Differentiating the cognitive development of early term births in Chinese infants and toddlers

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Differentiating the cognitive development of early term births in Chinese infants and toddlers

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ABSTRACT

Objectives: This study aimed to explore the cognitive development of low-risk children during early childhood for preterm births at 37 and 38 weeks of gestation compared to full term births at 39-41 weeks of gestation.

Setting and Participants: We conducted a cross-sectional study in Shanghai, one of the largest cities in China. A total of 1444 children from singleton pregnancies born at term gestation were included in the study.

Measures: The cognitive outcomes of the subjects were measured using the cognitive subtest of Bayley Scales of Infant and toddler Development-third Edition (BSID-III) across three cities in China. We analyzed the association between gestational age and cognitive development during infancy and toddler stages using multivariate linear modeling.

Results: The cognitive development scores for infants born at 37 gestational weeks were significantly lower than those born at 39 to 41 gestational weeks (β=-2.257, 95%CI:-4.280 to -0.235; p<0.05) after adjusting for children's and maternal characteristics, as well as socio-economic factors. However, there were no significant differences in cognitive ability between infants born at 38 gestational weeks compared to their full-term counterparts (p>0.05). Moreover, these effects were not found in toddlers (between 17 and 48 months of age) after adjusting for the possible confounders (p>0.05).

Conclusions: Infants born at 37 weeks of gestation exhibited weaker cognitive ability compared with those born at 39-41 weeks of gestation. Our findings provide clues for the close monitoring of potential developmental problems in early term children, especially those born at 37 gestational weeks.

***Keywords*:** Cognitive development; early term, infants and toddlers; China

Strengths and limitations of this study

- Our findings extend the limited available literature on the relationship of gestational age with cognitive developmental scores. Infants born at 37 weeks of gestation had significantly weaker cognitive ability compared with their full-term counterparts.

- Our finding provided clues for the close monitoring of potential developmental problems in early term children, especially in those born at 37 gestational weeks.

- The sample size was relatively small in our study (n=1444), and the results were not consistent across different age groups. Further studies are needed in order to verify this result.

- Although we examined a number of potential confounders, several other confounding factors were not measured. For instance, the detailed maternal and obstetric factors for early-term deliveries were not available in our study.

INTRODUCTION

It had been previously believed that children born between 37 and 41 weeks of gestational age share similar health outcomes, therefore including them in the same low-risk group.[1] In 2012, the American Academy of Pediatrics recommended that births occurring between 37 weeks 0 days and 38 weeks 6 days be defined as early term, while those from 39 weeks 0 days through to 40 weeks 6 days as full term.[2] Approximately 27.6% of all births in the United States are early term,[3,4] far exceeding the number of preterm births.[4,5] Many studies have reported that early-term births are associated with higher neonatal morbidity and higher probability of NICU admission compared with their full term counterparts (> 38 gestational weeks).[6] Early term children also have increased susceptibility to various metabolic, neurologic and respiratory diseases.[7-9]

Recently, research into the effect of gestational age on developmental outcomes has directed attention to the investigation of early term infants.[10] There have been increasing reports which show that early term births resulted in worsened cognitive and academic outcomes compared to those born at 39 weeks or later.[1,10-13] A systematic review showed that full-term cohorts performed 3% of a standard deviation higher in cognitive outcome than early term cohorts[10]. The gestation period between 37-40 weeks was associated with neuromotor and cognitive development in 9- to 15-week-old and 12-month-old infants.[13,14] Early term birth was associated with an increased risk of worsened academic achievements at ages 5 to 7 years.[15,16]

However, on the basis of recent research,[13,17-19] the exact boundary which separates early term and full term gestation periods should be carefully examined because of its implications for neonatal and developmental outcomes. The highest risk of mortality was observed for children born at 37 gestational weeks, but not for those born at 38 gestational weeks.[19] Furthermore, a prospective cohort study in Belarus showed that children born at 37 gestational weeks had a significantly lower full-scale intelligence quotient (IQ) score compared with those born at 39-41 weeks, however, this difference was not observed in children born at 38 gestational weeks.[20] Moreover, in a large sample of healthy infants, there was a significant difference in the mental development index (MDI) between infants born at 37 and 38 gestational weeks, but almost no difference between those born at 38 and 39 gestational weeks.[13] However, the degree to which earlier gestational age confers risk among infants born at term from 37 to 41 weeks of gestation remains unclear.[12,20,21]

In this study, we used a cross-sectional study design to examine a sample of urban Chinese singleton pregnancies born at term gestation. We hypothesized that early term births may result in significant cognitive delay, especially those born at 37 gestational weeks. We further examined the differences in cognitive ability in both infants and toddlers across various term births in order to determine the true underlying risk across different gestational weeks. The aim of the study is: 1) to differentiate the cognitive development of children born at 37, 38 and 39-41 gestational weeks; 2) to independently analyze the effects of gestational weeks on cognitive development in both short-term (infants) and long term (toddlers), in order

to provide clues for the close monitoring of potential developmental problems in early term children.

MATERIALS AND METHODS

Participants

We conducted a cross-sectional study in mainland China from May to December of 2011. We used a stratified sampling technique, with area, gender, and months of age as stratification variables. A total of 1589 children aged between 16 days to 42 months were selected from 3 children's healthcare institutions in medium-sized cities distributed across 3 geographic regions: North China, Middle China, and East China. The selection of age bands was based on the categories proposed in the Bayley-III technical manual (totaling 48 age bands). The inclusion criteria for infants and toddlers included: singleton and born at term, born without significant medical complications, did not have a history of medical complications, and not currently diagnosed with or receiving treatment for mental, physical or behavioral difficulties. The exclusion criteria included: confounding conditions or developmental risk factors such as abnormal hearing or vision, taking medications that could affect performance or admission to hospital at the time of testing, and any other problems involving nutrition, sleep or infections during the clinical visit. Of the 1589 eligible children who were recruited, a total of 1444 children were included for the study (Figure 1). All information was kept confidential and was only accessible to the researchers.

Patient and Public Involvement

None of the patients were involved in the research design or development of the research question and outcome measures. They were also not involved in the recruitment and conduct of the study. The results of the study would be disseminated to study participants by means of the participating children's healthcare institutions.

Measurements

The Bayley Scale of Infant and Toddler Development, Third Edition (Bayley-III) is an individually administered scale that assesses five key developmental domains in children between 1-42 months of age: cognition, language (receptive and expressive communication), motor (gross and fine), social-emotional and adaptive behavior. The first three domains are assessed through direct observation of the child in test situations, while the last two are assessed through questionnaires to be completed by the main caregiver. We first obtained formal permission to translate and validate the Bayley-III scale from the American publishers of this tool (Pearson). We then started developing a Chinese version of Bayley-III, following the recommendations of Hambleton and Patsula (1999), and Herdman, Fox-Rushby and Badia (1998) for the translation and adaptation of a test, taking into consideration conceptual, item, semantic, operational, measurement and functional equivalences. Each step of this process was presented in the results section. The Chinese version of the BSID-III was translated by a native Chinese speaker and independent professional who adapted the items into context and culture. Subsequently, the final Chinese version of the BSID-III was retranslated into English by two native English speakers who were blinded to the original version. The test manual and materials will utilize the same trademark, logo, and design as used on the English version of the test. We have explored the reliability and validity of the Bayley-III cognitive scale in a parallel study, which showed a good to excellent reliability of the Bayley-III cognitive scale (e.g. the coefficients of inter-item consistency were more than 0.75; the test-retest and inter-rater reliability of the scale were more than 0.90). The content, construct and known-group validity of Bayley-III cognitive scale were also sufficient in the parallel study. Additionally, gestational age is measured as the age of a pregnancy which was taken from the woman's last menstrual period, records of which were obtained from the hospital's medical record registration system following confirmation by ultrasound exam.

Procedure

The survey was conducted during the well-child visits in the participating children's healthcare institutions. Nurses who took part in the check in and physical examination (weight, height and head circumference) were responsible for handing out the questionnaires to the children's parents. Six developmental pediatricians were trained to administrate the Bayley-III cognitive scale. The testers had become familiar with the test guidance by carrying out a series of practice assessments on several children who did not take part in the study. Any problems associated with test administration during the training period were clarified by the administrator of this study prior to the

test. The test environment was quiet and non-interfering, and all infants and toddlers needed to be sober, stable and satiated. The tester encouraged the infants and toddlers to display their highest level of ability during the test. A trained pediatrician took the responsibility for conducting the entire test for each child in order to maximize both interpretation validity and assessment reliability.

Statistical analysis

All analyses were performed using SPSS 17.0 software. Chi-square analyses were used for comparing children and maternal characteristics between those born at 37 or 38 gestational weeks and those born at full term (39-41 gestational weeks). Means of cognitive scores among different gestational weeks was evaluated using one-way ANOVA and post-hoc comparison. Multivariate linear regression was used to test the relationship between gestational age and cognitive developmental scores, taking into account potential confounding variables including gender, weight-for-length Z-scores, parity, mother's age, delivery mode, parents' education and occupation. Social economic factors were not included because they were highly correlated with parental occupation. $p<0.05$ was considered statistically significant.

RESULTS

Of the 1444 children included in the study, 844 were infants aged between 16 days after birth to 16 months (58.4%), and 600 were toddlers aged between 17 months to 48 months (41.6%). Among these subjects, 1152 (79.8%) were full term births, 87

(6.02%) were born at 37 gestational weeks, and 205 (14.2%) were born at 38 gestational weeks. The mean cognitive composite score was 101.9, with a standard deviation of 6.9. The parity, the family's city of residence, and parents' education were significantly different among those born at 37, 38 and 39-41 gestational ages (Table 1).

The cognitive composite score was expressed as means and 95% confidence interval (Figure 2). In infants aged between 16 days to 16 months, the cognitive composite score for those born at 37 gestational weeks of age was significantly lower than those born at 39-41 gestation weeks ($p<0.05$).

Using multivariate linear regression model, cognitive composite scores for children born at 37 weeks were significantly lower than those born at 39-41 gestational weeks during infancy, when not adjusting for (β=-2.810, 95%CI:-4.847 to -0.774; p=0.007) or adjusting for the children's characteristics only (β=-2.723, 95%CI:-4.765 to -0.680; p=0.009), or in combination with maternal characteristics (β=-2.545, 95%CI:-4.590 to -0.500; p=0.015), as well as socio-economic factors (β=-2.257, 95%CI:-4.280 to -0.235; p=0.029; Table 2).

However, in toddlers aged between 17 months to 48 months (Table 2), there were almost no statistically significant associations between those born at 37 or 38 gestational weeks to those born in full term (39-41 gestational weeks). The only difference was a lower composite cognitive score in toddlers born at 38 gestational weeks compared to those born in full term (p=0.041), when not adjusting for any other variables.

DISCUSSION

To our knowledge, our paper is the first in China and one of few studies in the world to report on the short- and long-term neurobehavioral outcomes of early term children. A weaker cognitive ability was observed in infants born at 37 gestational weeks compared with their full-term (born at 39-41 gestational weeks) counterparts. Our findings extend the limited available literature on the relationship of gestational age to cognitive developmental scores.

In our study, we found that the effect of early term birth (37 gestational weeks) persisted in infancy even when a broad range of confounders including parental characteristics were considered. The mechanisms underlying the effect of early term birth on cognitive development scores may be multifactorial. The intrauterine and extrauterine environments differ dramatically in relationship to maternal and placental hormones, which may play an important role in brain development.[13] The intrauterine environment supports typical brain development, which is more likely to be disrupted in children born during early term gestation.[12] Moreover, brain development occurs in a very specific order and time frame.[10] The volume of total grey matter increases by approximately 1.4% per week from 29 to 41 weeks of gestation, while the volume of white matter sees a fivefold increase between 35 and 41 weeks of gestation.[22,23] Early term births may cause disruptions at specific times during the development of the brain's neural connections for specific cognitive areas.[24] Even at 38 weeks of gestation, the brain is still only 90% of full-term weight.[25] However, there have been no studies about the subtle differences in brain development between infants born at 37 and 38 gestational weeks. Future research is necessary to investigate the mechanisms behind this phenomenon.

Additionally, children who were born early term may have a shorter breastfeeding duration compared with children born at full term.[23,26-28] The breastfeeding duration was positively associated with children's cognitive development,[29,30] possibly due to the abundance of cognition-related nutrients found in breast milk such as docosahexaenoic (DHA) and arachidonic acid. Shorter breastfeeding duration may result in an increase in morbidity such as asthma and the number of hospital admissions, which was associated with a delay in achieving early developmental milestones that may have an effect educational achievements.[23]

This finding further supports the results from previous related research. For example, the highest mortality rate was observed among children born at 37 weeks of gestation, which necessitates caution in inducing labor for early term pregnancies (37 weeks of gestation). When gestational age in days was classified as gestational weeks, the mortality for children born at 37 weeks of gestation was higher compared to later-term births,[17,31-33] however, children born at 38 weeks of gestation was not associated with an increased mortality. Thus, the true underlying problems for children born in week 37, remains unknown. Our findings, combined with these studies, also provide the clues for the categorization of early term births. Close monitoring for any signs of developmental problems is of the utmost importance in children born at 37 gestational weeks.

Interestingly, in our study, the problems associated with early term birth was not found in toddlers (aged between 17 months to 48 months), possibly due to the fact that the family parenting environment had a greater impact on long-term outcomes, which 'weakened' the association between early term birth and cognitive development. A previous study showed that the quality of stimulation in the family environment is crucial for the child's cognitive development.[34] A randomized control trial suggested that intervention on family environment and maternal competency has positive effects on child development (including cognitive and motor development).[35] In China, the effects of home and educational environments can promote the motor performance in preschoolers.[36]

CONCLUSIONS

Our study showed that the cognitive development scores for children born at 37 gestational weeks were significantly lower than those born at 39 to 41 gestation weeks. Therefore, healthcare professionals need to be more aware of the potential short-term and long-term care requirements of early term children. Close monitoring for any signs of health and developmental problems in early term children born at 37 gestational weeks can allow the early detection and timely treatment of borderline abnormalities, as well as prevent any potential negative health outcomes. However, because the sample size of our study was relatively small, and the results were not consistent across different age groups, further studies are needed in order to verify these results. Moreover, although we examined a number of potential confounders, several other confounding factors were not measured. For instance, the detailed maternal and obstetric factors for early-term deliveries were not available in our study. Further, the cognitive developmental scores of children in our study are all normal (above 80 points), possibly because we selected singletons born at term birth who were mostly at low-risk.

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Contributors JH, JS, ZC and JG contributed to the study design and drafting of the paper. XD and SL were responsible for literature search, quality control of the testing, and data collection. WD and GG revised the paper and approved the finalized manuscript submission.

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Competing interests None declared.

Ethics approval The study received ethical approval from the Local Committee of Soochow University, China (201101). Written informed consent was obtained from the parents or legal guardians of the participants prior to the questionnaire survey. Oral parental consents were obtained prior to investigation and tests.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Data sets generated and/or analysed during the current study available from the corresponding author on reasonable request.

Conflict of interest statement

None declared.

References

1 Sengupta S, Carrion V, Shelton J, Wynn RJ, Ryan RM, Singhal K, et al. Adverse Neonatal Outcomes Associated With Early-Term Birth. *JAMA Pediatrics* 2013;**167**(11):1053 doi: 10.1001/jamapediatrics.2013.2581published Online First.

2 Spong CY. Defining “Term” Pregnancy. *Jama* 2013;**309**(23):2445 doi: 10.1001/jama.2013.6235published Online First.

3 Martin JA, Hamilton BE, Sutton PD, Ventura SJ, Mathews TJ, Kirmeyer S, et al. Births: final data for 2007. *Natl Vital Stat Rep* 2010;**58**(24):1-85 Online First: 2011/01/25].

4 Martin JA, Hamilton BE, Ventura SJ, Osterman MJ, Kirmeyer S, Mathews TJ, et al. Births: final data for 2009. *Natl Vital Stat Rep* 2011;**60**(1):1-70 Online First: 2012/06/08].

5 Mally PV, Agathis NT, Bailey SM. Early term infants are at increased risk of requiring neonatal intensive care. *World journal of pediatrics : WJP* 2016;**12**(1):76-81 doi: 10.1007/s12519-015-0049-8published Online First.

6 Craighead DV. Early term birth: understanding the health risks to infants. *Nursing for women's health* 2012;**16**(2):136-144; quiz 145 doi: 10.1111/j.1751-486X.2012.01719.xpublished Online First.

7 Schonhaut L, Armijo I, Perez M. Gestational age and developmental risk in moderately and late preterm and early term infants. *Pediatrics* 2015;**135**(4):e835-841 doi: 10.1542/peds.2014-1957published Online First.

8 Rabie NZ, Bird TM, Magann EF, Hall RW, McKelvey SS. ADHD and developmental speech/language disorders in late preterm, early term and term infants. *Journal of perinatology : official journal of the California Perinatal Association* 2015;**35**(8):660-664 doi: 10.1038/jp.2015.28published Online First.

9 Goyal NK, Attanasio LB, Kozhimannil KB. Hospital care and early breastfeeding outcomes among late preterm, early-term, and term infants. *Birth* 2014;**41**(4):330-338 doi: 10.1111/birt.12135published Online First.

10 Chan E, Leong P, Malouf R, Quigley MA. Long-term cognitive and school outcomes of late-preterm and early-term births: a systematic review. *Child: Care, Health and Development* 2016;**42**(3):297-312 doi: 10.1111/cch.12320published Online First.

11 Richards JL, Drews-Botsch C, Sales JM, Flanders WD, Kramer MR. Describing the Shape of the Relationship Between Gestational Age at Birth and Cognitive Development in a Nationally Representative U.S. Birth Cohort. *Paediatric and Perinatal Epidemiology* 2016;**30**(6):571-582 doi: 10.1111/ppe.12319published Online First.

12 Noble KG, Fifer WP, Rauh VA, Nomura Y, Andrews HF. Academic Achievement Varies With Gestational Age Among Children Born at Term. *Pediatrics*

2012;**130**(2):e257-e264 doi: 10.1542/peds.2011-2157published Online First.
13 Rose O, Blanco E, Martinez SM, Sim EK, Castillo M, Lozoff B, et al. Developmental scores at 1 year with increasing gestational age, 37-41 weeks. *Pediatrics* 2013;**131**(5):e1475-1481 doi: 10.1542/peds.2012-3215published Online First.
14 van Batenburg-Eddes T, de Groot L, Arends L, de Vries A, Moll HA, Steegers EA, et al. Does gestational duration within the normal range predict infant neuromotor development? *Early human development* 2008;**84**(10):659-665 doi: 10.1016/j.earlhumdev.2008.04.007published Online First.
15 Quigley MA, Poulsen G, Boyle E, Wolke D, Field D, Alfirevic Z, et al. Early term and late preterm birth are associated with poorer school performance at age 5 years: a cohort study. *Arch Dis Child Fetal Neonatal Ed* 2012;**97**(3):F167-173 doi: 10.1136/archdischild-2011-300888published Online First.
16 Chan E, Quigley MA. School performance at age 7 years in late preterm and early term birth: a cohort study. *Arch Dis Child Fetal Neonatal Ed* 2014;**99**(6):F451-F457 doi: 10.1136/archdischild-2014-306124published Online First.
17 Reddy UM, Bettegowda VR, Dias T, Yamada-Kushnir T, Ko CW, Willinger M. Term pregnancy: a period of heterogeneous risk for infant mortality. *Obstetrics and gynecology* 2011;**117**(6):1279-1287 doi: 10.1097/AOG.0b013e3182179e28published Online First.
18 Engle WA. Morbidity and mortality in late preterm and early term newborns: a continuum. *Clinics in perinatology* 2011;**38**(3):493-516 doi: 10.1016/j.clp.2011.06.009published Online First.
19 Wu CS, Sun Y, Nohr EA, Olsen J. Trends in All-Cause Mortality across Gestational Age in Days for Children Born at Term. *PloS one* 2015;**10**(12):e0144754 doi: 10.1371/journal.pone.0144754published Online First.
20 Yang S, Platt RW, Kramer MS. Variation in child cognitive ability by week of gestation among healthy term births. *American journal of epidemiology* 2010;**171**(4):399-406 doi: 10.1093/aje/kwp413published Online First.
21 Schonhaut L, Armijo I, Perez M. Gestational Age and Developmental Risk in Moderately and Late Preterm and Early Term Infants. *Pediatrics* 2015;**135**(4):e835-e841 doi: 10.1542/peds.2014-1957published Online First.
22 Kinney HC. The near-term (late preterm) human brain and risk for periventricular leukomalacia: a review. *Seminars in perinatology* 2006;**30**(2):81-88 doi: 10.1053/j.semperi.2006.02.006published Online First.
23 Quigley MA, Poulsen G, Boyle E, Wolke D, Field D, Alfirevic Z, et al. Early term and late preterm birth are associated with poorer school performance at

age 5 years: a cohort study. *Archives of Disease in Childhood - Fetal and Neonatal Edition* 2012;**97**(3):F167-F173 doi: 10.1136/archdischild-2011-300888published Online First.

24 Hensch TK. Critical period plasticity in local cortical circuits. *Nat Rev Neurosci* 2005;**6**(11):877-888 doi: 10.1038/nrn1787published Online First: 2005/11/02].

25 Kapellou O, Counsell SJ, Kennea N, Dyet L, Saeed N, Stark J, et al. Abnormal cortical development after premature birth shown by altered allometric scaling of brain growth. *PLoS Med* 2006;**3**(8):e265 doi: 10.1371/journal.pmed.0030265published Online First: 2006/07/27].

26 Ip S, Chung M, Raman G, Chew P, Magula N, DeVine D, et al. Breastfeeding and maternal and infant health outcomes in developed countries. *Evid Rep Technol Assess (Full Rep)* 2007(153):1-186 Online First: 2007/09/04].

27 Quigley MA, Hockley C, Carson C, Kelly Y, Renfrew MJ, Sacker A. Breastfeeding is associated with improved child cognitive development: a population-based cohort study. *The Journal of pediatrics* 2012;**160**(1):25-32 doi: 10.1016/j.jpeds.2011.06.035published Online First.

28 Boucher O, Julvez J, Guxens M, Arranz E, Ibarluzea J, Sanchez de Miguel M, et al. Association between breastfeeding duration and cognitive development, autistic traits and ADHD symptoms: a multicenter study in Spain. *Pediatric research* 2017;**81**(3):434-442 doi: 10.1038/pr.2016.238published Online First.

29 Girard LC, Doyle O, Tremblay RE. Breastfeeding, Cognitive and Noncognitive Development in Early Childhood: A Population Study. *Pediatrics* 2017;**139**(4) doi: 10.1542/peds.2016-1848published Online First.

30 Koh K. Maternal breastfeeding and children's cognitive development. *Social science & medicine* 2017;**187**:101-108 doi: 10.1016/j.socscimed.2017.06.012published Online First.

31 Räisänen SH, Wu CS, Sun Y, Nohr EA, Olsen J. Trends in All-Cause Mortality across Gestational Age in Days for Children Born at Term. *PloS one* 2015;**10**(12):e0144754 doi: 10.1371/journal.pone.0144754published Online First.

32 Crump C, Sundquist K, Winkleby MA, Sundquist J. Early-term birth (37-38 weeks) and mortality in young adulthood. *Epidemiology* 2013;**24**(2):270-276 doi: 10.1097/EDE.0b013e318280da0fpublished Online First: 2013/01/23].

33 Zhang X, Kramer MS. Variations in mortality and morbidity by gestational age among infants born at term. *J Pediatr* 2009;**154**(3):358-362, 362.e351 doi: 10.1016/j.jpeds.2008.09.013published Online First: 2008/10/28].

34 Andrade SA, Santos DN, Bastos AC, Pedromonico MR, de Almeida-Filho N, Barreto ML. [Family environment and child's cognitive development: an epidemiological approach]. *Revista de saude publica* 2005;**39**(4):606-611 doi: /S0034-89102005000400014published Online First.

35 Sierau S, Dahne V, Brand T, Kurtz V, von Klitzing K, Jungmann T. Effects of Home Visitation on Maternal Competencies, Family Environment, and Child Development: a Randomized Controlled Trial. *Prevention science : the official journal of the Society for Prevention Research* 2016;**17**(1):40-51 doi: 10.1007/s11121-015-0573-8published Online First.

36 Hua J, Duan T, Gu G, Wo D, Zhu Q, Liu JQ, et al. Effects of home and education environments on children's motor performance in China. *Developmental medicine and child neurology* 2016;**58**(8):868-876 doi: 10.1111/dmcn.13073published Online First.

Table 1

Characteristics by Gestational age (n=1444)

	Total	Early term children		Full term children	*P*
		37wk [a] n (%)	38wk [a] n (%)	39-41 wk [a] n (%)	
Children's characteristic [b]					
Weight for length Z-score					
Normal	1156(80.1)	72(82.8)	162(79.0)	922(80.0)	0.765
Over-weighted	288(19.9)	15(17.2)	43(21.0)	230(20.0)	
Gender					
Male	722(50.0)	51(58.6)	110(53.7)	561(48.7)	0.107
Female	722(50.0)	36(41.4)	95(46.3)	591(51.3)	
Maternal characteristic					
Parity, n(%)[b]					
Nulliparous	1255(8.9)	65(74.7)	181(88.3)	1009(87.6)	0.002**
Multiparous	189(13.1)	22(25.3)	24(11.7)	143(12.4)	
Maternal age at delivery					
≥35	49(3.4)	3(3.4)	6(2.9)	40(3.5)	0.924
<35	1395(9.6)	84(96.6)	199(97.1)	1112(96.5)	
Delivery mode, n(%)					
Caesarean Section	632(43.7)	43(49.4)	101(49.3)	664(57.6)	0.101
Vaginal birth	812(56.2)	44(50.6)	104(50.7)	488(42.4)	
Socio-economic status					
City					
Wuxi	480(33.2)	25(28.7)	92(44.9)	363(31.5)	<0.001***
Taiyuan	484(33.5)	2(2.3)	16(7.8)	466(40.5)	
Bingzhou	480(33.3)	60(69.0)	97(47.3)	323(28.0)	
Mother's higher education					
Yes	827(57.3)	53(60.9)	143(69.8)	631(54.8)	<0.001***
No	617(42.7)	34(39.1)	62(30.2)	521(45.2)	
Father's higher education					
Yes	880(60.9)	45(51.7)	151(73.7)	684(59.4)	<0.001***
No	564(39.1)	42(48.3)	54(26.3)	468(40.6)	
Mother's occupation					
Skilled	824(57.1)	45(51.7)	124(60.5)	655(56.9)	0.365
Non-skilled	620(42.9)	42(48.3)	81(39.5)	497(43.1)	
Father's occupation					
Skilled	869(60.2)	46(52.9)	129(62.9)	694(60.2)	0.275
Non-skilled	575(39.8)	41(47.1)	76(37.1)	458(39.8)	

[a] Gestational week

[b] Chi-square analysis

*P<0.05,** P<0.01,*** P<0.001

Table 2

Multivariate Linear Regression of Factors Associated With Bayley III Cognitive Development Scores

Characteristic	β[a](95%CI)	β[b](95%CI)	β[c](95%CI)	β[d](95%CI)
All subjects(n=1444)				
Full term[e]	Ref	Ref	Ref	Ref
Born at 37 gestational week	-1.213 (-2.718, 0.291)	-1.102(-2.604,0.400)	-0.950(-2.458, 0.557)	-0.620(-2.124, 0.885)
Born at 38 gestational week	0.968(-0.058,1.994)	0.997(-0.026,2.021)	0.963(-0.060, 1.986)	0.770(-0.248, 1.789)
Infants(n=844)				
Full term[e]	Ref	Ref	Ref	Ref
Born at 37 gestational week	-2.810 (-4.847,-0.774)**	-2.723(-4.765,-0.680)**	-2.545(-4.590, -0.500)*	-2.257(-4.280, -0.235)*
Born at 38 gestational week	0.450(-0.853,1.768)	0.532(-0.780,1.844)	0.548(-0.765, 1.861)	0.120(-1.180, 1.421)
Toddlers(n=600)				
Full term[e]	Ref	Ref	Ref	Ref
Born at 37 gestational week	0.623(-1.618,2.863)	0.639(-1.567,2.874)	0.720(-1.528,2.969)	0.935(-1.356,3.225)
Born at 38 gestational week	1.720(0.075,3.366)*	1.671(0.032,3.250)	1.449 (-0.140,3.139)	1.418(-0.243,3.076)

[a] Not adjusted for other variables

[b] Adjusted for children's characteristic (weight for length Z-score , gender ,)

[c] Adjusted for children's and maternal characteristic (delivery mode, parity, maternal age)

[d] Adjusted for children's and maternal characteristic, and socio-economic factors (city, mother' s and father's education and occupation)

[e] Children born at 39-41 gestational weeks

p*<0.05,*p*<0.01

Figure 1. **Number of infants and toddlers who completed the questionnaire and tests**

Figure 2. **Cognitive composite scores by gestational week in the study are expressed as means and 95% confidence intervals(n=1444)**

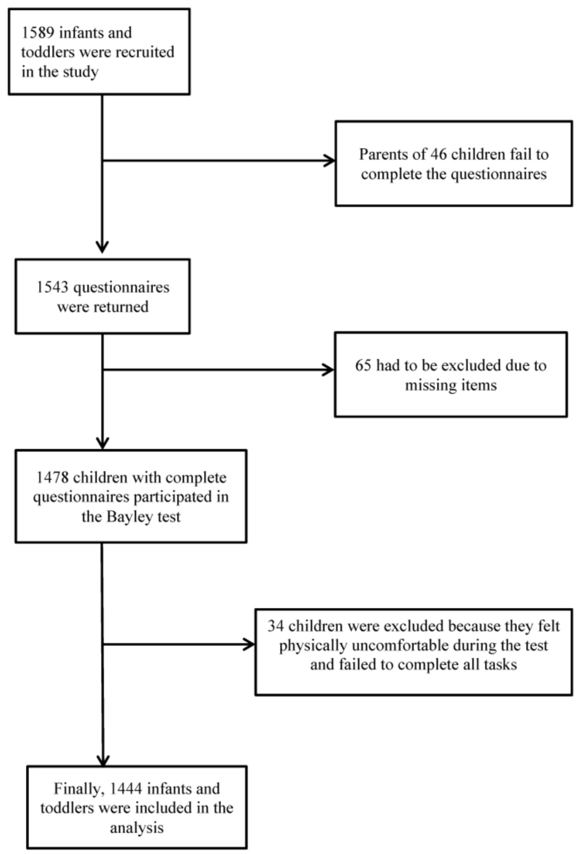

Figure 1. Number of infants and toddlers who completed the questionnaire and tests

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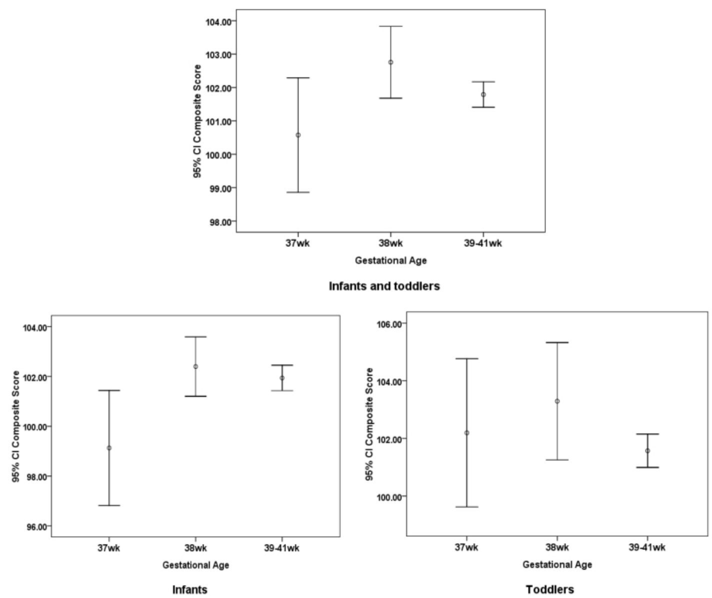

Figure 2. Cognitive composite scores by gestational week in the study are expressed as means and 95% confidence intervals(n=1444)

279x361mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	On page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3,4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5,6,7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4,5,6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	
Bias	9	Describe any efforts to address potential sources of bias	5,7,8
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6,7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7,8
		(*b*) Describe any methods used to examine subgroups and interactions	7,8
		(*c*) Explain how missing data were addressed	5, Figure1.
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	7,8
		(*e*) Describe any sensitivity analyses	

Continued on next page

Results			On page
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	5, Figure1.
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	Table I~IV
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9,10
		(*b*) Report category boundaries when continuous variables were categorized	9,10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9,10
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11,12
Generalisability	21	Discuss the generalisability (external validity) of the study results	10,11,12,13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Differentiating the cognitive development of early term births in Chinese infants and toddlers

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ABSTRACT

Objectives: This study aimed to explore the cognitive development of low-risk children during early childhood for early term births at 37 and 38 weeks of gestation compared to full term births at 39-41 weeks of gestation.

Setting and Participants: We conducted a cross-sectional study in Shanghai, one of the largest cities in China. A total of 1444 children from singleton pregnancies born at term gestation were included in the study.

Measures: The cognitive outcomes of the subjects were measured using the cognitive subtest of Bayley Scales of Infant and toddler Development-third Edition (BSID-III) across three cities in China. We analyzed the association between gestational age and cognitive development during infancy and toddler stages using multivariate linear modeling.

Results: The cognitive development scores for infants born at 37 gestational weeks were significantly lower than those born at 39 to 41 gestational weeks (β=-2.257, 95%CI:-4.280 to -0.235; $p<0.05$) after adjusting for children's and maternal characteristics, as well as socio-economic factors. However, there were no significant differences in cognitive ability between infants born at 38 gestational weeks compared to their full-term counterparts ($p>0.05$). Moreover, these effects were not found in toddlers (between 17 and 48 months of age) after adjusting for the possible confounders ($p>0.05$).

Conclusions: Infants born at 37 weeks of gestation exhibited weaker cognitive ability compared with those born at 39-41 weeks of gestation. Our findings provide evidences for the close monitoring of potential developmental problems in early term children, especially those born at 37 gestational weeks.

***Keywords*:** Cognitive development; early term, infants and toddlers; China

Strengths and limitations of this study

- Our findings extend the limited available literature on the relationship of gestational age with cognitive developmental scores. Infants born at 37 weeks of gestation had significantly weaker cognitive ability compared with their full-term counterparts.
- Our finding provided evidences for the close monitoring of potential developmental problems in early term children, especially in those born at 37 gestational weeks.
- The sample size was relatively small in our study (n=1444), and the results were not consistent across different age groups. Further studies are needed in order to verify this result.
- Although we examined a number of potential confounders, several other confounding factors were not measured. For instance, the detailed maternal and obstetric factors for early-term deliveries were not available in our study.

INTRODUCTION

It had been previously believed that children born between 37 and 41 weeks of gestational age share similar health outcomes, therefore including them in the same low-risk group.[1] In 2012, the American Academy of Pediatrics recommended that births occurring between 37 weeks 0 days and 38 weeks 6 days be defined as early term, while those from 39 weeks 0 days through to 40 weeks 6 days as full term.[2] Approximately 27.6% of all births in the United States are early term,[3,4] far exceeding the number of preterm births.[4,5] Many studies have reported that early-term births are associated with higher neonatal morbidity and higher probability of NICU admission compared with their full term counterparts (> 38 gestational weeks).[6] Early term children also have increased susceptibility to various metabolic, neurologic and respiratory diseases.[7-9]

Recently, research into the effect of gestational age on developmental outcomes has directed attention to the investigation of early term infants.[10] There have been increasing reports which show that early term births resulted in worsened cognitive and academic outcomes compared to those born at 39 weeks or later.[1,10-13] A systematic review showed that full-term cohorts performed 3% of a standard deviation higher in cognitive outcome than early term cohorts[10]. The gestation period between 37-40 weeks was associated with neuromotor and cognitive development in 9- to 15-week-old and 12-month-old infants.[13,14] Early term birth was associated with an increased risk of worsened academic achievements at ages 5 to 7 years.[15,16]

However, on the basis of recent research,[13,17-19] the exact boundary which separates early term and full term gestation periods should be carefully examined because of its implications for neonatal and developmental outcomes. The highest risk of mortality was observed for children born at 37 gestational weeks, but not for those born at 38 gestational weeks.[19] Furthermore, a prospective cohort study in Belarus showed that children born at 37 gestational weeks had a significantly lower full-scale intelligence quotient (IQ) score compared with those born at 39-41 weeks, however, this difference was not observed in children born at 38 gestational weeks.[20] Moreover, in a large sample of healthy infants, there was a significant difference in the mental development index (MDI) between infants born at 37 and 38 gestational weeks, but almost no difference between those born at 38 and 39 gestational weeks.[13] However, the degree to which earlier gestational age confers risk among infants born at term from 37 to 41 weeks of gestation remains unclear.[12,20,21]

In this study, we used a cross-sectional study design to examine a sample of urban Chinese singleton pregnancies born at term gestation. We hypothesized that early term births may result in significant cognitive delay, especially those born at 37 gestational weeks. We further examined the differences in cognitive ability in both infants and toddlers across various term births in order to determine the true underlying risk across different gestational weeks. The aim of the study is: 1) to differentiate the cognitive development of children born at 37, 38 and 39-41 gestational weeks; 2) to independently analyze the effects of gestational weeks on cognitive development in both short-term (infants) and long term (toddlers), in order

to provide evidences for the close monitoring of potential developmental problems in early term children.

MATERIALS AND METHODS

Participants

We conducted a cross-sectional study in mainland China from May to December of 2011. We used a stratified sampling technique, with area, gender, and months of age as stratification variables. A total of 1589 children aged between 16 days to 42 months were selected from 3 children's healthcare institutions in medium-sized cities distributed across 3 geographic regions: North China, Middle China, and East China. The selection of age bands was based on the categories proposed in the Bayley-III technical manual (totaling 48 age bands). The inclusion criteria for infants and toddlers included: singleton and born at term, born without significant medical complications, did not have a history of medical complications, and not currently diagnosed with or receiving treatment for mental, physical or behavioral difficulties. The exclusion criteria included: confounding conditions or developmental risk factors such as abnormal hearing or vision, taking medications that could affect performance or admission to hospital at the time of testing, and any other problems involving nutrition, sleep or infections during the clinical visit. Of the 1589 eligible children who were recruited, a total of 1444 children were included for the study (Figure 1). All information was kept confidential and was only accessible to the researchers.

Patient and Public Involvement

None of the patients were involved in the research design or development of the research question and outcome measures. They were also not involved in the recruitment and conduct of the study. The results of the study would be disseminated to study participants by means of the participating children's healthcare institutions.

Measurements

The Bayley Scale of Infant and Toddler Development, Third Edition (Bayley-III) is an individually administered scale that assesses five key developmental domains in children between 1-42 months of age: cognition, language (receptive and expressive communication), motor (gross and fine), social-emotional and adaptive behavior. The first three domains are assessed through direct observation of the child in test situations, while the last two are assessed through questionnaires to be completed by the main caregiver. We first obtained formal permission to translate and validate the Bayley-III scale from the American publishers of this tool (Pearson). We then started developing a Chinese version of Bayley-III, following the recommendations of Hambleton and Patsula (1999), and Herdman, Fox-Rushby and Badia (1998) for the translation and adaptation of a test, taking into consideration conceptual, item, semantic, operational, measurement and functional equivalences. Each step of this process was presented in the results section. The Chinese version of the BSID-III was translated by a native Chinese speaker and independent professional who adapted the items into context and culture. Subsequently, the final Chinese version of the

BSID-III was retranslated into English by two native English speakers who were blinded to the original version. The test manual and materials will utilize the same trademark, logo, and design as used on the English version of the test. We have explored the reliability and validity of the Bayley-III cognitive scale in a parallel study, which showed a good to excellent reliability of the Bayley-III cognitive scale (e.g. the coefficients of inter-item consistency were more than 0.75; the test-retest and inter-rater reliability of the scale were more than 0.90). The content, construct and known-group validity of Bayley-III cognitive scale were also sufficient in the parallel study. Additionally, gestational age is measured as the age of a pregnancy which was taken from the woman's last menstrual period, records of which were obtained from the hospital's medical record registration system following confirmation by ultrasound exam.

Procedure

The survey was conducted during the well-child visits in the participating children's healthcare institutions. Nurses who took part in the check in and physical examination (weight, height and head circumference) were responsible for handing out the questionnaires to the children's parents. Six developmental pediatricians were trained to administrate the Bayley-III cognitive scale. The testers had become familiar with the test guidance by carrying out a series of practice assessments on several children who did not take part in the study. Any problems associated with test administration during the training period were clarified by the administrator of this study prior to the

test. The test environment was quiet and non-interfering, and all infants and toddlers needed to be calm, stable and satiated. The tester encouraged the infants and toddlers to display their highest level of ability during the test. A trained pediatrician took the responsibility for conducting the entire test for each child in order to maximize both interpretation validity and assessment reliability.

Statistical analysis

All analyses were performed using SPSS 17.0 software. Chi-square analyses were used for comparing children and maternal characteristics between those born at 37 or 38 gestational weeks and those born at full term (39-41 gestational weeks). Means of cognitive scores among different gestational weeks was evaluated using one-way ANOVA and post-hoc comparison. Multivariate linear regression was used to test the relationship between gestational age and cognitive developmental scores, taking into account potential confounding variables including gender, weight-for-length Z-scores, parity, mother's age, delivery mode, parents' education and occupation. Social economic factors were not included because they were highly correlated with parental occupation. $p<0.05$ was considered statistically significant.

RESULTS

Of the 1444 children included in the study, 844 were infants aged between 16 days after birth to 16 months (58.4%), and 600 were toddlers aged between 17 months to 48 months (41.6%). Among these subjects, 1152 (79.8%) were full term births, 87

(6.02%) were born at 37 gestational weeks, and 205 (14.2%) were born at 38 gestational weeks. The mean cognitive composite score was 101.9, with a standard deviation of 6.9. The parity, the family's city of residence, and parents' education were significantly different among those born at 37, 38 and 39-41 gestational ages (Table 1).

The cognitive composite score was expressed as means and 95% confidence interval (Figure 2). In infants aged between 16 days to 16 months, the cognitive composite score for those born at 37 gestational weeks of age was significantly lower than those born at 39-41 gestation weeks (p<0.05).

Using multivariate linear regression model, cognitive composite scores for children born at 37 weeks decreased 2.810 (95%CI:-4.847 to -0.774) when compared with those born at 39-41 gestational weeks during infancy with statistical significance (p=0.007) without adjusting for (β=-2.810, . The effects remained when adjusting for the children's characteristics only (β=-2.723, 95%CI:-4.765 to -0.680; p=0.009), or in combination with maternal characteristics (β=-2.545, 95%CI:-4.590 to -0.500; p=0.015), as well as socio-economic factors (β=-2.257, 95%CI:-4.280 to -0.235; p=0.029; Table 2).

However, in toddlers aged between 17 months to 48 months (Table 2), there were almost no statistically significant associations between those born at 37 or 38 gestational weeks to those born in full term (39-41 gestational weeks). The only difference was a slightly higher composite cognitive score (β=1.723, 95%CI: 0.075 to 3.366; p=0.041) in toddlers born at 38 gestational weeks compared to those born in full term, when not adjusting for any other variables. The effects disappeared when adjusting the other variables.

DISCUSSION

To our knowledge, our paper is the first in China and one of few studies in the world to report on the short- and long-term neurobehavioral outcomes of early term children. A weaker cognitive ability was observed in infants born at 37 gestational weeks compared with their full-term (born at 39-41 gestational weeks) counterparts. Our findings extend the limited available literature on the relationship of gestational age to cognitive developmental scores.

In our study, we found that the effect of early term birth (37 gestational weeks) persisted in infancy even when a broad range of confounders including parental characteristics were considered. The mechanisms underlying the effect of early term birth on cognitive development scores may be multifactorial. The intrauterine and extrauterine environments differ dramatically in relationship to maternal and placental hormones, which may play an important role in brain development.[13] The intrauterine environment supports typical brain development, which is more likely to be disrupted in children born during early term gestation.[12] Moreover, brain development occurs in a very specific order and time frame.[10] The volume of total grey matter increases by approximately 1.4% per week from 29 to 41 weeks of gestation, while the volume of white matter sees a fivefold increase between 35 and 41 weeks of gestation.[15,22] Early term births may cause disruptions at specific times during the development of the brain's neural connections for specific cognitive areas. [23] Even at 38 weeks of gestation, the brain is still only 90% of full-term weight.[24] However, there have been no studies about the subtle differences in brain development between infants born at 37 and 38 gestational weeks. Future research is necessary to investigate the mechanisms behind this phenomenon.

Additionally, children who were born early term may have a shorter breastfeeding duration compared with children born at full term. [15,25-27] The breastfeeding duration was positively associated with children's cognitive development,[28,29] possibly due to the abundance of cognition-related nutrients found in breast milk such as docosahexaenoic (DHA) and arachidonic acid. Shorter breastfeeding duration may result in an increase in morbidity such as asthma and the number of hospital admissions, which was associated with a delay in achieving early developmental milestones that may have an effect educational achievements.[15]

This finding further supports the results from previous related research. For example, the highest mortality rate was observed among children born at 37 weeks of gestation, which necessitates caution in inducing labor for early term pregnancies (37 weeks of gestation). When gestational age in days was classified as gestational weeks, the mortality for children born at 37 weeks of gestation was higher compared to later-term births,[17,30-32] however, children born at 38 weeks of gestation was not associated with an increased mortality. Thus, the true underlying problems for children born in week 37, remains unknown. Our findings, combined with these studies, also provide the evidences for the categorization of early term births. Close monitoring for any signs of developmental problems is of the utmost importance in children born at 37 gestational weeks.

Interestingly, in our study, the problems associated with early term birth was not found in toddlers (aged between 17 months to 48 months), possibly due to the fact that the family parenting environment had a greater impact on long-term outcomes, which 'weakened' the association between early term birth and cognitive development. A previous study showed that the quality of stimulation in the family environment is crucial for the child's cognitive development.[33] A randomized control trial suggested that intervention on family environment and maternal competency has positive effects on child development (including cognitive and motor development).[34] In China, the effects of home and educational environments can promote the motor performance in preschoolers.[35]

CONCLUSIONS

Our study showed that the cognitive development scores for children born at 37 gestational weeks were significantly lower than those born at 39 to 41 gestation weeks. Therefore, healthcare professionals need to be more aware of the potential short-term and long-term care requirements of early term children. Close monitoring for any signs of health and developmental problems in early term children born at 37 gestational weeks can allow the early detection and timely treatment of borderline abnormalities, as well as prevent any potential negative health outcomes. However, because the sample size of our study was relatively small, and the results were not consistent across different age groups. Only early cognitive development was affected by early term birth, which may provide limited evidence for public health. Further studies are needed in order to verify these results.

Moreover, although we examined a number of potential confounders, several other confounding factors were not measured. For instance, fetal distress, hypertensive disorder complicating pregnancy, and gestational diabetes mellitus which may affect offspring's cognitive development according to the literature. These maternal and obstetric factors for early-term deliveries were not available in our study, and these factors will be considered in our further research. Further, the cognitive developmental scores of children in our study are all normal (above 80 points), possibly because we selected singletons born at term birth who were mostly at low-risk.

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Contributors JH, JS, ZC and JG contributed to the study design and drafting of the paper. XD and SL were responsible for literature search, quality control of the testing, and data collection. WD and GG revised the paper and approved the finalized manuscript submission.

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Competing interests None declared.

Ethics approval The study received ethical approval from the Local Committee of Soochow University, China (201101). Written informed consent was obtained from the parents or legal guardians of the participants prior to the questionnaire survey. Oral parental consents were obtained prior to investigation and tests.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Data sets generated and/or analysed during the current study available from the corresponding author on reasonable request.

Conflict of interest statement

None declared.

References

1 Sengupta S, Carrion V, Shelton J, Wynn RJ, Ryan RM, Singhal K, et al. Adverse Neonatal Outcomes Associated With Early-Term Birth. *JAMA Pediatrics* 2013;**167**(11):1053 doi: 10.1001/jamapediatrics.2013.2581published Online First.

2 Spong CY. Defining "Term" Pregnancy. *Jama* 2013;**309**(23):2445 doi: 10.1001/jama.2013.6235published Online First.

3 Martin JA, Hamilton BE, Sutton PD, Ventura SJ, Mathews TJ, Kirmeyer S, et al. Births: final data for 2007. *Natl Vital Stat Rep* 2010;**58**(24):1-85 Online First: 2011/01/25].

4 Martin JA, Hamilton BE, Ventura SJ, Osterman MJ, Kirmeyer S, Mathews TJ, et al. Births: final data for 2009. *Natl Vital Stat Rep* 2011;**60**(1):1-70 Online First: 2012/06/08].

5 Mally PV, Agathis NT, Bailey SM. Early term infants are at increased risk of requiring neonatal intensive care. *World journal of pediatrics : WJP* 2016;**12**(1):76-81 doi: 10.1007/s12519-015-0049-8published Online First.

6 Craighead DV. Early term birth: understanding the health risks to infants. *Nursing for women's health* 2012;**16**(2):136-144; quiz 145 doi: 10.1111/j.1751-486X.2012.01719.xpublished Online First.

7 Schonhaut L, Armijo I, Perez M. Gestational age and developmental risk in moderately and late preterm and early term infants. *Pediatrics* 2015;**135**(4):e835-841 doi: 10.1542/peds.2014-1957published Online First.

8 Rabie NZ, Bird TM, Magann EF, Hall RW, McKelvey SS. ADHD and developmental speech/language disorders in late preterm, early term and term infants. *Journal of perinatology : official journal of the California Perinatal Association* 2015;**35**(8):660-664 doi: 10.1038/jp.2015.28published Online First.

9 Goyal NK, Attanasio LB, Kozhimannil KB. Hospital care and early breastfeeding outcomes among late preterm, early-term, and term infants. *Birth* 2014;**41**(4):330-338 doi: 10.1111/birt.12135published Online First.

10 Chan E, Leong P, Malouf R, Quigley MA. Long-term cognitive and school outcomes of late-preterm and early-term births: a systematic review. *Child: Care, Health and Development* 2016;**42**(3):297-312 doi: 10.1111/cch.12320published Online First.

11 Richards JL, Drews-Botsch C, Sales JM, Flanders WD, Kramer MR. Describing the Shape of the Relationship Between Gestational Age at Birth and Cognitive Development in a Nationally Representative U.S. Birth Cohort. *Paediatric and Perinatal Epidemiology* 2016;**30**(6):571-582 doi: 10.1111/ppe.12319published Online First.

12 Noble KG, Fifer WP, Rauh VA, Nomura Y, Andrews HF. Academic Achievement Varies With Gestational Age Among Children Born at Term.

Pediatrics 2012;**130**(2):e257-e264 doi: 10.1542/peds.2011-2157published Online First.

13 Rose O, Blanco E, Martinez SM, Sim EK, Castillo M, Lozoff B, et al. Developmental scores at 1 year with increasing gestational age, 37-41 weeks. *Pediatrics* 2013;**131**(5):e1475-1481 doi: 10.1542/peds.2012-3215published Online First.

14 van Batenburg-Eddes T, de Groot L, Arends L, de Vries A, Moll HA, Steegers EA, et al. Does gestational duration within the normal range predict infant neuromotor development? *Early human development* 2008;**84**(10):659-665 doi: 10.1016/j.earlhumdev.2008.04.007published Online First.

15 Quigley MA, Poulsen G, Boyle E, Wolke D, Field D, Alfirevic Z, et al. Early term and late preterm birth are associated with poorer school performance at age 5 years: a cohort study. *Archives of disease in childhood. Fetal and neonatal edition* 2012;**97**(3):F167-173 doi: 10.1136/archdischild-2011-300888published Online First.

16 Chan E, Quigley MA. School performance at age 7 years in late preterm and early term birth: a cohort study. *Arch Dis Child Fetal Neonatal Ed* 2014;**99**(6):F451-F457 doi: 10.1136/archdischild-2014-306124published Online First.

17 Reddy UM, Bettegowda VR, Dias T, Yamada-Kushnir T, Ko CW, Willinger M. Term pregnancy: a period of heterogeneous risk for infant mortality. *Obstetrics and gynecology* 2011;**117**(6):1279-1287 doi: 10.1097/AOG.0b013e3182179e28published Online First.

18 Engle WA. Morbidity and mortality in late preterm and early term newborns: a continuum. *Clinics in perinatology* 2011;**38**(3):493-516 doi: 10.1016/j.clp.2011.06.009published Online First.

19 Wu CS, Sun Y, Nohr EA, Olsen J. Trends in All-Cause Mortality across Gestational Age in Days for Children Born at Term. *PloS one* 2015;**10**(12):e0144754 doi: 10.1371/journal.pone.0144754published Online First.

20 Yang S, Platt RW, Kramer MS. Variation in child cognitive ability by week of gestation among healthy term births. *American journal of epidemiology* 2010;**171**(4):399-406 doi: 10.1093/aje/kwp413published Online First.

21 Schonhaut L, Armijo I, Perez M. Gestational Age and Developmental Risk in Moderately and Late Preterm and Early Term Infants. *Pediatrics* 2015;**135**(4):e835-e841 doi: 10.1542/peds.2014-1957published Online First.

22 Kinney HC. The near-term (late preterm) human brain and risk for periventricular leukomalacia: a review. *Seminars in perinatology* 2006;**30**(2):81-88 doi: 10.1053/j.semperi.2006.02.006published Online First.

23 Hensch TK. Critical period plasticity in local cortical circuits. *Nat Rev Neurosci* 2005;**6**(11):877-888 doi: 10.1038/nrn1787published Online

First: 2005/11/02].

24 Kapellou O, Counsell SJ, Kennea N, Dyet L, Saeed N, Stark J, et al. Abnormal cortical development after premature birth shown by altered allometric scaling of brain growth. *PLoS Med* 2006;**3**(8):e265 doi: 10.1371/journal.pmed.0030265published Online First: 2006/07/27].

25 Ip S, Chung M, Raman G, Chew P, Magula N, DeVine D, et al. Breastfeeding and maternal and infant health outcomes in developed countries. *Evid Rep Technol Assess (Full Rep)* 2007(153):1-186 Online First: 2007/09/04].

26 Quigley MA, Hockley C, Carson C, Kelly Y, Renfrew MJ, Sacker A. Breastfeeding is associated with improved child cognitive development: a population-based cohort study. *The Journal of pediatrics* 2012;**160**(1):25-32 doi: 10.1016/j.jpeds.2011.06.035published Online First.

27 Boucher O, Julvez J, Guxens M, Arranz E, Ibarluzea J, Sanchez de Miguel M, et al. Association between breastfeeding duration and cognitive development, autistic traits and ADHD symptoms: a multicenter study in Spain. *Pediatric research* 2017;**81**(3):434-442 doi: 10.1038/pr.2016.238published Online First.

28 Girard LC, Doyle O, Tremblay RE. Breastfeeding, Cognitive and Noncognitive Development in Early Childhood: A Population Study. *Pediatrics* 2017;**139**(4) doi: 10.1542/peds.2016-1848published Online First.

29 Koh K. Maternal breastfeeding and children's cognitive development. *Social science & medicine* 2017;**187**:101-108 doi: 10.1016/j.socscimed.2017.06.012published Online First.

30 Räisänen SH, Wu CS, Sun Y, Nohr EA, Olsen J. Trends in All-Cause Mortality across Gestational Age in Days for Children Born at Term. *PloS one* 2015;**10**(12):e0144754 doi: 10.1371/journal.pone.0144754published Online First.

31 Crump C, Sundquist K, Winkleby MA, Sundquist J. Early-term birth (37-38 weeks) and mortality in young adulthood. *Epidemiology* 2013;**24**(2):270-276 doi: 10.1097/EDE.0b013e318280da0fpublished Online First: 2013/01/23].

32 Zhang X, Kramer MS. Variations in mortality and morbidity by gestational age among infants born at term. *J Pediatr* 2009;**154**(3):358-362, 362.e351 doi: 10.1016/j.jpeds.2008.09.013published Online First: 2008/10/28].

33 Andrade SA, Santos DN, Bastos AC, Pedromonico MR, de Almeida-Filho N, Barreto ML. [Family environment and child's cognitive development: an epidemiological approach]. *Revista de saude publica* 2005;**39**(4):606-611 doi: /S0034-89102005000400014published Online First.

34 Sierau S, Dahne V, Brand T, Kurtz V, von Klitzing K, Jungmann T. Effects of Home Visitation on Maternal Competencies, Family Environment, and Child Development: a Randomized Controlled Trial. *Prevention science : the official journal of the Society for Prevention Research* 2016;**17**(1):40-51 doi: 10.1007/s11121-015-0573-8published Online

First.
35 Hua J, Duan T, Gu G, Wo D, Zhu Q, Liu JQ, et al. Effects of home and education environments on children's motor performance in China. *Developmental medicine and child neurology* 2016;**58**(8):868-876 doi: 10.1111/dmcn.13073published Online First.

Table 1

Characteristics by Gestational age (n=1444)

	Total	Early term children		Full term children	*P*
		37wk [a] n (%)	38wk [a] n (%)	39-41 wk [a] n (%)	
Children's characteristic [b]					
Weight for length Z-score					
Normal	1156(80.1)	72(82.8)	162(79.0)	922(80.0)	0.765
Over-weighted	288(19.9)	15(17.2)	43(21.0)	230(20.0)	
Gender					
Male	722(50.0)	51(58.6)	110(53.7)	561(48.7)	0.107
Female	722(50.0)	36(41.4)	95(46.3)	591(51.3)	
Maternal characteristic					
Parity, n(%)[b]					
Nulliparous	1255(8.9)	65(74.7)	181(88.3)	1009(87.6)	0.002**
Multiparous	189(13.1)	22(25.3)	24(11.7)	143(12.4)	
Maternal age at delivery					
≥35	49(3.4)	3(3.4)	6(2.9)	40(3.5)	0.924
<35	1395(9.6)	84(96.6)	199(97.1)	1112(96.5)	
Delivery mode, n(%)					
Caesarean Section	632(43.7)	43(49.4)	101(49.3)	664(57.6)	0.101
Vaginal birth	812(56.2)	44(50.6)	104(50.7)	488(42.4)	
Socio-economic status					
City					
Wuxi	480(33.2)	25(28.7)	92(44.9)	363(31.5)	<0.001***
Taiyuan	484(33.5)	2(2.3)	16(7.8)	466(40.5)	
Bingzhou	480(33.3)	60(69.0)	97(47.3)	323(28.0)	
Mother's higher education					
Yes	827(57.3)	53(60.9)	143(69.8)	631(54.8)	<0.001***
No	617(42.7)	34(39.1)	62(30.2)	521(45.2)	
Father's higher education					
Yes	880(60.9)	45(51.7)	151(73.7)	684(59.4)	<0.001***
No	564(39.1)	42(48.3)	54(26.3)	468(40.6)	
Mother's occupation					
Skilled	824(57.1)	45(51.7)	124(60.5)	655(56.9)	0.365
Non-skilled	620(42.9)	42(48.3)	81(39.5)	497(43.1)	
Father's occupation					
Skilled	869(60.2)	46(52.9)	129(62.9)	694(60.2)	0.275
Non-skilled	575(39.8)	41(47.1)	76(37.1)	458(39.8)	

[a] Gestational week

[b] Chi-square analysis

*$P<0.05$,** $P<0.01$,*** $P<0.001$

Table 2
Multivariate Linear Regression of Factors Associated With Bayley III Cognitive Development Scores

Characteristic	n (%)	β[a](95%CI)	β[b](95%CI)	β[c](95%CI)	β[d](95%CI)
All subjects(n=1444)					
Full term[e]	87(6.0)	Ref	Ref	Ref	Ref
Born at 37 gestational week	205(14.2)	-1.213 (-2.718, 0.291)	-1.102(-2.604,0.400)	-0.950(-2.458, 0.557)	-0.620(-2.124, 0.885)
Born at 38 gestational week	1152(79.8)	0.968(-0.058,1.994)	0.997(-0.026,2.021)	0.963(-0.060, 1.986)	0.770(-0.248, 1.789)
Infants(n=844)					
Full term[e]	46(5.5)	Ref	Ref	Ref	Ref
Born at 37 gestational week	123(14.6)	-2.810 (-4.847,-0.774)**	-2.723(-4.765,-0.680)**	-2.545(-4.590, -0.500)*	-2.257(-4.280, -0.235)*
Born at 38 gestational week	675(80.0)	0.450(-0.853,1.768)	0.532(-0.780,1.844)	0.548(-0.765, 1.861)	0.120(-1.180, 1.421)
Toddlers(n=600)					
Full term[e]	41(6.8)	Ref	Ref	Ref	Ref
Born at 37 gestational week	82(13.7)	0.623(-1.618,2.863)	0.639(-1.567,2.874)	0.720(-1.528,2.969)	0.935(-1.356,3.225)
Born at 38 gestational week	477(79.5)	1.720(0.075,3.366)*	1.671(0.032,3.250)	1.449 (-0.140,3.139)	1.418(-0.243,3.076)

[a] Not adjusted for other variables
[b] Adjusted for children's characteristic (weight for length Z-score , gender ,)
[c] Adjusted for children's and maternal characteristic (delivery mode, parity, maternal age)
[d] Adjusted for children's and maternal characteristic, and socio-economic factors (city, mother' s and father's education and occupation)
[e] Children born at 39-41 gestational weeks
*$p<0.05$,**$p<0.01$

Figure 1. Number of infants and toddlers who completed the questionnaire and tests

Figure 2. Cognitive composite scores by gestational week in the study are expressed as means and 95% confidence intervals(n=1444)

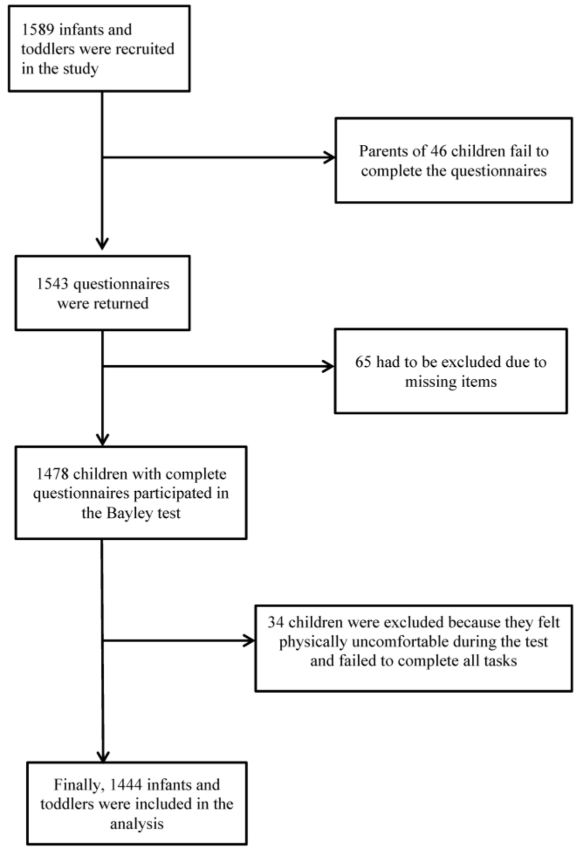

Figure 1. Number of infants and toddlers who completed the questionnaire and tests

279x361mm (300 x 300 DPI)

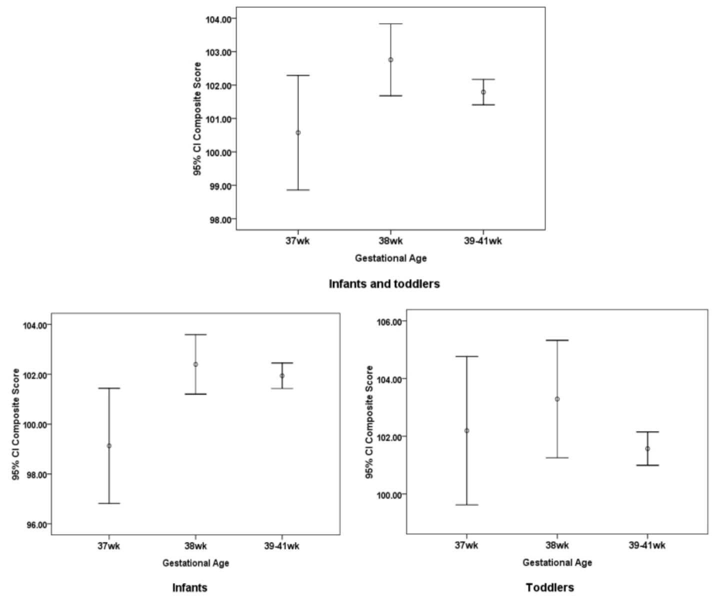

Figure 2. Cognitive composite scores by gestational week in the study are expressed as means and 95% confidence intervals(n=1444)

279x361mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	On page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3,4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5,6,7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4,5,6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	
Bias	9	Describe any efforts to address potential sources of bias	5,7,8
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6,7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7,8
		(*b*) Describe any methods used to examine subgroups and interactions	7,8
		(*c*) Explain how missing data were addressed	5, Figure1.
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	7,8
		(*e*) Describe any sensitivity analyses	

Continued on next page

Results			On page
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	5, Figure1.
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	Table I~IV
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9,10
		(*b*) Report category boundaries when continuous variables were categorized	9,10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9,10
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11,12
Generalisability	21	Discuss the generalisability (external validity) of the study results	10,11,12,13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Differentiating the cognitive development of early term births in infants and toddlers: a cross-sectional study in China

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Differentiating the cognitive development of early term births in infants and toddlers: a cross-sectional study in China

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ABSTRACT

Objectives: This study aimed to explore the cognitive development of low-risk children during early childhood for early term births at 37 and 38 weeks of gestation compared to full term births at 39-41 weeks of gestation.

Setting and Participants: We conducted a cross-sectional study in Shanghai, one of the largest cities in China. A total of 1444 children from singleton pregnancies born at term gestation were included in the study.

Measures: The cognitive outcomes of the subjects were measured using the cognitive subtest of Bayley Scales of Infant and toddler Development-third Edition (BSID-III) across three cities in China. We analyzed the association between gestational age and cognitive development during infancy and toddler stages using multivariate linear modeling.

Results: The cognitive development scores for infants born at 37 gestational weeks were significantly lower than those born at 39 to 41 gestational weeks (β=-2.257, 95%CI:-4.280 to -0.235; p<0.05) after adjusting for children's and maternal characteristics, as well as socio-economic factors. However, there were no significant differences in cognitive ability between infants born at 38 gestational weeks compared to their full-term counterparts (p>0.05). Moreover, these effects were not found in toddlers (between 17 and 48 months of age) after adjusting for the possible confounders (p>0.05).

Conclusions: Infants born at 37 weeks of gestation exhibited weaker cognitive ability compared with those born at 39-41 weeks of gestation. Our findings provide evidences for the close monitoring of potential developmental problems in early term children, especially those born at 37 gestational weeks.

***Keywords*:** Cognitive development; early term, infants and toddlers; China

Strengths and limitations of this study

- Our findings extend the limited available literature on the relationship of gestational age with cognitive developmental scores. Infants born at 37 weeks of gestation had significantly weaker cognitive ability compared with their full-term counterparts.
- Our finding provided evidences for the close monitoring of potential developmental problems in early term children, especially in those born at 37 gestational weeks.
- The sample size was relatively small in our study (n=1444), and the results were not consistent across different age groups. Further studies are needed in order to verify this result.
- Although we examined a number of potential confounders, several other confounding factors were not measured. For instance, the detailed maternal and obstetric factors for early-term deliveries were not available in our study.

INTRODUCTION

It had been previously believed that children born between 37 and 41 weeks of gestational age share similar health outcomes, therefore including them in the same low-risk group.[1] In 2012, the American Academy of Pediatrics recommended that births occurring between 37 weeks 0 days and 38 weeks 6 days be defined as early term, while those from 39 weeks 0 days through to 40 weeks 6 days as full term.[2] Approximately 27.6% of all births in the United States are early term,[3,4] far exceeding the number of preterm births.[4,5] Many studies have reported that early-term births are associated with higher neonatal morbidity and higher probability of NICU admission compared with their full term counterparts (> 38 gestational weeks).[6] Early term children also have increased susceptibility to various metabolic, neurologic and respiratory diseases.[7-9]

Recently, research into the effect of gestational age on developmental outcomes has directed attention to the investigation of early term infants.[10] There have been increasing reports which show that early term births resulted in worsened cognitive and academic outcomes compared to those born at 39 weeks or later.[1,10-13] A systematic review showed that full-term cohorts performed 3% of a standard deviation higher in cognitive outcome than early term cohorts[10]. The gestation period between 37-40 weeks was associated with neuromotor and cognitive development in 9- to 15-week-old and 12-month-old infants.[13,14] Early term birth was associated with an increased risk of worsened academic achievements at ages 5 to 7 years.[15,16]

However, on the basis of recent research,[13,17-19] the exact boundary which separates early term and full term gestation periods should be carefully examined because of its implications for neonatal and developmental outcomes. The highest risk of mortality was observed for children born at 37 gestational weeks, but not for those born at 38 gestational weeks.[19] Furthermore, a prospective cohort study in Belarus showed that children born at 37 gestational weeks had a significantly lower full-scale intelligence quotient (IQ) score compared with those born at 39-41 weeks, however, this difference was not observed in children born at 38 gestational weeks.[20] Moreover, in a large sample of healthy infants, there was a significant difference in the mental development index (MDI) between infants born at 37 and 38 gestational weeks, but almost no difference between those born at 38 and 39 gestational weeks.[13] However, the degree to which earlier gestational age confers risk among infants born at term from 37 to 41 weeks of gestation remains unclear.[12,20,21]

In this study, we used a cross-sectional study design to examine a sample of urban Chinese singleton pregnancies born at term gestation. We hypothesized that early term births may result in significant cognitive delay, especially those born at 37 gestational weeks. We further examined the differences in cognitive ability in both infants and toddlers across various term births in order to determine the true underlying risk across different gestational weeks. The aim of the study is: 1) to differentiate the cognitive development of children born at 37, 38 and 39-41 gestational weeks; 2) to independently analyze the effects of gestational weeks on cognitive development in both short-term (infants) and long term (toddlers), in order

to provide evidences for the close monitoring of potential developmental problems in early term children.

MATERIALS AND METHODS

Participants

We conducted a cross-sectional study in mainland China from May to December of 2011. We used a stratified sampling technique, with area, gender, and months of age as stratification variables. A total of 1589 children aged between 16 days to 42 months were selected from 3 children's healthcare institutions in medium-sized cities distributed across 3 geographic regions: North China, Middle China, and East China. The selection of age bands was based on the categories proposed in the Bayley-III technical manual (totaling 48 age bands). The inclusion criteria for infants and toddlers included: singleton and born at term, born without significant medical complications, did not have a history of medical complications, and not currently diagnosed with or receiving treatment for mental, physical or behavioral difficulties. The exclusion criteria included: confounding conditions or developmental risk factors such as abnormal hearing or vision, taking medications that could affect performance or admission to hospital at the time of testing, and any other problems involving nutrition, sleep or infections during the clinical visit. Of the 1589 eligible children who were recruited, a total of 1444 children were included for the study (Figure 1). All information was kept confidential and was only accessible to the researchers.

Patient and Public Involvement

None of the patients were involved in the research design or development of the research question and outcome measures. They were also not involved in the recruitment and conduct of the study. The results of the study would be disseminated to study participants by means of the participating children's healthcare institutions.

Measurements

The Bayley Scale of Infant and Toddler Development, Third Edition (Bayley-III) is an individually administered scale that assesses five key developmental domains in children between 1-42 months of age: cognition, language (receptive and expressive communication), motor (gross and fine), social-emotional and adaptive behavior. The first three domains are assessed through direct observation of the child in test situations, while the last two are assessed through questionnaires to be completed by the main caregiver. We first obtained formal permission to translate and validate the Bayley-III scale from the American publishers of this tool (Pearson). We then started developing a Chinese version of Bayley-III, following the recommendations of Hambleton and Patsula (1999), and Herdman, Fox-Rushby and Badia (1998) for the translation and adaptation of a test, taking into consideration conceptual, item, semantic, operational, measurement and functional equivalences. Each step of this process was presented in the results section. The Chinese version of the BSID-III was translated by a native Chinese speaker and independent professional who adapted the items into context and culture. Subsequently, the final Chinese version of the

BSID-III was retranslated into English by two native English speakers who were blinded to the original version. The test manual and materials will utilize the same trademark, logo, and design as used on the English version of the test. We have explored the reliability and validity of the Bayley-III cognitive scale in a parallel study, which showed a good to excellent reliability of the Bayley-III cognitive scale (e.g. the coefficients of inter-item consistency were more than 0.75; the test-retest and inter-rater reliability of the scale were more than 0.90). The content, construct and known-group validity of Bayley-III cognitive scale were also sufficient in the parallel study. Additionally, gestational age is measured as the age of a pregnancy which was taken from the woman's last menstrual period, records of which were obtained from the hospital's medical record registration system following confirmation by ultrasound exam.

Procedure

The survey was conducted during the well-child visits in the participating children's healthcare institutions. Nurses who took part in the check in and physical examination (weight, height and head circumference) were responsible for handing out the questionnaires to the children's parents. Six developmental pediatricians were trained to administrate the Bayley-III cognitive scale. The testers had become familiar with the test guidance by carrying out a series of practice assessments on several children who did not take part in the study. Any problems associated with test administration during the training period were clarified by the administrator of this study prior to the

test. The test environment was quiet and non-interfering, and all infants and toddlers needed to be calm, stable and satiated. The tester encouraged the infants and toddlers to display their highest level of ability during the test. A trained pediatrician took the responsibility for conducting the entire test for each child in order to maximize both interpretation validity and assessment reliability.

Statistical analysis

All analyses were performed using SPSS 17.0 software. Chi-square analyses were used for comparing children and maternal characteristics between those born at 37 or 38 gestational weeks and those born at full term (39-41 gestational weeks). Means of cognitive scores among different gestational weeks was evaluated using one-way ANOVA and post-hoc comparison. Multivariate linear regression was used to test the relationship between gestational age and cognitive developmental scores, taking into account potential confounding variables including gender, weight-for-length Z-scores, parity, mother's age, delivery mode, parents' education and occupation. Social economic factors were not included because they were highly correlated with parental occupation. $p<0.05$ was considered statistically significant.

RESULTS

Of the 1444 children included in the study, 844 were infants aged between 16 days after birth to 16 months (58.4%), and 600 were toddlers aged between 17 months to 48 months (41.6%). Among these subjects, 1152 (79.8%) were full term births, 87

(6.02%) were born at 37 gestational weeks, and 205 (14.2%) were born at 38 gestational weeks. The mean cognitive composite score was 101.9, with a standard deviation of 6.9. The parity, the family's city of residence, and parents' education were significantly different among those born at 37, 38 and 39-41 gestational ages (Table 1).

The cognitive composite score was expressed as means and 95% confidence interval (Figure 2). In infants aged between 16 days to 16 months, the cognitive composite score for those born at 37 gestational weeks of age was significantly lower than those born at 39-41 gestation weeks (p<0.05).

Using multivariate linear regression model, cognitive composite scores for children born at 37 weeks decreased 2.810 (95%CI:-4.847 to -0.774) when compared with those born at 39-41 gestational weeks during infancy with statistical significance (p=0.007) without adjusting for (β=-2.810, . The effects remained when adjusting for the children's characteristics only (β=-2.723, 95%CI:-4.765 to -0.680; p=0.009), or in combination with maternal characteristics (β=-2.545, 95%CI:-4.590 to -0.500; p=0.015), as well as socio-economic factors (β=-2.257, 95%CI:-4.280 to -0.235; p=0.029; Table 2).

However, in toddlers aged between 17 months to 48 months (Table 2), there were almost no statistically significant associations between those born at 37 or 38 gestational weeks to those born in full term (39-41 gestational weeks). The only difference was a slightly higher composite cognitive score (β=1.723, 95%CI: 0.075 to 3.366; p=0.041) in toddlers born at 38 gestational weeks compared to those born in full term, when not adjusting for any other variables. The effects disappeared when adjusting the other variables.

DISCUSSION

To our knowledge, our paper is the first in China and one of few studies in the world to report on the short- and long-term neurobehavioral outcomes of early term children. A weaker cognitive ability was observed in infants born at 37 gestational weeks compared with their full-term (born at 39-41 gestational weeks) counterparts. Our findings extend the limited available literature on the relationship of gestational age to cognitive developmental scores.

In our study, we found that the effect of early term birth (37 gestational weeks) persisted in infancy even when a broad range of confounders including parental characteristics were considered. The mechanisms underlying the effect of early term birth on cognitive development scores may be multifactorial. The intrauterine and extrauterine environments differ dramatically in relationship to maternal and placental hormones, which may play an important role in brain development.[13] The intrauterine environment supports typical brain development, which is more likely to be disrupted in children born during early term gestation.[12] Moreover, brain development occurs in a very specific order and time frame.[10] The volume of total grey matter increases by approximately 1.4% per week from 29 to 41 weeks of gestation, while the volume of white matter sees a fivefold increase between 35 and 41 weeks of gestation. [15,22] Early term births may cause disruptions at specific times during the development of the brain's neural connections for specific cognitive areas. [23] Even at 38 weeks of gestation, the brain is still only 90% of full-term weight.[24] However, there have been no studies about the subtle differences in brain development between infants born at 37 and 38 gestational weeks. Future research is necessary to investigate the mechanisms behind this phenomenon.

Additionally, children who were born early term may have a shorter breastfeeding duration compared with children born at full term. [15,25-27] The breastfeeding duration was positively associated with children's cognitive development,[28,29] possibly due to the abundance of cognition-related nutrients found in breast milk such as docosahexaenoic (DHA) and arachidonic acid. Shorter breastfeeding duration may result in an increase in morbidity such as asthma and the number of hospital admissions, which was associated with a delay in achieving early developmental milestones that may have an effect educational achievements.[15]

This finding further supports the results from previous related research. For example, the highest mortality rate was observed among children born at 37 weeks of gestation, which necessitates caution in inducing labor for early term pregnancies (37 weeks of gestation). When gestational age in days was classified as gestational weeks, the mortality for children born at 37 weeks of gestation was higher compared to later-term births,[17,30-32] however, children born at 38 weeks of gestation was not associated with an increased mortality. Thus, the true underlying problems for children born in week 37, remains unknown. Our findings, combined with these studies, also provide the evidences for the categorization of early term births. Close monitoring for any signs of developmental problems is of the utmost importance in children born at 37 gestational weeks.

Interestingly, in our study, the problems associated with early term birth was not found in toddlers (aged between 17 months to 48 months), possibly due to the fact that the family parenting environment had a greater impact on long-term outcomes, which 'weakened' the association between early term birth and cognitive development. A previous study showed that the quality of stimulation in the family environment is crucial for the child's cognitive development.[33] A randomized control trial suggested that intervention on family environment and maternal competency has positive effects on child development (including cognitive and motor development).[34] In China, the effects of home and educational environments can promote the motor performance in preschoolers.[35]

CONCLUSIONS

Our study showed that the cognitive development scores for children born at 37 gestational weeks were significantly lower than those born at 39 to 41 gestation weeks. Therefore, healthcare professionals need to be more aware of the potential short-term and long-term care requirements of early term children. Close monitoring for any signs of health and developmental problems in early term children born at 37 gestational weeks can allow the early detection and timely treatment of borderline abnormalities, as well as prevent any potential negative health outcomes. However, because the sample size of our study was relatively small, and the results were not consistent across different age groups. Only early cognitive development was affected by early term birth, which may provide limited evidence for public health. Further studies are needed in order to verify these results.

Moreover, although we examined a number of potential confounders, several other confounding factors were not measured. For instance, fetal distress, hypertensive disorder complicating pregnancy, and gestational diabetes mellitus which may affect offspring's cognitive development according to the literature. These maternal and obstetric factors for early-term deliveries were not available in our study, and these factors will be considered in our further research. Further, the cognitive developmental scores of children in our study are all normal (above 80 points), possibly because we selected singletons born at term birth who were mostly at low-risk.

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Contributors JH, JS, ZC and JG contributed to the study design and drafting of the paper. XD and SL were responsible for literature search, quality control of the testing, and data collection. WD and GG revised the paper and approved the finalized manuscript submission.

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Competing interests None declared.

Ethics approval The study received ethical approval from the Local Committee of Soochow University, China (201101). Written informed consent was obtained from the parents or legal guardians of the participants prior to the questionnaire survey. Oral parental consents were obtained prior to investigation and tests.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Data sets generated and/or analysed during the current study available from the corresponding author on reasonable request.

Conflict of interest statement

None declared.

References

1 Sengupta S, Carrion V, Shelton J, Wynn RJ, Ryan RM, Singhal K, et al. Adverse Neonatal Outcomes Associated With Early-Term Birth. *JAMA Pediatrics* 2013;**167**(11):1053 doi: 10.1001/jamapediatrics.2013.2581published Online First.

2 Spong CY. Defining "Term" Pregnancy. *Jama* 2013;**309**(23):2445 doi: 10.1001/jama.2013.6235published Online First.

3 Martin JA, Hamilton BE, Sutton PD, Ventura SJ, Mathews TJ, Kirmeyer S, et al. Births: final data for 2007. *Natl Vital Stat Rep* 2010;**58**(24):1-85 Online First: 2011/01/25].

4 Martin JA, Hamilton BE, Ventura SJ, Osterman MJ, Kirmeyer S, Mathews TJ, et al. Births: final data for 2009. *Natl Vital Stat Rep* 2011;**60**(1):1-70 Online First: 2012/06/08].

5 Mally PV, Agathis NT, Bailey SM. Early term infants are at increased risk of requiring neonatal intensive care. *World journal of pediatrics : WJP* 2016;**12**(1):76-81 doi: 10.1007/s12519-015-0049-8published Online First.

6 Craighead DV. Early term birth: understanding the health risks to infants. *Nursing for women's health* 2012;**16**(2):136-144; quiz 145 doi: 10.1111/j.1751-486X.2012.01719.xpublished Online First.

7 Schonhaut L, Armijo I, Perez M. Gestational age and developmental risk in moderately and late preterm and early term infants. *Pediatrics* 2015;**135**(4):e835-841 doi: 10.1542/peds.2014-1957published Online First.

8 Rabie NZ, Bird TM, Magann EF, Hall RW, McKelvey SS. ADHD and developmental speech/language disorders in late preterm, early term and term infants. *Journal of perinatology : official journal of the California Perinatal Association* 2015;**35**(8):660-664 doi: 10.1038/jp.2015.28published Online First.

9 Goyal NK, Attanasio LB, Kozhimannil KB. Hospital care and early breastfeeding outcomes among late preterm, early-term, and term infants. *Birth* 2014;**41**(4):330-338 doi: 10.1111/birt.12135published Online First.

10 Chan E, Leong P, Malouf R, Quigley MA. Long-term cognitive and school outcomes of late-preterm and early-term births: a systematic review. *Child: Care, Health and Development* 2016;**42**(3):297-312 doi: 10.1111/cch.12320published Online First.

11 Richards JL, Drews-Botsch C, Sales JM, Flanders WD, Kramer MR. Describing the Shape of the Relationship Between Gestational Age at Birth and Cognitive Development in a Nationally Representative U.S. Birth Cohort. *Paediatric and Perinatal Epidemiology* 2016;**30**(6):571-582 doi: 10.1111/ppe.12319published Online First.

12 Noble KG, Fifer WP, Rauh VA, Nomura Y, Andrews HF. Academic Achievement Varies With Gestational Age Among Children Born at Term. *Pediatrics* 2012;**130**(2):e257-e264 doi: 10.1542/peds.2011-2157published Online First.

13 Rose O, Blanco E, Martinez SM, Sim EK, Castillo M, Lozoff B, et al. Developmental scores at 1 year with increasing gestational age, 37-41 weeks. *Pediatrics* 2013;**131**(5):e1475-1481 doi: 10.1542/peds.2012-3215published Online First.

14 van Batenburg-Eddes T, de Groot L, Arends L, de Vries A, Moll HA, Steegers EA, et al. Does gestational duration within the normal range predict infant neuromotor development? *Early human development* 2008;**84**(10):659-665 doi: 10.1016/j.earlhumdev.2008.04.007published Online First.

15 Quigley MA, Poulsen G, Boyle E, Wolke D, Field D, Alfirevic Z, et al. Early term and late preterm birth are associated with poorer school performance at age 5 years: a cohort study. *Archives of disease in childhood. Fetal and neonatal edition* 2012;**97**(3):F167-173 doi: 10.1136/archdischild-2011-300888published Online First.

16 Chan E, Quigley MA. School performance at age 7 years in late preterm and early term birth: a cohort study. *Arch Dis Child Fetal Neonatal Ed* 2014;**99**(6):F451-F457 doi: 10.1136/archdischild-2014-306124published Online First.

17 Reddy UM, Bettegowda VR, Dias T, Yamada-Kushnir T, Ko CW, Willinger M. Term pregnancy: a period of heterogeneous risk for infant mortality. *Obstetrics and gynecology* 2011;**117**(6):1279-1287 doi: 10.1097/AOG.0b013e3182179e28published Online First.

18 Engle WA. Morbidity and mortality in late preterm and early term newborns: a continuum. *Clinics in perinatology* 2011;**38**(3):493-516 doi: 10.1016/j.clp.2011.06.009published Online First.

19 Wu CS, Sun Y, Nohr EA, Olsen J. Trends in All-Cause Mortality across Gestational Age in Days for Children Born at Term. *PloS one* 2015;**10**(12):e0144754 doi: 10.1371/journal.pone.0144754published Online First.

20 Yang S, Platt RW, Kramer MS. Variation in child cognitive ability by week of gestation among healthy term births. *American journal of epidemiology* 2010;**171**(4):399-406 doi: 10.1093/aje/kwp413published Online First.

21 Schonhaut L, Armijo I, Perez M. Gestational Age and Developmental Risk in Moderately and Late Preterm and Early Term Infants. *Pediatrics* 2015;**135**(4):e835-e841 doi: 10.1542/peds.2014-1957published Online First.

22 Kinney HC. The near-term (late preterm) human brain and risk for periventricular leukomalacia: a review. *Seminars in perinatology* 2006;**30**(2):81-88 doi: 10.1053/j.semperi.2006.02.006published Online First.

23 Hensch TK. Critical period plasticity in local cortical circuits. *Nat Rev Neurosci* 2005;**6**(11):877-888 doi: 10.1038/nrn1787published Online First: 2005/11/02].

24 Kapellou O, Counsell SJ, Kennea N, Dyet L, Saeed N, Stark J, et al. Abnormal cortical development after premature birth shown by altered allometric scaling of brain growth. *PLoS Med* 2006;**3**(8):e265 doi: 10.1371/journal.pmed.0030265published Online First: 2006/07/27].

25 Ip S, Chung M, Raman G, Chew P, Magula N, DeVine D, et al. Breastfeeding

and maternal and infant health outcomes in developed countries. *Evid Rep Technol Assess (Full Rep)* 2007(153):1-186 Online First: 2007/09/04].

26 Quigley MA, Hockley C, Carson C, Kelly Y, Renfrew MJ, Sacker A. Breastfeeding is associated with improved child cognitive development: a population-based cohort study. *The Journal of pediatrics* 2012;**160**(1):25-32 doi: 10.1016/j.jpeds.2011.06.035published Online First.

27 Boucher O, Julvez J, Guxens M, Arranz E, Ibarluzea J, Sanchez de Miguel M, et al. Association between breastfeeding duration and cognitive development, autistic traits and ADHD symptoms: a multicenter study in Spain. *Pediatric research* 2017;**81**(3):434-442 doi: 10.1038/pr.2016.238published Online First.

28 Girard LC, Doyle O, Tremblay RE. Breastfeeding, Cognitive and Noncognitive Development in Early Childhood: A Population Study. *Pediatrics* 2017;**139**(4) doi: 10.1542/peds.2016-1848published Online First.

29 Koh K. Maternal breastfeeding and children's cognitive development. *Social science & medicine* 2017;**187**:101-108 doi: 10.1016/j.socscimed.2017.06.012published Online First.

30 Räisänen SH, Wu CS, Sun Y, Nohr EA, Olsen J. Trends in All-Cause Mortality across Gestational Age in Days for Children Born at Term. *PloS one* 2015;**10**(12):e0144754 doi: 10.1371/journal.pone.0144754published Online First.

31 Crump C, Sundquist K, Winkleby MA, Sundquist J. Early-term birth (37-38 weeks) and mortality in young adulthood. *Epidemiology* 2013;**24**(2):270-276 doi: 10.1097/EDE.0b013e318280da0fpublished Online First: 2013/01/23].

32 Zhang X, Kramer MS. Variations in mortality and morbidity by gestational age among infants born at term. *J Pediatr* 2009;**154**(3):358-362, 362.e351 doi: 10.1016/j.jpeds.2008.09.013published Online First: 2008/10/28].

33 Andrade SA, Santos DN, Bastos AC, Pedromonico MR, de Almeida-Filho N, Barreto ML. [Family environment and child's cognitive development: an epidemiological approach]. *Revista de saude publica* 2005;**39**(4):606-611 doi: /S0034-89102005000400014published Online First.

34 Sierau S, Dahne V, Brand T, Kurtz V, von Klitzing K, Jungmann T. Effects of Home Visitation on Maternal Competencies, Family Environment, and Child Development: a Randomized Controlled Trial. *Prevention science : the official journal of the Society for Prevention Research* 2016;**17**(1):40-51 doi: 10.1007/s11121-015-0573-8published Online First.

35 Hua J, Duan T, Gu G, Wo D, Zhu Q, Liu JQ, et al. Effects of home and education environments on children's motor performance in China. *Developmental medicine and child neurology* 2016;**58**(8):868-876 doi: 10.1111/dmcn.13073published Online First.

Table 1

Characteristics by Gestational age (n=1444)

	Total	Early term children		Full term children	*P*
		37wk [a] n (%)	38wk [a] n (%)	39-41 wk [a] n (%)	
Children's characteristic [b]					
Weight for length Z-score					
Normal	1156(80.1)	72(82.8)	162(79.0)	922(80.0)	0.765
Over-weighted	288(19.9)	15(17.2)	43(21.0)	230(20.0)	

Gender					
Male	722(50.0)	51(58.6)	110(53.7)	561(48.7)	0.107
Female	722(50.0)	36(41.4)	95(46.3)	591(51.3)	
Maternal characteristic					
Parity, n(%)[b]					
Nulliparous	1255(8.9)	65(74.7)	181(88.3)	1009(87.6)	0.002**
Multiparous	189(13.1)	22(25.3)	24(11.7)	143(12.4)	
Maternal age at delivery					
≥35	49(3.4)	3(3.4)	6(2.9)	40(3.5)	0.924
<35	1395(9.6)	84(96.6)	199(97.1)	1112(96.5)	
Delivery mode, n(%)					
Caesarean Section	632(43.7)	43(49.4)	101(49.3)	664(57.6)	0.101
Vaginal birth	812(56.2)	44(50.6)	104(50.7)	488(42.4)	
Socio-economic status					
City					
Wuxi	480(33.2)	25(28.7)	92(44.9)	363(31.5)	<0.001***
Taiyuan	484(33.5)	2(2.3)	16(7.8)	466(40.5)	
Bingzhou	480(33.3)	60(69.0)	97(47.3)	323(28.0)	
Mother's higher education					
Yes	827(57.3)	53(60.9)	143(69.8)	631(54.8)	<0.001***
No	617(42.7)	34(39.1)	62(30.2)	521(45.2)	
Father's higher education					
Yes	880(60.9)	45(51.7)	151(73.7)	684(59.4)	<0.001***
No	564(39.1)	42(48.3)	54(26.3)	468(40.6)	
Mother's occupation					
Skilled	824(57.1)	45(51.7)	124(60.5)	655(56.9)	0.365
Non-skilled	620(42.9)	42(48.3)	81(39.5)	497(43.1)	
Father's occupation					
Skilled	869(60.2)	46(52.9)	129(62.9)	694(60.2)	0.275
Non-skilled	575(39.8)	41(47.1)	76(37.1)	458(39.8)	

[a] Gestational week

[b] Chi-square analysis

*P<0.05,** P<0.01,*** P<0.001

Table 2
Multivariate Linear Regression of Factors Associated With Bayley III Cognitive Development Scores

Characteristic	n (%)	β[a](95%CI)	β[b](95%CI)	β[c](95%CI)	β[d](95%CI)
All subjects(n=1444)					
Full term[e]	87(6.0)	Ref	Ref	Ref	Ref
Born at 37 gestational week	205(14.2)	-1.213 (-2.718, 0.291)	-1.102(-2.604,0.400)	-0.950(-2.458, 0.557)	-0.620(-2.124, 0.885)
Born at 38 gestational week	1152(79.8)	0.968(-0.058,1.994)	0.997(-0.026,2.021)	0.963(-0.060, 1.986)	0.770(-0.248, 1.789)
Infants(n=844)					
Full term[e]	46(5.5)	Ref	Ref	Ref	Ref
Born at 37 gestational week	123(14.6)	-2.810 (-4.847,-0.774)**	-2.723(-4.765,-0.680)**	-2.545(-4.590, -0.500)*	-2.257(-4.280, -0.235)*
Born at 38 gestational week	675(80.0)	0.450(-0.853,1.768)	0.532(-0.780,1.844)	0.548(-0.765, 1.861)	0.120(-1.180, 1.421)
Toddlers(n=600)					
Full term[e]	41(6.8)	Ref	Ref	Ref	Ref
Born at 37 gestational week	82(13.7)	0.623(-1.618,2.863)	0.639(-1.567,2.874)	0.720(-1.528,2.969)	0.935(-1.356,3.225)
Born at 38 gestational week	477(79.5)	1.720(0.075,3.366)*	1.671(0.032,3.250)	1.449 (-0.140,3.139)	1.418(-0.243,3.076)

[a] Not adjusted for other variables
[b] Adjusted for children's characteristic (weight for length Z-score , gender ,)
[c] Adjusted for children's and maternal characteristic (delivery mode, parity, maternal age)
[d] Adjusted for children's and maternal characteristic, and socio-economic factors (city, mother' s and father's education and occupation)
[e] Children born at 39-41 gestational weeks
*$p<0.05$,**$p<0.01$

Figure 1. **Number of infants and toddlers who completed the questionnaire and tests**

Figure 2. **Cognitive composite scores by gestational week in the study are expressed as means and 95% confidence intervals(n=1444)**

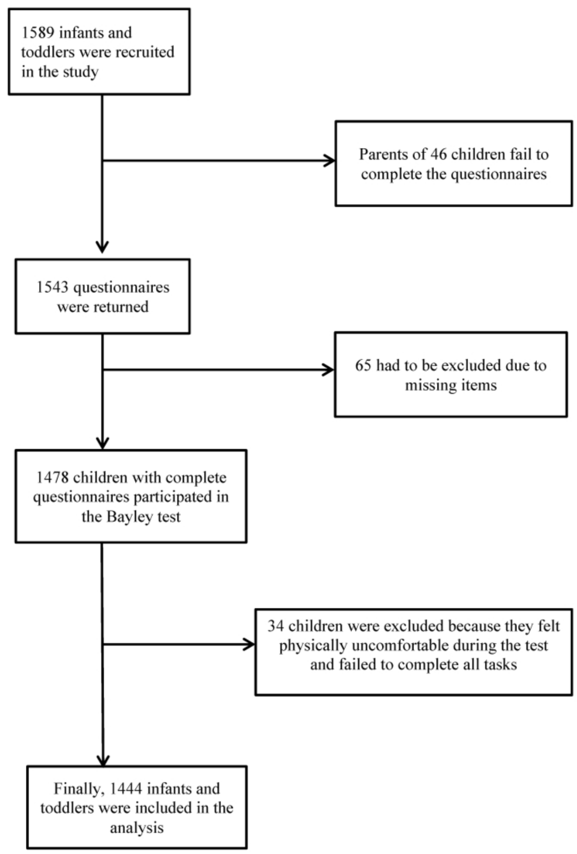

Figure 1. Number of infants and toddlers who completed the questionnaire and tests

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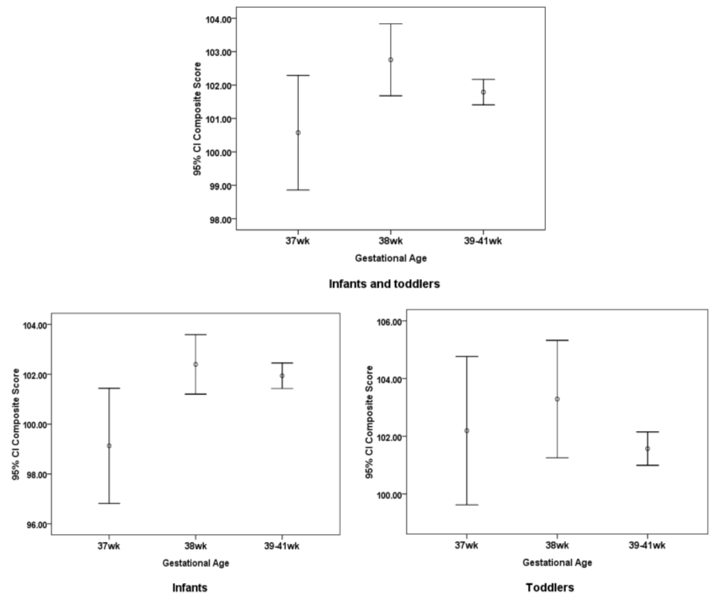

Figure 2. Cognitive composite scores by gestational week in the study are expressed as means and 95% confidence intervals(n=1444)

279x361mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	On page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3,4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5,6,7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4,5,6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	
Bias	9	Describe any efforts to address potential sources of bias	5,7,8
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6,7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7,8
		(*b*) Describe any methods used to examine subgroups and interactions	7,8
		(*c*) Explain how missing data were addressed	5, Figure1.
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	7,8
		(*e*) Describe any sensitivity analyses	

Continued on next page

Results			On page
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	5, Figure1.
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	Table I~IV
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9,10
		(*b*) Report category boundaries when continuous variables were categorized	9,10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9,10
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11,12
Generalisability	21	Discuss the generalisability (external validity) of the study results	10,11,12,13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.