

Infancy weight gain and neurodevelopmental outcomes among term-born infants at age one year: a large prospective cohort study in China

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Short title: Infancy weight gain and neurodevelopment

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Abstract

Aim: To investigate the association between infancy weight gain and neurodevelopment among term-born infants.

Methods: Singleton term-born infants (n=5837) were included from the Born in Guangzhou Cohort Study.

Absolute weight gain was obtained by calculating the weight difference from birth to exactly 12 months. The primary outcome was neurodevelopment at age one year, which included 5 developmental domains. Global developmental delay was defined as delays in ≥ 3 domains. Multivariable logistic regression was used to examine the associations between infancy weight gain and neurodevelopment.

Results: Compared with infants gaining 6001 - 7000 g (reference group), infants gaining ≤ 5000 g had higher odds of delay in adaptive, gross motor, fine motor, social, and global developmental delay, infants gaining 5001 - 6000 g had higher odds of gross motor delay and social delay. A sex-stratified analysis showed that compared with the reference group, gaining ≤ 5000 g was associated with higher odds of fine motor delay in male infants, while gaining > 7000 g was associated with higher odds of fine motor delay in females.

Conclusion: Inadequate infancy weight gain is associated with higher odds of poor neurodevelopment at age one year among term-born infants.

Keywords: Infancy growth, neurodevelopment, postnatal health care, term-born infants, weight gain

1 Introduction

2 The formation and development of neural circuits and structures during early neurodevelopment have lasting
 3 influences on an individual's health status throughout their life course.¹ With dramatic changes in structure
 4 and function during the early postnatal period, the brain grows up to 70% of its size in adulthood by one year
 5 of age.² Adverse environmental factors in early postnatal life, such as malnutrition, decrease brain size in
 6 infancy and adversely influence neural circuit development, often heralding the onset of neurodevelopmental
 7 disorders in the later life.¹ Globally, the double burden of malnutrition and over-nutrition amongst children
 8 remains high and continues to rise, with over 52 million children under the age of 5 suffering from
 9 malnutrition, and over 41 million deemed overweight in 2016.³ It is therefore, of great importance to
 10 investigate the effects of both malnutrition and over-nutrition in infancy on early neurodevelopment.

11 Growth in infancy is recognized internationally as an important indicator of infant nutritional status. To
 12 date, research examining the associations between weight gain and neurodevelopment has focused on
 13 preterm-born infants. In this group, increasing weight gain during infancy appears to be associated with
 14 improved neurodevelopmental performance in preterm children.^{4, 5} Over the past few years in China, the
 15 majority of infants (96%) are being born at term (>37 weeks gestation).⁶ Understanding the associations
 16 between weight gain and neurodevelopment among term-born infants may provide further evidence to guide
 17 infant care and develop feeding plans for the majority of infants. Studies focusing on term-born infants have
 18 shown mixed results. Some studies have found that increasing infancy weight gain is associated with
 19 improved neurodevelopmental outcomes,⁷⁻¹⁴ while others have not shown this association.¹⁵⁻¹⁷ Male infants
 20 have been known to be more sensitive to neonatal morbidity and adverse neurological outcome among
 21 preterm infants.¹⁸ The question thus arises, whether there are gender differences in the relationship between
 22 infancy weight gain and neurodevelopment among term-born infants.

We hypothesize that insufficient weight gain and also excessive weight gain during infancy could impair early neurodevelopment. The aim of this study was to investigate the relationship between infancy weight gain and early neurodevelopmental outcomes (at one year of age) among term-born infants using data from a large birth cohort in China, including sex differences.

Materials and Methods

Study design and participants

The data used in this study were obtained from the Born in Guangzhou Cohort Study (BIGCS). BIGCS is a birth cohort study started in February 2012 at the Guangzhou Women and Children's Medical Center (GWCMC). It aims at investigating the short- and long-term effects of pre- and postnatal exposures on the health of a young generation in Guangzhou, China. The protocol of BIGCS is described in more detail elsewhere.¹⁹ All pregnant women attending their first routine antenatal examinations at GWCMC were screened by trained study personnel to see if they met the eligibility criteria for the study. Mothers who were under 20 gestational weeks, resided within Guangzhou, and intended to deliver and attend infant health care in GWCMC for ≥ 3 years were invited to participate. BIGCS has been approved by the Institutional Ethics Committee of GWCMC. All the pregnant women who agreed to participate gave their signed informed consent.

Infancy weight gain assessment

Birth weight was obtained from medical records using the hospital-based information system. Weight measurements at one year of age were conducted by trained nurses, and measured in kilograms to two decimal places, using an intelligent check-up instrument (Shekel Healthweigh™). When taking the measurement,

infants were weighed with single layer clothes on. Two hundred grams (0.2 kg) was subtracted from the weight to decrease the system error caused by clothing. To limit the variation in the time of the measurement for 12 months, measurements performed before 10 months or later than 15 months were regarded as missing. To increase comparability of infants of different age at the follow-up (10-15 months, Table S1), we first used the WHO growth reference to calculate sex- and age-specific z-scores for weight, and estimated the weight at 12 months accordingly.²⁰ For example, a male infant aged 13 months had a weight of 10.50 kg, with a z-score of 0.56; his weight at 12 months was estimated as the weight corresponding to the same z-score (0.56) at 12 months, which was 10.257 kg. Absolute weight gain was obtained by calculating the weight difference from birth to exactly 12 months. According to the absolute weight gain during infancy, infants were categorized into 5 groups: ≤ 5000 g, 5001 - 6000 g, 6001 - 7000 g, 7001 - 8000 g, and > 8000 g, to facilitate weight-management consultations in clinical practice.

Infant neurodevelopment assessment

Examination of each infant's neurodevelopment was conducted at one year of age follow-up visit, using the Chinese revised Gesell Developmental Schedule (GDS).^{21, 22} The Chinese revised GDS has been validated and adopted by the Chinese Pediatric Association.^{23, 24} The scale consists of five developmental domains: adaptive; gross motor; fine motor; language; and social. GDS was highly correlated with the gross motor skills, fine motor skills, adaptive, and language of the Bayley Scales of Infant and Toddler Development-3rd Edition (Bayley-III cognitive scale).²⁵ A recent study exploring the consistency of Sign-Significate relations test (S-S Test) and GDS in language development assessment also showed that the sensitivity was relatively high (73.65%) between these two scales.²⁶ A previous study reported that there was a significant correlation between developmental assessment at 12 months on the GDS and mental development at 6-7 years on the

Chinese version of the Wechsler Intelligence Scale for Children (C-WISC) ($p < 0.01$), showing that DQ could be a moderate predictor for subsequent intelligence.²⁷ Infants' performance in each domain was recorded as the corresponding neurodevelopmental age in months. The developmental quotient (DQ) was calculated based on the infant's performance in each domain (neurodevelopmental age or age equivalent) as compared to their chronological age at the time of administration (neurodevelopmental age/chronological age $\times 100$). This indicated the infant's neurodevelopmental capabilities for each domain; a higher score reflected better neurodevelopment. In any of the five domains, neurodevelopmental delay was defined as $DQ < 86$. Global developmental delay (GDD) was defined as delays in three or more neurodevelopmental domains. All the neurodevelopment assessments were performed by trained professionals.

Covariates

Information on maternal age, maternal education level, maternal monthly income, maternal pre-pregnancy weight (kg) and height (m) was self-reported by the mothers through a comprehensive baseline questionnaire conducted before 20 gestational weeks. BMI (kg/m^2) was calculated by dividing weight in kilograms by height in meters squared. Mothers were divided into three groups as follows: $\text{BMI} < 18.5 \text{ kg}/\text{m}^2$ (underweight); $\text{BMI} 18.5 - 23.9 \text{ kg}/\text{m}^2$ (normal); $\text{BMI} \geq 24 \text{ kg}/\text{m}^2$ (overweight/obese). Infant birth of order, gestational age, and gender were obtained from medical records. Infant height at one year of age was measured using a calibrated stadiometer (Shekel Healthweigh™) and recorded to the nearest 0.1 centimeter (cm), whereas head circumference was measured using a tape (Seca 212) and recorded to the nearest 0.1 centimeter (cm). The WHO growth reference was used to calculate sex- and age-specific z-scores for height and head circumference (20). Duration of breastfeeding was evaluated through a questionnaire at one year follow-up, and was further categorized as follows: none (never breast fed); < 6 months; and ≥ 6 months.

Statistical analyses

The categorized characteristics of the participants were described by counts and proportions, and continuous variables were described as means and standard deviation (SD). Logistic regression was conducted to estimate the odds ratios (ORs) and their 95% confidence intervals (CI) of the association between infancy weight gain (continuous and categorical) and the risk of neurodevelopmental delay in each of the 5 domains, and GDD. Infants with an intermediate level of infancy weight gain (6001-7000 g) were chosen as the reference group, since this group had largest sample size and appropriate weight gain range. Adjusted models were adjusted for maternal age, maternal education level, maternal monthly income, pre-pregnancy BMI, infant sex, parity, and infant birth weight. Duration of breastfeeding (in categories) and infant head circumference for age Z score at one year of age were further adjusted in sensitivity analyses. Stratified analyses by sex were also conducted. The interaction between sex and infancy weight gain in relation to neurodevelopmental delay risk was evaluated by multiplicative models by including the product term in multivariate logistic regression. We also conducted sensitivity analyses restricted in appropriate for gestational age (AGA) infants.

A p value of < 0.05 was considered statistically significant for all statistical tests. All analyses were performed using SAS statistical software version 9.3 (SAS Institute Inc., Cary, NC, USA) and SPSS software version 20.0 (SPSS, Inc).

Results

In total, 6194 single-term infants in BIGCS delivered from July 2012 to December 2015 attended health check at one year of age follow-up and finished neurodevelopmental assessment. After excluding 50 infants with

missing delivery data, 279 preterm-born infants, and 28 infants with missing weight data at one year of age; a total of 5837 infants were included in the study (Figure 1).

Table 1 demonstrates the characteristics of the infants and their mothers across different weight gain from birth to one year of age. The average maternal age at recruitment was 29y 4mo (SD 3y 5mo). 23.8% of the mothers were underweight while 9.2% were overweight/obese before pregnancy. Among infants, 52.8% were male, with a mean birth weight of 3233 g (SD 377 g). The average weight gain from birth to one year of age was 6375 g (SD 1033 g). 2113 (36.2%) infants gained weight range from 6001 to 7000 g during infancy, compared with 456 (7.8%), 1773 (30.4%), 1103 (18.9%), and 392 (6.7%) infants gained weight \leq 5000 g, 5001- 6000 g, 7001- 8000 g, and $>$ 8000 g, respectively. Mothers of infants with low weight gain were younger, more likely to have lower education level, lower income and lower pre-pregnancy BMI. The mean DQ scores \pm SD in the adaptive, gross motor, fine motor, language, and social were 97.62 ± 7.30 , 93.78 ± 9.33 , 99.11 ± 8.20 , 90.64 ± 9.70 , and 98.47 ± 9.48 , respectively. The proportions of developmental delay in this five domains and GDD were 4.7%, 17.1%, 3.9%, 29.7%, 7.6% and 4.6%, respectively.

Table 2 demonstrates the associations between weight gain from birth to one year of age and neurodevelopmental delay. Higher infancy weight gain was associated with lower odds of gross motor delay, the adjusted odds ratio (OR) of per-kg increment for infancy weight gain in gross motor delay is 0.92 [95% confidence interval (CI): (0.86, 0.99)]. No associations were found between continuous infancy weight gain and other neurodevelopmental outcomes. After controlling for potential confounders, compared with infants with weight gain of 6001- 7000 g, infants gaining \leq 5000 g had a larger probability of delay in adaptive behavior [OR (95% CI):1.69 (1.08, 2.65)], gross motor [OR (95% CI): 1.79 (1.39, 2.31)], fine motor [OR (95% CI): 1.78 (1.09, 2.92)], social behaviors [OR (95% CI): 1.62 (1.10, 2.41)], and GDD [OR (95% CI): 1.94 (1.23, 3.06)], infants gaining 5001-6000 g had a larger probability of delay in gross motor [OR (95% CI):

1.22 (1.03, 1.45)], and social behaviors [OR (95% CI): 1.42 (1.11, 1.81)]. A sex-stratified analysis showed that compared with weight gain of 6001- 7000 g, lower infancy weight gain (≤ 5000 g) was associated with higher odds of fine motor delay in male infants; while higher infancy weight gain (> 7000 g) was associated with higher odds of fine motor delay in females. The difference between male and female infants reached statistical significance ($P_{\text{interaction}} = 0.026$) in the association of infancy weight gain and fine motor delay.

We further adjusted for duration of breastfeeding and infant head circumference for age Z score at one year of age in the models, the relationships between infancy weight gain and neurodevelopmental outcomes did not differ (data not shown). When the analysis was restricted to AGA infants, the associations between infancy weight gain with gross motor, fine motor and GDD were similar, but slightly attenuated with adaptive and social behavior, to those among all infants. (Table S2).

Discussion

Using data from a large Chinese birth cohort study, we found that increasing infancy weight gain was associated with lower odds of gross motor delay. Term-born infants with ≤ 5000 g weight gain in the first year of life had worse neurodevelopment outcomes than infants gaining 6001 - 7000 g in weight. Outcomes for this group (≤ 5000 g), were worse for adaptive, gross motor, fine motor and social developmental domains, and global development delay, independent of a wide array of potential confounding variables. We also found a sex-specific association of infancy weight gain and fine motor delay. Lower infancy weight gain (≤ 5000 g) in male infants, and higher infancy weight gain (> 7000 g) in females, were associated with higher odds of fine motor delay comparing with weight gain of 6001- 7000 g.

Besides finding a statistically significant associations between continuous infancy weight gain and motor

gross, we also found that inadequate weight gain during infancy was associated with higher odds of extensive adverse neurodevelopment. Few studies have applied absolute weight gain as the main indicator to explore associations between infant growth and neurodevelopment. However, increasing infancy weight gain has been associated with improved neurodevelopmental outcomes among term-born children.⁷⁻¹⁴ A recent study conducted in a high-income country, showed that greater weight gain in infancy was associated with higher IQ at age 5 y in term-born children.⁷ A pooled study, including cohorts from four low- and middle-income countries showed that growth from: conception to 1 year; age 1-5 years and; 5-8 years, were each positively and significantly associated with cognitive achievement at age 8 years.⁸ A further study of 8389 Chinese term-born children showed rapid postnatal weight gain was associated with increased IQ.⁹ The existing evidence and our findings suggest that among term born infants, weight gain is important in relation to neurodevelopment.

Our results provide little evidence to support the hypothesis that excessive weight gain during infancy could impair early neurodevelopment, although we found higher infancy weight gain (> 7000 g) in females was associated with higher odds of fine motor delay comparing with reference group. A study conducted in the U.S found that gain in weight-for-height from 1 to 2 y postpartum was possibly negatively associated with IQ at 5- 8 y,²⁸ indicating that early-life adiposity could also affect neurodevelopment. Thus, the evidence is inconclusive. The inconsistencies between studies may partly be explained by differences in study population, measurement methods, time periods, and sample sizes.

Of interest is the sex-specific association we noted. To the best of our knowledge, no previous studies have reported sex differences in the associations between child growth and neurodevelopment status in term-born infants. Growth patterns might differ between male and female infants. Girls and boys tended to show different specific cognitive abilities in rural China.²⁹ In our study, male infants seemed to have worse

neurodevelopment performance than female infants. A previous study also showed that male neurodevelopment appears to be much more sensitive to poor postnatal growth in very preterm infants.¹⁸

Early neurological development can be affected by both genetic and environmental factors, such as nutrition and inflammation. The effect of postnatal infant malnutrition on the intellectual functioning of children has been linked to multiple aetiological factors, including micronutrient deficiencies, fat energy malnutrition, and protein energy malnutrition. Early brain development may be a root cause of most neurological disorders, and microglial function and neuro-inflammation during development play a prominent role in the process.³⁰ Microglia are very sensitive to both genetic and environmental perturbations, such as nutrition. Experiments on mice have demonstrated that the hippocampus (an area in the brain important in establishing learning and memory) is adversely affected by early nutritional stress, such as a protein-deficient diet.³¹ Another possible explanation for the relationship between malnutrition and neurodevelopment is that undernourishment in children is associated with behavioral changes, which lead to poor developmental outcomes and poorer intellectual performance over the longer term. Insulin-like growth factor I (IGF-I) has been proven to be associated with both growth during infancy and early brain development. It can be a possible mechanism underlying the relationship between infancy weight gain and neurodevelopment. IGF-I is known to positively correlate with early postnatal growth, and has lasting effects on body composition into childhood.³² IGF-I levels correlate with brain volume³³ and white matter organization³⁴. Future research is needed to investigate the underlying physiological mechanisms. We failed to find an association between infancy weight gain and language delay at one year of age even though language delay is the most prevalent neurodevelopmental delay documented at one year of age. Delays in language are the most common types of developmental delay and might be caused by multiple conditions besides nutrition factors.³⁵ Over-nourished babies infants are not good at gross motor such as crawling and walking. They may attract guardians' more

attention and acquire more physical touch like hugging and skin contact, thus improving the development of social domain.³⁶

Understanding the association between weight gain during infancy (a convenient indicator used to evaluate the nutritional status), and early neurodevelopmental performance among term-born children, has important clinical and public health implications. Historically, standardized indicators such as z scores or SD scores have been employed to investigate the associations between infant growth and neurodevelopment. The clinical applications of these standardized scores have been questioned by researchers in light of potential limitations. For example, Freedman DS et al. conducted an examination of the accuracy of BMI z-score transformation, and found that very high BMIs were converted into a narrow range of BMI z scores.³⁷ Aaron S. Kelly et al. proposed a ‘Tower of Babel’ phenomenon to describe the situation; there are so many different ‘BMI languages’ (standardized indicators), with no consensus on an optimal measure.³⁸ Measures of weight gain are similarly problematic. Findings from our study provide a new, but simple method (employing absolute weight gain of term-born infants) to address the problems of consistency and reproducibility, whilst also being easier to measure and more intuitive and clinically-relevant. Our findings facilitate doctor-patient communication of infant weight-related issues, particularly in resource-limited settings.

We used data from a large longitudinal designed study with more than 5,000 mother-infant pairs included in the final analyses. Data were collected from the time of pregnancy to early infancy to avoid recall bias. There are some limitations that may influence the robustness of the association estimates. First, reverse causality should be carefully considered for this association study was cross-sectional though in a longitudinal cohort. Data of weight and neurodevelopmental scores at one year of age were collected simultaneously. We cannot ascertain the temporality that extreme weight gain or neurodevelopmental delay occurred first. Second, generalizability could be limited, because the present study was based predominantly on Chinese individuals.

The mothers had a lower proportion of overweight/obese (pre-pregnancy BMI ≥ 24 kg/m², 9.2%) than that of mothers in the U.S (pre-pregnancy BMI ≥ 25 kg/m², 50.36%).³⁹ Third, misclassification of developmental scores cannot be fully eliminated although we used a standardized, validated tool. We set Gesell score < 86 as neurodevelopment delay in accordance with previous research. Lastly, residual confounders might exist due to the nature of observational study.

In conclusion, inadequate weight gain during infancy is associated with higher odds of poor neurodevelopment outcomes at one year of age among term-born infants. Children with a history of low infancy weight gain might at a risk of neurodevelopment disorders in later life. Our findings suggest that appropriate weight gain during infancy may be beneficial to term-born infants. Further studies are needed to investigate the effects of infant growth in different periods (e.g. neonatal period vs later) on neurodevelopment. Future work should aid in determining optimal growth patterns in infants to balance risks and benefits of health outcomes through the life course.

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Table 1. Distributions of characteristics by infancy weight gain in 5837 mother-child pairs

Characteristics	All	Weight gain (g) from birth to 1 year of age *				
		≤ 5000 g	5001 - 6000 g	6001 - 7000 g	7001 - 8000 g	> 8000 g
N (%)	5837	456 (7.8)	1773 (30.4)	2113 (36.2)	1103 (18.9)	392 (6.7)
Maternal characteristics						
Age at conception, mean ± SD	29y 4mo ± 3y 5mo	29y 2mo ± 3y 5mo	29y 1mo ± 3y 4mo	29y 3mo ± 3y 4mo	29y 4mo ± 3y 4mo	29y 7mo ± 3y 3mo
Education level, n (%)						
High school or below	470 (8.1)	52 (11.4)	179 (10.1)	148 (7.0)	77 (7.0)	14 (3.6)
Vocational/technical college	1473 (25.2)	122 (26.8)	476 (26.8)	540 (25.6)	247 (22.4)	88 (22.4)
Undergraduate	3196 (54.8)	238 (52.2)	951 (53.6)	1173 (55.5)	609 (55.2)	225 (57.4)
Postgraduate	698 (12.0)	44 (9.6)	167 (9.4)	252 (11.9)	170 (15.4)	65 (16.6)
Monthly income, Yuan, n (%)						
≤ 1500	524 (9.0)	50 (11.0)	168 (9.5)	194 (9.2)	84 (7.6)	28 (7.1)
1501 - 4500	1838 (31.5)	168 (36.8)	638 (36.0)	643 (30.4)	301 (27.3)	88 (22.4)
4501 - 9000	2365 (40.5)	159 (34.9)	688 (38.8)	884 (41.8)	469 (42.5)	165 (42.1)
≥ 9001	919 (15.7)	59 (12.9)	233 (13.1)	325 (18.9)	209 (18.9)	93 (23.7)
Refused to answer	191 (3.3)	20 (4.4)	46 (2.6)	67 (3.2)	40 (3.6)	18 (4.6)
Pre-pregnancy BMI, kg/m ² , n (%)						
< 18.5	1389 (23.8)	126 (27.6)	479 (27.0)	496 (23.5)	228 (20.7)	60 (15.3)
18.5 - 23.9	3718 (63.7)	276 (60.5)	1099 (62.0)	1346 (63.7)	722 (65.5)	275 (70.2)
≥ 24	539 (9.2)	32 (7.0)	147 (8.3)	197 (9.3)	115 (10.4)	48 (12.2)
Missing	191 (3.3)	22 (4.8)	48 (2.7)	74 (3.5)	38 (3.4)	9 (2.3)
Infant characteristics at birth						
Male, n (%)	3080 (52.8)	119 (26.1)	720 (40.6)	1195 (56.6)	746 (67.6)	300 (76.5)
Birth of order (first born), n (%)	5173 (88.6)	402 (88.2)	1588 (89.6)	1869 (88.5)	985 (89.3)	329 (83.9)
Birth weight, g, mean ± SD	3233 ± 377	3264 ± 356	3210 ± 397	3221 ± 359	3249 ± 376	3315 ± 399
Birth weight Z score, mean ± SD	0.12 ± 0.94	0.19 ± 0.96	0.05 ± 0.98	0.09 ± 0.91	0.17 ± 0.91	0.32 ± 0.91
Gestational age, mean ± SD	39w 2d ± 1w	39w 5d ± 6d	39w 3d ± 6d	39w 2d ± 1w	39w 1d ± 1w	39w 1d ± 1w
Birth weight for gestational age, n (%)						
SGA	404 (6.9)	24 (5.3)	162 (9.1)	146 (6.9)	53 (4.8)	19 (4.8)
AGA	5080 (87.0)	403 (88.4)	1500 (84.6)	1859 (88.0)	978 (88.7)	340 (86.7)
LGA	353 (6.0)	29 (6.4)	111 (6.3)	108 (5.1)	72 (6.5)	33 (8.4)
Duration of breastfeeding, n (%)						
None	211 (3.6)	9 (2.0)	70 (3.9)	72 (3.4)	48 (4.4)	12 (3.1)
< 6 months	1268 (21.7)	104 (22.8)	374 (21.1)	472 (22.3)	235 (21.3)	83 (21.2)
≥ 6 months	2933 (50.2)	249 (54.6)	908 (51.2)	1050 (49.7)	542 (49.1)	184 (46.9)
Missing	1425 (24.4)	94 (20.6)	421 (23.7)	519 (24.6)	278 (25.2)	113 (28.8)
Infant characteristics at 1 year follow-up						
Follow-up age, mean ± SD	12mo 9d ± 20d	12mo 8d ± 21d	12mo 9d ± 22d	12mo 10d ± 23d	12mo 10d ± 21d	12mo 12d ± 23d
Weight for age Z score, mean ± SD	0.11 ± 0.95	-1.36 ± 0.60	-0.55 ± 0.54	0.20 ± 0.49	0.96 ± 0.44	1.89 ± 0.53
Weight (g) at 1 year of age *, mean ± SD	9607 ± 1116	7887 ± 489	8780 ± 482	9699 ± 466	10663 ± 476	11892 ± 685
Length for age Z score, mean ± SD	-0.12 ± 1.01	-0.99 ± 0.89	-0.55 ± 0.85	-0.06 ± 0.86	0.43 ± 0.88	1.02 ± 0.98

Weight gain (g) from birth to 1 year of age*, n (%)	6375 ± 1033	4622 ± 351	5569 ± 283	6477 ± 283	7414 ± 274	8577 ± 539
Neurodevelopmental quotients						
Adaptive, mean ± SD	97.62 ± 7.30	97.12 ± 7.35	97.76 ± 7.26	97.61 ± 7.28	97.63 ± 7.26	97.51 ± 7.64
Gross motor, mean ± SD	93.78 ± 9.33	91.72 ± 8.86	93.57 ± 9.35	94.20 ± 9.16	94.08 ± 9.39	94.07 ± 10.14
Fine motor, mean ± SD	99.11 ± 8.20	98.40 ± 8.45	99.07 ± 8.14	99.29 ± 8.09	99.13 ± 8.40	99.11 ± 8.21
Language, mean ± SD	90.64 ± 9.70	90.88 ± 9.16	90.65 ± 9.53	90.66 ± 9.93	90.61 ± 9.78	90.34 ± 9.67
Social, mean ± SD	98.47 ± 9.48	97.79 ± 9.37	98.02 ± 9.43	98.72 ± 9.27	98.64 ± 9.76	99.37 ± 10.00
Neurodevelopmental delay						
Adaptive, n (%)	277 (4.7)	28 (6.1)	89 (5.0)	89 (4.2)	49 (4.4)	22 (5.6)
Gross motor, n (%)	1000 (17.1)	106 (23.2)	314 (17.7)	321 (15.2)	186 (16.9)	73 (18.6)
Fine motor, n (%)	230 (3.9)	23 (5.0)	69 (3.9)	70 (3.3)	52 (4.7)	16 (4.1)
Language, n (%)	1734 (29.7)	127 (27.9)	517 (29.2)	642 (30.4)	324 (29.4)	124 (31.6)
Social, n (%)	446 (7.6)	36 (7.9)	144 (8.1)	140 (6.6)	96 (8.7)	30 (7.7)
Global developmental delay, n (%)	270 (4.6)	28 (6.1)	80 (4.5)	84 (4.0)	59 (5.3)	19 (4.8)

* Weight at 1 year (exactly 12 months) was estimated with the WHO growth reference.

SD: standard deviation; BMI: body mass index; SGA: small for gestational age; AGA: appropriate for gestational age; LGA: large for gestational age.

Table 2. Association between weight gain from birth to one year of age and neurodevelopmental delay

Delay in domain	Weight gain	N (%)	All		Male		Female		P ³
			Crude OR (95% CI)	Adjusted OR ¹ (95% CI)	N (%)	Adjusted OR ² (95% CI)	N (%)	Adjusted OR ² (95% CI)	
Adaptive	Continuous (kg)	277 (4.7)	0.98 (0.87-1.10)	0.94 (0.83-1.06)	166 (5.4)	0.94 (0.80-1.11)	111 (4.0)	0.94 (0.77-1.15)	0.311
	≤ 5000 g	28 (6.1)	1.49 (0.96-2.30)	1.69 (1.08-2.65)	11 (9.2)	1.97 (1.00-3.88)	17 (5.0)	1.67 (0.90-3.09)	
	5001 - 6000 g	89 (5.0)	1.20 (0.89-1.62)	1.29 (0.95-1.74)	44 (6.1)	1.24 (0.83-1.86)	45 (4.3)	1.37 (0.85-2.21)	
	6001 - 7000 g	89 (4.2)	Ref.	Ref.	60 (5.0)	Ref.	29 (3.2)	Ref.	
	7001 - 8000 g	49 (4.4)	1.06 (0.74-1.51)	1.03 (0.72-1.47)	33 (4.4)	0.89 (0.57-1.38)	16 (4.5)	1.44 (0.77-2.70)	
	> 8000 g	22 (5.6)	1.35 (0.84-2.18)	1.28 (0.79-2.09)	18 (6.0)	1.23 (0.71-2.12)	4 (4.3)	1.58 (0.54-4.66)	
Gross motor	Continuous (kg)	1000 (17.1)	0.93 (0.87-1.00)	0.92 (0.86-0.99)	539 (17.5)	0.99 (0.90-1.08)	461 (16.7)	0.84 (0.75-0.94)	0.227
	≤ 5000 g	106 (23.2)	1.69 (1.32-2.17)	1.79 (1.39-2.31)	26 (21.8)	1.61 (1.01-2.58)	80 (23.7)	1.78 (1.30-2.43)	
	5001 - 6000 g	314 (17.7)	1.20 (1.01-1.42)	1.22 (1.03-1.45)	140 (19.4)	1.37 (1.07-1.75)	174 (16.5)	1.10 (0.86-1.41)	
	6001 - 7000 g	321 (15.2)	Ref.	Ref.	183 (15.3)	Ref.	138 (15.0)	Ref.	
	7001 - 8000 g	186 (16.9)	1.13 (0.93-1.38)	1.12 (0.92-1.37)	135 (18.1)	1.23 (0.96-1.57)	51 (14.3)	0.95 (0.67-1.34)	
	> 8000 g	73 (18.6)	1.28 (0.96-1.69)	1.30 (0.98-1.73)	55 (18.3)	1.29 (0.92-1.81)	18 (19.6)	1.46 (0.84-2.55)	
Fine motor	Continuous (kg)	230 (3.9)	1.01 (0.89-1.15)	0.98 (0.85-1.12)	139 (4.5)	0.90 (0.75-1.07)	91 (3.3)	1.11 (0.89-1.39)	0.026
	≤ 5000 g	23 (5.0)	1.55 (0.96-2.51)	1.78 (1.09-2.92)	11 (9.2)	2.47 (1.24-4.95)	12 (3.6)	1.68 (0.81-3.48)	
	5001 - 6000 g	69 (3.9)	1.18 (0.84-1.66)	1.23 (0.87-1.74)	33 (4.6)	1.12 (0.71-1.76)	36 (3.4)	1.48 (0.85-2.59)	
	6001 - 7000 g	70 (3.3)	Ref.	Ref.	50 (4.2)	Ref.	20 (2.2)	Ref.	
	7001 - 8000 g	52 (4.7)	1.44 (1.00-2.08)	1.40 (0.96-2.02)	34 (4.6)	1.08 (0.69-1.69)	18 (5.0)	2.38 (1.24-4.58)	
	> 8000 g	16 (4.1)	1.24 (0.71-2.16)	1.20 (0.69-2.11)	11 (3.7)	0.87 (0.45-1.70)	5 (5.4)	3.11 (1.12-8.63)	
Language	Continuous (kg)	1734 (29.7)	1.03 (0.98-1.09)	0.96 (0.90-1.01)	1080 (35.1)	1.00 (0.92-1.07)	654 (23.7)	0.90 (0.82-0.99)	0.121
	≤ 5000 g	127 (27.9)	0.88 (0.71-1.11)	1.06 (0.84-1.33)	39 (32.8)	0.90 (0.60-1.35)	88 (26.1)	1.09 (0.82-1.46)	
	5001 - 6000 g	517 (29.2)	0.94 (0.82-1.08)	1.03 (0.90-1.19)	261 (36.3)	1.06 (0.87-1.29)	256 (24.3)	0.99 (0.80-1.21)	
	6001 - 7000 g	642 (30.4)	Ref.	Ref.	417 (34.9)	Ref.	225 (24.5)	Ref.	
	7001 - 8000 g	324 (29.4)	0.95 (0.81-1.12)	0.90 (0.76-1.05)	259 (34.7)	0.99 (0.82-1.20)	65 (18.2)	0.67 (0.49-0.91)	
	> 8000 g	124 (31.6)	1.06 (0.84-1.34)	0.96 (0.76-1.22)	104 (34.7)	1.01 (0.77-1.32)	20 (21.7)	0.89 (0.53-1.50)	
Social	Continuous (kg)	446 (7.6)	1.02 (0.93-1.12)	0.92 (0.83-1.02)	312 (10.1)	0.91 (0.80-1.02)	134 (4.9)	0.97 (0.81-1.17)	0.081
	≤ 5000 g	36 (7.9)	1.21 (0.83-1.77)	1.62 (1.10-2.41)	15 (12.6)	1.48 (0.83-2.66)	21 (6.2)	1.96 (1.11-3.49)	
	5001 - 6000 g	144 (8.1)	1.25 (0.98-1.59)	1.42 (1.11-1.81)	91 (12.6)	1.45 (1.08-1.96)	53 (5.0)	1.47 (0.93-2.31)	
	6001 - 7000 g	140 (6.6)	Ref.	Ref.	109 (9.1)	Ref.	31 (3.4)	Ref.	
	7001 - 8000 g	96 (8.7)	1.34 (1.03-1.76)	1.26 (0.96-1.66)	72 (9.7)	1.08 (0.79-1.48)	24 (6.7)	2.12 (1.22-3.68)	
	> 8000 g	30 (7.7)	1.17 (0.78-1.76)	1.07 (0.71-1.63)	25 (8.3)	0.97 (0.61-1.53)	5 (5.4)	1.94 (0.73-5.17)	
GDD	Continuous (kg)	270 (4.6)	0.99 (0.88-1.11)	0.93 (0.82-1.06)	174 (5.6)	0.92 (0.78-1.07)	96 (3.5)	0.97 (0.78-1.20)	0.210
	≤ 5000 g	28 (6.1)	1.58 (1.02-2.45)	1.94 (1.23-3.06)	13 (10.9)	2.37 (1.25-4.50)	15 (4.5)	1.89 (0.97-3.68)	
	5001 - 6000 g	80 (4.5)	1.14 (0.83-1.56)	1.24 (0.90-1.70)	42 (5.8)	1.16 (0.77-1.74)	38 (3.6)	1.42 (0.84-2.40)	
	6001 - 7000 g	84 (4.0)	Ref.	Ref.	61 (5.1)	Ref.	23 (2.5)	Ref.	
	7001 - 8000 g	59 (5.3)	1.37 (0.97-1.92)	1.31 (0.93-1.85)	43 (5.8)	1.16 (0.78-1.74)	16 (4.5)	1.82 (0.95-3.52)	
	> 8000 g	19 (4.8)	1.23 (0.74-2.05)	1.19 (0.71-1.99)	15 (5.0)	1.04 (0.58-1.88)	4 (4.3)	2.08 (0.70-6.25)	

Weight gain was obtained by calculating the weight difference from birth to exactly 12 months; Weight at exactly 12 months was estimated with the WHO growth reference. Statistically significant associations (at P < 0.05) are shown in bold.

OR: odds ratio; 95% CI: 95% confidence interval; GDD: global developmental delay, was defined as delays in three or more neurodevelopmental domains.

¹ Adjusted for maternal age, maternal education level, maternal monthly income, maternal pre-pregnancy body mass index (in categories), infant sex, birth of order, and birth weight.

² Adjusted for the various above confounders excluding infant sex.

³ Indicated *P* for interaction.

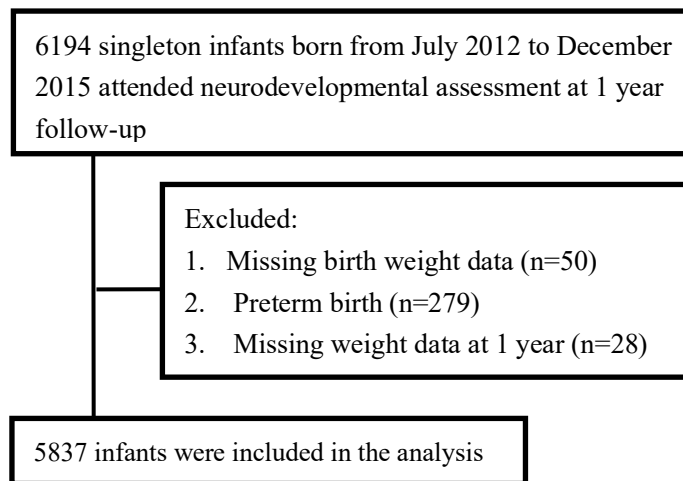
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Figure 1. Flowchart of the study population.**Supplemental material**

Table S1. Weight at one year follow-up of 5837 infants

Table S2. Association between weight gain from birth to 1 year of age and neurodevelopmental outcomes in AGA infants (n=5080)

Accepted manuscript

Figure 1:**Figure 1. Flowchart of the study population****Supporting Information:****Table S1. Weight at one year follow-up of 5837 infants**

Follow-up age, month	N (%)	Weight, kg, mean \pm SD	Weight for age Z score, mean \pm SD	Weight at 1 year of age ¹ , kg, mean \pm SD
All	5837 (100)	9.56 \pm 1.12	0.11 \pm 0.95	9.61 \pm 1.12
10	12 (0.2)	9.11 \pm 1.36	-0.04 \pm 1.11	9.60 \pm 1.43
11	2186 (37.5)	9.41 \pm 1.10	0.10 \pm 0.96	9.65 \pm 1.12
12	2785 (47.7)	9.57 \pm 1.13	0.10 \pm 0.96	9.57 \pm 1.13
13	653 (11.2)	9.88 \pm 1.07	0.15 \pm 0.89	9.64 \pm 1.04
14	175 (3.0)	10.10 \pm 1.09	0.20 \pm 0.90	9.63 \pm 1.04
15	26 (0.4)	9.82 \pm 1.28	-0.28 \pm 1.05	9.17 \pm 1.20
<i>P</i> value ²		<0.001	0.200	0.038

¹ Weight at 1 year (exactly 12 months) was estimated with the WHO growth reference.

² ANOVA was used to analyze the difference between different follow-up ages.

Table S2. Association between weight gain from birth to 1 year of age and neurodevelopmental outcomes in AGA infants (n=5080)

Delay in domain	Weight gain (g) from birth to 1 year of age *				
	≤ 5000	5001 - 6000	6001 – 7000	7001 – 8000	> 8000
	403 (7.9)	1500 (29.5)	1859 (36.6)	978 (19.3)	340 (6.7)
Adaptive, n (%)	24 (6.0)	77 (5.1)	79 (4.2)	44 (4.5)	19 (5.6)
Adjusted OR (95% CI)	1.58 (0.98-2.57)	1.29 (0.93-1.78)	Ref.	1.04 (0.71-1.52)	1.30 (0.77-2.19)
Gross motor, n (%)	90 (22.3)	266 (17.7)	280 (15.1)	158 (16.2)	61 (17.9)
Adjusted OR (95% CI)	1.71 (1.30-2.25)	1.24 (1.03-1.50)	Ref.	1.06 (0.86-1.32)	1.23 (0.91-1.68)
Fine motor, n (%)	20 (5.0)	59 (3.9)	60 (3.2)	45 (4.6)	12 (3.5)
Adjusted OR (95% CI)	1.76 (1.04-3.00)	1.28 (0.88-1.85)	Ref.	1.38 (0.93-2.06)	1.07 (0.56-2.02)
Language, n (%)	107 (26.6)	442 (29.5)	575 (30.9)	287 (29.3)	108 (31.8)
Adjusted OR (95% CI)	0.97 (0.76-1.24)	1.02 (0.88-1.18)	Ref.	0.87 (0.74-1.04)	0.95 (0.74-1.22)
Social, n (%)	28 (6.9)	113 (7.5)	119 (6.4)	87 (8.9)	27 (7.9)
Adjusted OR (95% CI)	1.48 (0.96-2.30)	1.36 (1.04-1.79)	Ref.	1.32 (0.99-1.77)	1.13 (0.73-1.76)
GDD, n (%)	23 (5.7)	70 (4.7)	71 (3.8)	52 (5.3)	15 (4.4)
Adjusted OR (95% CI)	1.83 (1.11-3.01)	1.33 (0.95-1.88)	Ref.	1.35 (0.93-1.95)	1.12 (0.63-2.00)

* Weight at 1 year (exactly 12 months) was estimated with the WHO growth reference.

AGA: appropriate for gestational age; OR: odds ratio; 95% CI: 95% confidence interval; GDD: global developmental delay, was defined as delays in three or more neurodevelopmental domains.

Adjusted model was adjusted for maternal age, maternal education level, maternal monthly income, maternal pre-pregnancy body mass index (in categories), infant sex, birth of order, and birth weight.

Statistically significant associations (at P < 0.05) are shown in bold.