investigation from US reported that infant cognitive function moderately correlated with adolescent development outcomes with a correlation coefficient of 0.5733, which was higher than that observed in our study (0.18 for 12 months and 0.30 for 24 months, respectively; Supplementary Table S8). Taken together, these findings suggest that using single-time assessment of infant cognitive development has limitations to predict long-term outcomes and identify high-risk children for delayed development. In the present study, adolescents from Subgroup 4 (consistently above average) had the highest cognitive test scores, suggesting that the developmental advantages established in early life could persist through middle childhood into early adolescence. In addition, the infants from subgroup 1 (started below average then decreased) had the lowest test scores in middle childhood and early adolescence. These findings suggest that infant cognitive development trajectories are strong predictors of children long-term development outcomes, and highlight the importance of providing appropriate interventions as early as possible, which could ameliorate restricted development and have important implications for human capital and well-being across the life course.

The results in the present study should be interpreted with a few limitations. First, the follow-up rate for children in middle childhood and adolescence in the present study was approximately 50% of the original cohort and therefore bias due to dependent censoring is possible. Nevertheless, we found minimal to no differences in background characteristics for children who had development assessed as compared to those who did not. Besides, a sensitivity analysis using IPW to account for outcome censoring also suggested the main study findings were robust and the risk of bias due to censoring was likely minimal. Second, the use of data-driven approach allowed us to identify distinct cognitive trajectories over age and was appropriate for several repeated measurements of the same individuals. However, the trajectory modeling approach shares inherent limitations including that extracting the optimal number of subgroups, which is a process guided by statistical fit indices and some degree of investigators’ decision, and that the size of each trajectory was produced by the model that may result in small sizes and consequently limited power to further analysis. Third, the cognitive development trajectories that we identified in our study population in rural China may not be directly applicable to other settings. Finally, the underlying biological mechanisms between these predictors and cognitive trajectories cannot be examined in the present study.

In summary, we identified groups of distinct trajectories of cognitive development during the first two years of life in rural China. Prospectively, we found that these trajectory groups robustly predicted development scores through middle childhood into adolescence. In addition, our risk factor analyses indicated that integrated of nutritional, environmental, and educational interventions during the first 1,000 days of life may affect early life cognitive development trajectories and produce long-term effects on development and human capital across the life course.

Methods
Participants. We used data from a prospective birth cohort of children born to women who participated in a randomized, double-blind trial of antenatal micronutrient supplementation in rural western China. Children were followed in early childhood (age 3 to 30 months), middle childhood (age 7–9 years) and early adolescence (age 10–12 years). Details and procedures of the trial and follow-up studies have been described elsewhere23–25,32.

Briefly, all pregnant women across villages from two counties were randomized to take a daily capsule of either folic acid, folic acid plus iron, or multiple micronutrients between August 2002 and February 2006. In the trial 4604 singleton births occurred, and 1400 births born in 2004–2006 were enrolled in long-term follow-up cohort. A total of 1388 was enrolled after excluding deaths (n = 3), birth defects (n = 7) and disabled parents (n = 2). Among them, 660 were followed at 7–9 years of age between October 2012 and September 2013, and 735 at 10–12 years of age between June 2016 and December 2016 for cognitive assessment.

Assessments of cognitive development. At the 3, 6, 12, 18, 24- and 30-month visit, mental development (MD) was assessed using a culturally appropriate, and locally validated Chinese version of Bayley Scales of Infant Development (BSID-II)33. MD raw scores were transformed into age-standardized scores based on the data for infants in US34.

In middle childhood and adolescence, we used the Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV) to assess cognitive development35. According to Chinese norms of WISC-IV with satisfied reliability and validity, age-standardized full-scale intelligence quotient (FSIQ), representing the general cognitive development, and aspects of verbal comprehension (VCI), perceptual reasoning (PRI), working memory (WMI), and processing speed index (PSI) were derived36.

Cognitive tests were standardly administered by public health graduates at subjects’ own home, local school or hospital meeting room that were free of distractions. Field staff administering these cognitive tests were unaware of the socioeconomic background, randomized treatment allocation, birth outcomes or other health status of participants.

Covariates. Information on socioeconomic status (parental age, occupation, education and household wealth), maternal nutrition status before pregnancy (mid-upper arm circumference), randomized regimen (folic acid, folic acid plus iron, and multiple micronutrients), maternal parity and birth outcomes (preterm birth, low birth weight [LBW], small for gestational age [SGA] birth and infant sex) was collected as part of the original trial using standard questionnaire, methods and/or procedures. These details are documented elsewhere33. A wealth index was established from an inventory of 16 household assets or facilities by principal component analysis, which was then classified into thirds as an indicator of low-, middle- and high-income households37. Preterm birth was defined as babies born alive before 37 weeks’ gestational age, and low birth weight was defined as a birth weight of less than 2500 g, as per the World Health Organization (WHO) guidelines38,39. According to Intergrowth standards, SGA birth was defined as birth weight below the 10th percentile of weight-for-age and sex40.
Given our prior findings that multiple micronutrient supplementation could significantly improve cognitive development with the largest benefits observed with supplementation of at least 180 days\textsuperscript{25}, we combined the randomized treatment regimens and duration into a categorical variable, i.e., folic acid or iron/folic acid lasting for <180 days (as reference), iron/folic acid lasting for ≥180 days, multiple micronutrients lasting for <180 days, and multiple micronutrients lasting for ≥180 days.

Statistical analysis. To increase comparability across ages, we transformed the age-standardized cognitive test scores into z-scores based on age-specific medians and SD within the sample. We then used a group-based trajectory modelling, specifically the “traj” macro in Stata, to identify infant cognitive z-score developmental trajectories across 3, 6, 12, 18, and 24 months of age\textsuperscript{41–43}. GBTM can identify subgroups of individuals who share similar patterns of development\textsuperscript{42,43}, and has been used to identify distinct trajectories of body composition and body mass index (BMI) that are associated with risks for obesity, asthma, morbidity and mortality later in life\textsuperscript{44–51}. Models with two or more subgroups were compared to identify the optimal number of subgroups and shapes that best characterized the data, with maximum likelihood estimation accounting for missing z scores at any time point. The final model was selected based on general recommendations including: (i) tests for parameter estimates for linear, quadratic and cubic terms, (ii) Bayesian and Akaike information criterion value, (ii) average of the posterior probabilities of group membership for individuals assigned to each group, (iv) odds of correct classification based on the posterior probabilities of group membership, and (v) minimizing overlap in confidence intervals (CIs) while summarizing the distinctive features of the data as parsimonious as possible\textsuperscript{15}.

Once the most appropriate trajectories were derived, the subgroup categories variable was used in all subsequent analyses. Baseline characteristics by the trajectory groups were compared using Chi-squared tests or analysis of variance, and multivariate multinomial logistic regression models. We then used generalized estimating equations with an independent correlation structure to assess the relationship of the trajectory groups with cognitive development outcomes at 30 months, middle childhood and early adolescence. To hand the missing data of cognitive outcome in middle childhood and early adolescence and examine its potential to influence the results, we applied the inverse probability weighting (IPW)\textsuperscript{35}. We also conducted analyses using single-time point Bayley scores at 12 and 24 months to compare the magnitude of association for the GBTM approach.

Age-standardized FSIQ and VCI, WMI, PRI, and PSI scores were taken as the primary and secondary outcomes, respectively. All statistical analyses were performed using Stata 12.0 (Stata Corp, College Station, Texas, USA).

Ethical approval. The protocols of the original trial and all follow-up studies conformed to the ethical principles of the 1964 Declaration of Helsinki, and were approved by UNICEF and the ethics committee of Xian Jiaotong University Health Science Center. Informed written content from pregnant women, and parents/caregivers, and oral consent from children were obtained.

Data availability All data generated or analysed during this study are included in this published article (and its Supplementary Information files).

Received: 19 July 2019; Accepted: 19 November 2019;
Published online: 04 December 2019

References
1. Black, M. M. et al. Early childhood development coming of age: Science through the life course. *Lancet*. 389, 77–90 (2017).
2. Wadhwa, P. D., Buss, C., Entringer, S. & Swanson, J. M. Developmental origins of health and disease: Brief history of the approach and current focus on epigenetic mechanisms. *Semin Reprod Med.* 27, 358–367 (2009).
3. Peter, D. G., Tatjana, B. & Mark, A. H. The Developmental Origins of Health and Disease (DOHaD) Concept: Past, Present, and Future. *The Epigenome and Developmental Origins of Health and Disease*, https://doi.org/10.1016/B978-0-12-801383-0.00001-3 (2016).
4. Moody, L., Chen, H. & Pan, Y. Early-life nutritional programming of cognition—the fundamental role of epigenetic mechanisms in mediating the relation between early-life environment and learning and memory process. *Adv Nutr.* 8, 337–350 (2017).
5. Deary, I. J., Whiteman, M. C., Starr, J. M., Whalley, L. J. & Fox, H. C. The Impact of childhood intelligence on later life: Following up the Scottish mental surveys of 1932 and 1947. *J Pers Soc Psychol.* 86, 130–147 (2004).
6. McGurn, B., Deary, I. J. & Starr, J. M. Childhood cognitive ability and risk of late-onset Alzheimer and vascular dementia. *Neurology*. 71, 1051–1056 (2008).
7. Gale, C. R., Deary, I. J., Schoon, I. & Batty, G. D. IQ in childhood and vegetarianism in adulthood: 1970 British cohort study. *BMJ*. 334, 245, https://doi.org/10.1136/bmj.39030.675069.55 (2007).
8. Calvin, C. M. et al. Intelligence in youth and all-cause-mortality: Systematic review with meta-analysis. *Int J Epidemiol.* 40, 626–644 (2011).
9. Walker, S. P. et al. Child development: Risk factors for adverse outcomes in developing countries. *Lancet*. 369, 145–157 (2007).
10. Walker, S. P. et al. Inequality in early childhood: Risk and protective factors for early child development. *Lancet*. 378, 1325–1338 (2011).
11. Linsell, L. et al. Cognitive trajectories from infancy to early adulthood following birth before 26 weeks of gestation: A prospective, population-based cohort study. *Arch Dis Child*. 103, 363–370 (2018).
12. Liiu, T. M. et al. Trajectories of receptive language development from 3 to 12 years of age for very preterm children. *Pediatrics*. 124, 333–341 (2009).
13. Ukoumunne, O. C. et al. Profiles of language development in pre-school children: A longitudinal latent class analysis of data from the Early Language in Victoria Study. *Child: Care, Health Dev.* 38, 341–349 (2012).
14. de Wit, C. C., Sas, T. C., Wit, J. M. & Cutfield, W. S. Patterns of catch-up growth. *J Pediatr*. 162, 415–420 (2013).
15. Fitzhardinge, P. M. & Steven, E. M. The small-for-date infant. *Later growth patterns. Pediatrics*. 49, 671–681 (1972).
16. Victor, C. G. et al. Association between breastfeeding and intelligence, educational attainment, and income at 30 years of age: A prospective birth cohort study from Brazil. *Lancet Glob Health*. 3, e199–e205 (2015).
Author contributions
Z.Z., S.C., Y.C., H.Y., M.J.D. and L.Z.: planned and designed the study; Z.Z., Q.Q., S.L. and M.E.: conducted the study; Z.Z., S.C., C.R.S. and W.W.F.: analyzed data and interpreted results; Z.Z.: wrote the paper; L.Z.: had primary responsibility for final content; and all authors: reviewed, revised and approved the final paper.

Competing interests
Dr. Suying Chang is a nutrition specialist of UNICEF China Office. The other authors have no conflicts of interest relevant to this article to disclose.

Additional information
Supplementary information is available for this paper at https://doi.org/10.1038/s41598-019-54755-1.

Correspondence and requests for materials should be addressed to L.Z.

Reprints and permissions information is available at www.nature.com/reprints.

Publisher’s note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this license, visit http://creativecommons.org/licenses/by/4.0/.

© The Author(s) 2019