Insufficient maternal gestational weight gain and infant neurodevelopment at 12 months of age: the Japan Environment and Children’s Study

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Received: 13 April 2021 / Revised: 29 July 2021 / Accepted: 30 July 2021 / Published online: 12 October 2021 © The Author(s) 2021

Abstract
Abnormal maternal gestational weight gain (GWG) increases the risk of obstetric-related complications. This investigation examined the impact of GWG on infant neurodevelopmental abnormalities at 12 months of age using the data of a nationwide Japanese cohort study. Questionnaire data were obtained from the ongoing Japan Environment and Children’s Study cohort study. Maternal GWG was subdivided as below, within, or above the reference values of the Institution of Medicine pregnancy weight guidelines. The Ages and Stages Questionnaire, third edition (ASQ-3) is a parent-reported developmental screening instrument for children across five domains: communication, gross motor, fine motor, problem-solving, and personal–social. Multiple logistic regression analysis was employed to identify correlations between GWG and developmental delay defined as ASQ-3 scores of less than two standard deviations below the mean. A total of 30,694 mothers with singleton live births and partners who completed the questionnaire were analyzed. The prevalence of mothers below, within, and above the GWG guidelines was 60.4% (18,527), 32.1% (9850), and 7.5% (2317), respectively. We recorded 10,943 infants (35.7%) who were outliers in at least one ASQ-3 domain. After controlling for covariates, GWG below established guidelines was associated with a significantly higher risk of developmental delay for the communication (odds ratio [OR] 1.21, 95% confidence interval [CI] 1.09–1.34), gross motor (OR 1.14, 95% CI 1.05–1.24), fine motor (OR 1.13, 95% CI 1.04–1.24), problem-solving (OR 1.09, 95% CI 1.01–1.18), and personal–social (OR 1.15, 95% CI 1.07–1.24) domains.

Conclusion: This large survey revealed a possible deleterious effect of insufficient maternal GWG on infant neurodevelopment.

Trial registration: The Japan Environment and Children’s Study (JECS) was registered in the UMIN Clinical Trials Registry on January 15, 2018 (number UMIN000030786).

What is Known:
• Inappropriate maternal gestational weight gain may cause obstetric complications and adverse birth outcomes.
• Excess maternal weight gain may result in gestational diabetes, hypertension, eclampsia, caesarean delivery, and macrosomia, while insufficient maternal weight gain has been associated with pre-term birth and small for gestational age.

What is New:
• This study provides important information on a possible adverse effect of insufficient maternal gestational weight gain on offspring neurodevelopment at 12 months of age.
• Our findings indicate a need to reconsider the optimal body mass index and gestational weight gain for women desiring pregnancy.

Communicated by Gregorio Paolo Milani.

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Keywords  Gestational weight gain · Infant · Neurodevelopment · Developmental delay · ASQ-3

Abbreviations
ANOVA  Analysis of variance
ASD  Autism spectrum disorder
ASQ-3  Ages and Stages Questionnaire, third edition
BMI  Body mass index
CI  Confidence interval
DD  Developmental delay
DM/GDM  Diabetes mellitus/gestational diabetes mellitus
GWG  Gestational weight gain
HDP  Hypertensive disorders of pregnancy
IOM  Institute of Medicine
JECS  Japan Environment and Children’s Study
OR  Odds ratio
SGA  Small for gestational age
WHO  World Health Organization

Introduction

Developmental delay is defined as delays in the areas of speech and language, motor, social, and cognitive development [1]. The incidence of developmental delay has increased dramatically in recent decades [2, 3]. Although the estimated prevalence of developmental delay is generally 5–15% in pediatric populations [2–4], reported rates vary depending on the socioeconomic characteristics of the study population, case definition, and age range [5].

Excess maternal weight gain increases the risk of obstetric complications, such as gestational diabetes, hypertensive disorder of pregnancy (HDP), eclampsia, caesarean delivery, and macrosomia [6]. On the other hand, insufficient maternal gestational weight gain (GWG) and low GWG rate have been associated with adverse birth outcomes, including pre-term birth and small for gestational age (SGA) [7, 8]. The Institute of Medicine (IOM; now known as the National Academy of Medicine) developed GWG guidelines in 1990 and later updated them in 2009 [9]. The IOM guidelines incorporate the World Health Organization (WHO) categories of maternal body mass index (BMI) and recommend lower GWG for obese women. Japan has not formally adopted the IOM guidelines, having instead developed an original set of rules for pregnancy weight management owing to limited ethnic diversity (Supplemental table S1) [10]. The Japanese guidelines are stricter for weight gain primarily to reduce obstetric complications. One large limitation of the guidelines, however, is that they lack validation from a large national study. An emerging problem in Japan is the increase in underweight pregnant women [11, 12]. Among Japanese pregnant women registered in the Japan Society of Obstetrics and Gynecology registry system, the prevalence of underweight pre-pregnancy BMI was 18.2%, versus 5.3% in the USA [12, 13]. Such a condition has been associated with an augmented risk of pre-term birth and SGA [7, 8] and possibly delayed offspring development. In Japanese women, underweight may be a larger issue than obesity.

Recent reports on the longer-term risks of maternal obesity have suggested a relationship with developmental delay in early childhood, and several epidemiologic studies have found associations between maternal obesity and various neurodevelopmental outcomes [14, 15]. In contrast, there is little evidence on the early childhood effects of maternal underweight, with none on whether excess or insufficient GWG increases the risk of offspring developmental delay. We therefore conducted a large birth cohort study with the specific objective of examining the impact of maternal GWG on early neurodevelopment.

Materials and methods

Study design, population, and settings

The data used in this study were obtained from the Japan Environment and Children’s Study (JECS), an ongoing cohort study that began in January 2011 to determine the effect of environmental factors on children’s health. The target number of enrolled pregnant women was 100,000. Partners were also recruited, although their participation was not mandatory. In the JECS, pregnant women were recruited between January 2011 and March 2014. The eligibility criteria for participants were as follows: (1) residing in the study area at the time of recruitment, (2) expected delivery after August 1, 2011, and (3) capable of comprehending the Japanese language and completing the self-administered structured questionnaire in Japanese. This study was registered in the UMIN Clinical Trials Registry (number UMIN000030786). Details of the JECS project have been described previously [16–18]. The JECS protocol was reviewed and approved by the Institutional Review Board on Epidemiological Studies of the Ministry of the Environment (ethical number 100910001) as well as by the ethics committees of all participating institutions. The JECS was conducted in accordance with the Helsinki declaration and other nationally valid regulations and guidelines. Written informed consent was obtained from each participant.

The present study was based on the “jecs-an-20180131” dataset released in March 2018 containing information on 98,255 mothers who had a singleton live birth, including 50,563 with the fathers’ registration. Specifically, we focused on questionnaire data regarding developmental screening as
self-described by mothers when their child was 12 months old. The screening tool was the Ages and Stages Questionnaire, third edition (ASQ-3) [19]. Maternal medical information, additional pregnancy details, and medical history were collected from subject medical record transcriptions for adoption as other covariates.

Data collection

Information on socioeconomic status, smoking habit of the mother and partner, and maternal alcohol consumption during pregnancy was collected during the second/third trimester of pregnancy (T2) by means of self-reported questionnaires. Details on a parental history of neurodevelopmental disorders, epilepsy, and mental disease were also collected from T2 questionnaires as described by the mother and partner. Maternal anthropometric data before and during pregnancy, complications and medication during pregnancy related to HDP, diabetes mellitus/gestational diabetes mellitus (DM/GDM), and neonatal information was gathered from medical records. Pre-pregnancy BMI was calculated according to WHO standards as body weight (kg)/height (m)^2 and categorized as underweight (BMI < 18.5), normal weight (BMI 18.5–24.9), overweight (BMI 25.0–29.9), and obese (BMI ≥ 30).

Outcomes

The main outcomes of interest were ASQ-3 domain scores at the age of 12 months. The ASQ-3 is a parent-reported comprehensive first-level developmental screening tool for children aged 1–66 months with 30 items in five domains: communication, gross motor, fine motor, problem-solving, and personal–social skills. Each item describes a skill, ability, or behavior to which the parent responds “yes” (10 points), “sometimes” (5 points), or “not yet” (0 points). Parents sometimes omit items when they are unsure of how to respond or

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**Fig. 1** Case selection flowchart

104,065 Fetal record

3,921 Excluded
1,254 Miscarriages
382 Stillbirths
2,285 Missing data on pregnancy

100,144 Live births

1,889 Excluded due to multiple births
1,845 Twin, 44 Triplets

98,255 Singleton live births

50,563 Singleton live births with participating fathers

47,692 No registration of fathers

9,053 Missing score in one or more of the five domains in the ASQ-3 questionnaires

7,821 Missing data for analysis

33,689 Eligible live births

2,995 Excluded
144 Infants with low Apgar score of 5 minutes (< 7 points)
2,663 Infants with some physical abnormality
32 Infants diagnosed as having congenital metabolic disorder by screening test
156 Infants with abnormality in hearing ability screening test

30,694 Analyzed live births
Male: 15,436, Female: 15,258

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because they have concerns about their child’s performance of the item. ASQ-3 scores were not calculated if there were three or more omitted items in a given domain. In the case of one or two omitted items, an adjusted total domain score was calculated by adding the averaged item score either once for one omission or twice for two omissions. The score calculated for each domain was categorized as normal development (above cutoff) or referral zone (below two standard deviations). The manual for the original ASQ recommends that a child be considered as screen positive if his/her score falls below the referral cutoff in any one of the five domains [19]. Participants with established risk factors of developmental delay, such as neonatal asphyxia, and physical abnormality at birth, including infection, respiratory distress, congenital abnormality, hearing disability, and chromosomal abnormalities, were excluded to investigate the effects of maternal GWG on neurodevelopment in infants without obvious underlying disease during the neonatal period (Fig. 1).

Table 1  Demographic characteristics of participants with or without developmental abnormality

| Variable                                      | Total participants | Normal development | Positive ASQ-3 screen ≥ 1 domain | P value* |
|-----------------------------------------------|--------------------|--------------------|----------------------------------|---------|
| Participants, n                               | 30,694             | 19,751             | 10,943                           |         |
| Pre-pregnancy BMI, kg/m²                       | 20.6 (19.1, 22.5)  | 20.6 (19.1, 22.5)  | 20.5 (19.1, 22.6)                | 0.61†   |
| Pre-pregnancy BMI group, n (%)                |                    |                    |                                  |         |
| Underweight (BMI < 18.5)                      | 4730 (15.4)        | 2995 (15.2)        | 1735 (15.9)                      |         |
| Normal weight (BMI 18.5–24.9)                 | 22,761 (74.2)      | 14,721 (74.5)      | 8040 (73.5)                      |         |
| Overweight (BMI 25.0–29.9)                    | 2485 (8.1)         | 1590 (8.1)         | 895 (8.2)                        |         |
| Obese (BMI ≥ 30.0)                            | 718 (2.3)          | 445 (2.3)          | 273 (2.5)                        |         |
| Maternal GWG, kg                              | 10.2 (8.0, 12.5)   | 10.4 (8.1, 12.8)   | 9.9 (7.7, 12.2)                  | <0.001† |
| Maternal GWG group, n (%)                     |                    |                    |                                  | <0.001  |
| Below                                         | 18,527 (60.4)      | 11,567 (58.6)      | 6960 (63.6)                      |         |
| Within                                        | 9850 (32.1)        | 6575 (33.3)        | 3275 (29.9)                      |         |
| Above                                         | 2317 (7.5)         | 1609 (8.1)         | 708 (6.5)                        |         |
| Maternal age at delivery, years               | 31 (28, 35)        | 31 (28, 34)        | 32 (29, 35)                      | <0.001† |
| Maternal age group, n (%)                     |                    |                    |                                  | <0.001  |
| <35 years                                     | 20,463 (66.7)      | 13,647 (69.1)      | 6816 (62.3)                      |         |
| ≥35 years                                     | 10,231 (33.3)      | 6104 (30.9)        | 4127 (37.7)                      |         |
| Highest level of maternal education, n (%)    |                    |                    |                                  | <0.001  |
| Junior high school                            | 1020 (3.3)         | 735 (3.7)          | 285 (2.6)                        |         |
| High school                                   | 9094 (29.6)        | 5932 (30.0)        | 3162 (28.9)                      |         |
| Vocational school/junior college              | 13,366 (43.5)      | 8670 (43.9)        | 4696 (42.9)                      |         |
| University/graduate school                    | 7214 (23.5)        | 4414 (22.3)        | 2800 (25.6)                      |         |
| Annual household income,‡ n (%)               |                    |                    |                                  | 0.001   |
| <4,000,000 JPY                                | 11,894 (38.8)      | 7796 (39.5)        | 4098 (37.4)                      |         |
| 4,000,000–7,999,999 JPY                       | 15,503 (50.5)      | 9893 (50.1)        | 5610 (51.3)                      |         |
| ≥8,000,000 JPY                                | 3297 (10.7)        | 2062 (10.4)        | 1235 (11.3)                      |         |
| Maternal smoking during pregnancy, n (%)      | 1037 (3.4)         | 741 (3.8)          | 296 (2.7)                        | <0.001  |
| Partner’s smoking during pregnancy, n (%)     | 12,812 (41.7)      | 8637 (43.8)        | 4155 (38.0)                      | <0.001  |
| Maternal drinking during pregnancy, n (%)     | 568 (1.9)          | 366 (1.9)          | 202 (1.8)                        | 0.97    |
| Maternal history of mental disease, n (%)     | 1567 (5.1)         | 996 (5.0)          | 571 (5.2)                        | 0.50    |
| Maternal history of developmental disorder, n (%) | 14 (0.05)       | 5 (0.03)           | 9 (0.08)                         | 0.046   |
| Maternal history of epilepsy, n (%)           | 158 (0.5)          | 87 (0.4)           | 71 (0.6)                         | 0.015   |
| Partner’s history of mental disease, n (%)    | 753 (2.5)          | 462 (2.3)          | 291 (2.7)                        | 0.083   |
| Partner’s history of developmental disorder, n (%) | 21 (0.07)       | 13 (0.07)          | 8 (0.07)                         | 0.82    |
| Partner’s history of epilepsy, n (%)          | 123 (0.4)          | 72 (0.4)           | 51 (0.5)                         | 0.19    

ASQ-3 Ages and Stages Questionnaire, third edition, BMI body mass index, GWG gestational weight gain, JPY Japanese yen

*P value for normal development versus positive screen

†Mann–Whitney U test of normal development versus positive screen. Continuous variables are expressed as the median (interquartile range)

‡The average (median) annual Japanese household income in 2018 was 5,523,000 JPY (4,370,000 JPY). The currency exchange rates on July 12, 2021, were 1 USD = 110 JPY and 1 EUR = 130 JPY
Table 2 ASQ-3 domain scores and proportions at risk of delay according to maternal gestational weight gain

| ASQ-3 domain (cutoff score) | Below n=18,527 | Within n=9850 | Above n=2317 | P value |
|-----------------------------|----------------|--------------|--------------|---------|
| Communication (15.64 points) |                |              |              |         |
| Score (points)              | 37.3±13.4      | 38.7±13.2    | 40.3±13.0*   | <0.001  |
| On track, n (%)             | 17,141 (92.5)  | 9266 (94.1)  | 2211 (95.4)  |         |
| Referral, n (%)             | 1386 (7.5)     | 584 (5.9)    | 106 (4.6)    | <0.001  |
| Gross motor (21.49 points)  |                |              |              |         |
| Score (points)              | 42.4±17.5      | 44.0±16.7    | 45.1±16.6*   | <0.001  |
| On track, n (%)             | 15,833 (85.5)  | 8652 (87.8)  | 2056 (88.7)  |         |
| Referral, n (%)             | 2694 (14.5)    | 1198 (12.2)  | 261 (11.3)   | <0.001  |
| Fine motor (34.50 points)   |                |              |              |         |
| Score (points)              | 48.0±11.5      | 48.9±11.0*   | 49.8±10.6*   | <0.001  |
| On track, n (%)             | 16,600 (89.6)  | 8977 (91.1)  | 2147 (92.7)  |         |
| Referral, n (%)             | 1927 (10.4)    | 873 (8.9)    | 170 (7.3)    | <0.001  |
| Problem-solving (27.32 points) |            |              |              |         |
| Scores (points)             | 42.2±13.4      | 43.1±13.2*   | 43.8±13.0*   | <0.001  |
| On track, n (%)             | 15,633 (84.4)  | 8437 (85.7)  | 2023 (87.3)  |         |
| Referral, n (%)             | 2894 (15.6)    | 1413 (14.3)  | 294 (12.7)   | <0.001  |
| Personal-social (21.73 points) |          |              |              |         |
| Scores (points)             | 36.6±14.4      | 38.2±14.1*   | 39.4±14.0*   | <0.001  |
| On track, n (%)             | 15,225 (82.2)  | 8399 (85.3)  | 2006 (86.6)  |         |
| Referral, n (%)             | 3302 (17.8)    | 1451 (14.7)  | 311 (13.4)   | <0.001  |

Plus-minus variables are the mean±standard deviation. Differences in scores of ASQ-3 domains were assessed with one-way repeated measures of variance (ANOVA) followed by post hoc (Bonferroni) testing.

ASQ-3 Ages and Stages Questionnaire, third edition

*P<0.001 versus the GWG below guidelines group; †P<0.001, ‡P<0.01, and §P<0.05 versus the GWG within guidelines group.

Exposure

GWG in this study was subdivided as below, within, or above the reference values of the 2009 IOM guidelines widely used throughout the world. The IOM guideline ranges for total GWG based on pre-pregnancy BMI are as follows: 12.7–18.1 kg for underweight women, 11.3–15.9 kg for women of normal weight, 6.8–11.3 kg for overweight women, and 5.0–9.1 kg for obese women (Supplemental table S1).

Covariates

The covariates in our models were selected a priori based on previous literature and biologic plausibility [20–24].

We estimated the effects of GWG after adjusting for demographic data including maternal age, pre-pregnancy BMI, parental smoking habit, maternal drinking habit, maternal highest level of education, annual household income, parental history of neurodevelopmental disorders, epilepsy, and mental disease, as well as obstetric and medical variables such as parity, means of pregnancy (including spontaneous pregnancy and assisted reproductive techniques, such as ovulation induction and artificial insemination or in vitro fertilization), use of folic acid supplements, complications during pregnancy (including DM/GDM, HDP, and intrauterine growth restriction), means of delivery, birth weight, gender, method of feeding, and neonatal jaundice in the newborn period requiring treatment such as phototherapy and exchange transfusion. Parental medical history of neurodevelopmental disorders included attention deficit hyperactivity disorder, learning disability, autism, Asperger’s syndrome, pervasive developmental disorder, and others. Parental history of mental disease included depression, schizophrenia, and anxiety disorder. Intrauterine growth restriction was defined as estimated fetal weight less than –1.5 standard deviations of standard weight based on gestational age in Japan.

Statistical analysis

Distribution normality was confirmed by the Kolmogorov–Smirnov test. Data are expressed as the mean±standard deviation or the median (interquartile range) depending on whether they are normally distributed or not. Possible differences in maternal age, pre-pregnancy BMI, GWG, gestational age, and birth weight between subjects with normal development and developmental delay were assessed by the unpaired t-test or the Mann–Whitney U test based on the presence or absence of normal distribution, respectively. We also categorized continuous and ordinal variables, such as maternal age (<35 or ≥35 years), pre-pregnancy BMI, GWG (below, within, or above), annual household income (<4,000,000, 4,000,000–7,999,999, or ≥8,000,000 JPY), gestational age (<37 or ≥37 weeks), and birth weight (<1500, 1500–2499, or ≥2500 g). Fisher’s exact tests or chi-square tests were performed to compare covariates between groups stratified by category as well as by the presence of developmental delay. Additionally, differences in the scores of each domain among the three GWG groups were assessed by one-way repeated measures of analysis of variance (ANOVA) followed by post hoc (Bonferroni) testing. We employed multiple logistic regression models to investigate developmental delay at 1 year as the dependent variable in association with maternal GWG. Infants below and above the cutoff for each domain were categorized as “delayed” and “normal,” respectively. GWG was
subdivided as below, within (reference), or above IOM guidelines. The models were adopted to calculate adjusted odds ratios (ORs) and their 95% confidence intervals (CIs) controlling covariates, as described above. Spearman’s rank correlation coefficient was used to check for multicollinearity of covariates. The variable of gestational age was excluded from the covariates because it was multicollinear with birth weight. Hosmer–Lemeshow testing was used to assess the goodness of fit of the models. We also analyzed the subjects without registered fathers to evaluate for possible selection bias.

All statistical analyses were performed using SPSS statistical software version 27 (SPSS Inc., Chicago, IL). All tests were two-tailed, and P-values of less than 0.05 were considered to indicate statistical significance.

Results

A total of 30,694 mothers with singleton live births and partners who completed the JECS questionnaire were available for analysis (Fig. 1). According to the pre-pregnancy BMI categories, the prevalence of underweight, normal weight,
Fig. 3 Odds ratios (ORs) for the association between maternal gestational weight gain (GWG) below and above guidelines with developmental delay in ASQ-3 domains according to the pre-pregnancy body mass index (BMI) categories. ORs are shown for the association between GWG below (A) and above (B) guidelines with developmental delay at 12 months according to maternal GWG. The regression models for all domains demonstrated good fit in Hosmer–Lemeshow testing. Chi-square analysis revealed significant differences in the prevalence of developmental delay in the communication, gross motor, fine motor, problem-solving, and personal–social domains among maternal GWG groups. ANOVA showed that the scores for every ASQ-3 domain were significantly lower in the GWG below guidelines group than in the GWG within and above guidelines groups.

The regression models for all domains demonstrated good fit in Hosmer–Lemeshow testing. In multivariate logistic regression analysis after adjustment for covariates, compared with ideal GWG, GWG below guidelines was significantly associated with a higher incidence of developmental delay in the communication (OR 1.21, 95% CI 1.09–1.34), overweight, and obese mothers was 15.4% (4730), 74.2% (22,761), 8.1% (2485), and 2.3% (718), respectively. The prevalence of mothers below, within, and above the IOM-based GWG guidelines was 60.4% (18,527), 32.1% (9850), 8.1% (2485), and 2.3% (718), respectively. There were 10,943 participants (35.7%) who were outliers in at least one ASQ-3 domain (Table 1 and Supplemental table S2).

Table 1 and Supplemental table S2 summarize the participants’ characteristics and offspring outcomes for developmental delay. There were significant differences in the rates of the GWG groups. We observed significant differences between the normal development and developmental delay groups for demographic categories including maternal age, maternal educational level, annual household income, parental smoking status, and maternal history of epilepsy (Table 1). Significant differences were also seen in such perinatal categories as parity, means of pregnancy of current birth, maternal use of folic acid supplements, HDP, mode of delivery, gestational age, birth weight, gender, method of feeding, and neonatal jaundice.

### Table 1

| ASQ-3 Domain          | No | OR (95% CI) |
|-----------------------|----|-------------|
| **Communication**     |    |             |
| < 18.5                | 288| 1.39 (1.04–1.87) |
| 18.5–24.9             | 1018| 1.16 (1.03–1.31) |
| 25.0–29.9             | 63 | 1.34 (0.96–2.17) |
| ≥ 30.0                | 17 | 0.81 (0.54–1.34) |
| Overall               | 1.21 (1.09–1.34) |
| **Gross motor**       |    |             |
| < 18.5                | 546| 1.22 (0.98–1.52) |
| 18.5–24.9             | 1986| 1.15 (1.05–1.26) |
| 25.0–29.9             | 126| 0.99 (0.74–1.30) |
| ≥ 30.0                | 36 | 0.57 (0.32–1.01) |
| Overall               | 1.14 (1.05–1.23) |
| **Fine motor**        |    |             |
| < 18.5                | 383| 1.20 (0.94–1.53) |
| 18.5–24.9             | 1392| 1.10 (0.99–1.22) |
| 25.0–29.9             | 103 | 1.20 (0.88–1.64) |
| ≥ 30.0                | 49 | 1.14 (0.63–2.06) |
| Overall               | 1.13 (1.04–1.24) |
| **Problem solving**   |    |             |
| < 18.5                | 560| 1.01 (0.83–1.23) |
| 18.5–24.9             | 2117| 1.10 (1.01–1.20) |
| 25.0–29.9             | 157 | 1.09 (0.84–1.41) |
| ≥ 30.0                | 60 | 1.08 (0.63–1.77) |
| Overall               | 1.09 (1.01–1.18) |
| **Personal-social**   |    |             |
| < 18.5                | 597| 1.15 (0.93–1.41) |
| 18.5–24.9             | 2465| 1.16 (1.07–1.26) |
| 25.0–29.9             | 176| 1.20 (0.95–1.54) |
| ≥ 30.0                | 64 | 0.94 (0.86–1.57) |
| Overall               | 1.15 (1.07–1.24) |

### Table S2

| ASQ-3 Domain          | No | OR (95% CI) |
|-----------------------|----|-------------|
| **Communication**     |    |             |
| < 18.5                | 106 | 0.44 (0.13–1.48) |
| 18.5–24.9             | 61 | 0.70 (0.53–0.93) |
| 25.0–29.9             | 35 | 1.25 (0.78–2.01) |
| ≥ 30.0                | 7  | 1.16 (0.38–3.50) |
| Overall               | 0.82 (0.66–1.03) |
| **Gross motor**       |    |             |
| < 18.5                | 8  | 0.73 (0.34–1.60) |
| 18.5–24.9             | 170| 1.00 (0.84–1.20) |
| 25.0–29.9             | 63 | 0.83 (0.59–1.16) |
| ≥ 30.0                | 20 | 0.91 (0.46–1.78) |
| Overall               | 0.98 (0.84–1.13) |
| **Fine motor**        |    |             |
| < 18.5                | 7  | 0.87 (0.38–1.98) |
| 18.5–24.9             | 91 | 0.74 (0.59–0.93) |
| 25.0–29.9             | 55 | 0.91 (0.63–1.32) |
| ≥ 30.0                | 17 | 1.11 (0.52–2.34) |
| Overall               | 0.84 (0.70–1.00) |
| **Problem solving**   |    |             |
| < 18.5                | 7  | 0.39 (0.17–0.89) |
| 18.5–24.9             | 166| 0.79 (0.66–0.95) |
| 25.0–29.9             | 86 | 0.87 (0.64–1.19) |
| ≥ 30.0                | 35 | 1.36 (0.76–2.43) |
| Overall               | 0.85 (0.74–0.98) |
| **Personal-social**   |    |             |
| < 18.5                | 8  | 0.72 (0.33–1.56) |
| 18.5–24.9             | 177| 0.85 (0.72–1.02) |
| 25.0–29.9             | 103| 1.14 (0.85–1.52) |
| ≥ 30.0                | 23 | 0.99 (0.52–1.90) |
| Overall               | 0.94 (0.82–1.08) |

The regression models for all domains demonstrated good fit in Hosmer–Lemeshow testing. Chi-square analysis revealed significant differences in the prevalence of developmental delay in the communication, gross motor, fine motor, problem-solving, and personal–social domains among maternal GWG groups. ANOVA showed that the scores for every ASQ-3 domain were significantly lower in the GWG below guidelines group than in the GWG within and above guidelines groups.

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gross motor (OR 1.14, 95% CI 1.05–1.24), fine motor (OR 1.13, 95% CI 1.04–1.24), problem-solving (OR 1.09, 95% CI 1.01–1.18), and personal–social (OR 1.15, 95% CI 1.07–1.24) domains (Table 3). For every 2.3 kg (5 lb) of GWG, the risk of abnormalities was reduced by 4–9% in each domain of ASQ-3 (communication, OR 0.91 [95% CI 0.88–0.94]; gross motor, OR 0.96 [95% CI 0.94–0.98]; fine motor, OR 0.94 [95% CI 0.91–0.96]; problem-solving, OR 0.95 [0.93–0.97]; personal–social, OR 0.94 [0.92–0.96]) (Table 3).

Across BMI categories, GWG below guidelines tended to associate with a higher risk of developmental delay (i.e., OR > 1.0) in ASQ-3 screening than did GWG within guidelines (Fig. 3A). In contrast, GWG above guidelines often tended to associate with a lower risk of developmental delay across domains as compared with GWG within guidelines (Fig. 3B).

Lastly, we analyzed the 24,823 subjects without registered fathers. Supplemental table S2 shows the characteristics of the normal development and developmental delay groups. We observed a significant difference in the proportion of GWG categories between the groups similar to that in the main analysis (Supplemental table S3). Multivariate regression analysis also revealed significant associations between GWG below guidelines and the incidence of developmental delay in all five domains. For every 2.3 kg (5 lb) of GWG, the risk of abnormalities was reduced by 5–11% in each domain of ASQ-3 (Supplemental table S4).

Discussion

We herein describe the first large-scale nationwide birth cohort study in Japan to clarify the impact of insufficient maternal weight gain during pregnancy on offspring neurodevelopment at 12 months. Across pre-pregnancy BMI categories, the association was particularly significant in mothers with a lower pre-pregnancy BMI.

In this Japanese nationwide birth cohort study, the prevalence rate of screen positive measured by ASQ-3 at 12 months of age for communication, gross motor, fine motor, problem-solving, and personal–social domains was 6.8%, 13.5%, 9.7%, 15.0%, and 16.5%, respectively. However, the prevalence of developmental delay can differ according to demographic status and underlying disease [4, 5, 20–22]. Several perinatal risk factors of developmental delay have been reported, including pre-term birth, perinatal maternal mental health, and maternal educational level [20–22]. Relationships between maternal obesity during pregnancy and poor pregnancy results have also been described [6, 7, 14, 15]. The number of underweight pregnant women in Japan is on the rise [11, 12, 25, 26], possibly since the ideal body shape of young women is becoming thinner [27] in addition to strict GWG management to facilitate delivery without obstetric complications [28]. The obesity classification and GWG recommendations used in Japan differ considerably from those prescribed by the IOM (Supplemental table S1) [10]. Several recent Japanese studies showed that underweight women carried a higher risk of adverse birth outcomes, such as pre-term birth and SGA [25, 26, 29]. However, they did not assess subsequent neurodevelopment in infants of underweight women. A Swedish cohort study investigating the association between maternal GWG and risk of offspring autism spectrum disorder (ASD) supported our findings, whereby an elevated risk of ASD was observed for both insufficient and excess GWG [30]. They also suggested that maternal undernutrition during pregnancy contributed to the risk developmental abnormality.

It is uncertain why insufficient GWG may cause neurodevelopmental disorders. One reason is that malnutrition may restrict fetal brain growth. In Japan, total calorie intake among pregnant women was far below nationally recommended levels [31, 32]. Maternal dietary quality is of critical importance since specific nutrients are required during sensitive or critical periods of fetal development [33]. Folic acid has been recognized as necessary for neural tube development [34]. Iron is the most common nutrient deficiency during pregnancy and is necessary for myelination and the development of the frontal cortex and basal ganglia [35]. The studies on Japanese pregnant women mentioned above reported that the proportions of carbohydrates and lipids in total calories were respectively lower and higher than those required by pregnant women [31, 32]. Sussman et al. suggested that prenatal exposure to a carbohydrate-restricted diet, such as recently popular ketogenic diet programs, influenced not only offspring neuroanatomy such as brain structure and volumetric change [36], but also behavioral alterations that included reduced susceptibility to anxiety and depression and elevated hyperactivity in adult mouse offspring [36, 37]. Indeed, optimal diet and weight gain guidance for underweight women of child-bearing age appear critical.

It is important to determine whether neurodevelopmental evaluations at 12 months are clinically valid for subsequent diagnosis. In one study longitudinally comparing child ASQ-3 domain screening results based on cutoff scores, the vast majority (88.9–96.7%) received the same categorization results at 9, 18, and 24 months of age [38]. Other studies have provided evidence on the concurrent validity of the ASQ-3 and the clinical diagnosis of developmental delay, as well as on the reliability of the ASQ-3 in a multiethnic population [39–41]. However, the number of children who were screen positive (i.e., failed at least one of the five domains) in this study was high at 35.7%. This rate varies among age, developmental area, and country at 13–48% [38–42].
A strength of this investigation was that not only maternal, but also paternal history of neurodevelopmental problems was adjusted for as covariates. Genetic influences could be larger than those of a shared environment on the incidence of neurodevelopmental disorders [23, 24]. Since selection bias might have been produced by excluding the subjects without father registration, we also analyzed the group without father registration to assess this possibility. GWG below guidelines was significantly associated with a higher incidence of developmental delay than in the main analysis, although paternal medical history was not adjusted as a covariate in this subpopulation (Supplemental table S3).

This study has several limitations. First, the data regarding developmental scores as measured by ASQ-3 were collected from parental self-reported questionnaires and therefore subjective. Second, as data on abnormalities were evaluated at 12 months of age, no neurodevelopmental disorders diagnosed afterwards were included. Third, the large attrition rate of either unpaired participants or those not completing the ASQ-3 questionnaire may have constituted selection bias; we cannot conclusively rule out the possibility of underreporting the incidence of developmental disorders. Fourth, the parental histories of neurodevelopmental disorders, epilepsy, and mental disease were also collected from self-reported questionnaires. Therefore, these answers might not have conformed to diagnostic criteria or ICD coding. Finally, the participants of this study contained a large group of underweight mothers, which was representative of the Japanese population [12]. Therefore, although the analysis of obesity and/or excessive GWG may have been inadequate, this study provides valuable and unique research that is impossible in other countries.

Despite the above limitations, this is the first investigation using a large dataset from a Japanese nationwide birth cohort study to examine the independent influence of insufficient maternal GWG on offspring’s neurodevelopment that controlled for confounders identified by previous reports including birth weight. This study indicates a need to reconsider the optimal BMI and GWG for women desiring pregnancy not only in Japan, but also in other developed countries.

**Supplementary information** The online version contains supplementary material available at https://doi.org/10.1007/s00431-021-04232-7.

**Acknowledgements** The findings and conclusions of this article are solely the responsibility of the authors and do not represent the official views of the Ministry of the Environment. The authors would like to thank all participants of this study and all individuals involved in data collection, as well as Ms. Tomoko Kamijo for her assistance in data analysis and Mr. Trevor Ralph for his English editorial support.

**Authors’ contributions** Dr. Motoki conceptualized and designed the study, carried out the analyses, and drafted the initial manuscript. Prof. Inaba conceptualized and designed the study and reviewed and revised the manuscript.

Dr. Shibazaki, Dr. Misawa, Dr. Ohira, Prof. Kanai, Prof. Kurita, Prof. Tsukahara, and Prof. Nomiyama designed the data collection instruments, collected data, and critically reviewed the manuscript for important intellectual content.

The JECS group reviewed the manuscript and provided critical advice.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

**Data availability** Data are unsuitable for public deposition due to ethical restrictions and legal framework of Japan. It is prohibited by the Act on the Protection of Personal Information (Act No. 57 of 30 May 2003, amendment on 9 September 2015) to publicly deposit the data containing personal information. Ethical Guidelines for Medical and Health Research Involving Human Subjects enforced by the Japan Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare also restrict the open sharing of the epidemiologic data. All inquiries about access to data should be sent to jecs-en@nies.go.jp. The person responsible for handling enquiries sent to this e-mail address is Dr. Shoji F. Nakayama, JECS Programme Office, National Institute for Environmental Studies.

**Code availability** Not applicable.

**Compliance with ethical standards**

**Financial disclosure** The JECS was funded by the Ministry of the Environment, Japan. The findings and conclusions contained in this article are solely those of the authors and do not represent the official views of the above government.

**Ethics approval** The study received the approval of the Institutional Review Board on Epidemiological Studies of the Ministry of the Environment as well as the ethics committees of all participating institutions.

**Consent to participate** All participants gave informed consent to participate.

**Consent for publication** All participants gave informed consent to publish data from the study.

**Conflict of interest** The authors declare no competing interests.

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References

1. Oberklaid F, Efron D (2005) Developmental delay–identification and management. Aust Fam Physician 34:739–742
2. Blumberg SJ, Bramlett MD, Kogan MD, Schieve LA, Jones JR, Lu MC (2013) Changes in prevalence of parent-reported autism spectrum disorder in school-aged U.S. children: 2007 to 2011–2012. Natl Health Stat Report 65:1–11
3. Boyle CA, Boulet S, Schieve LA et al (2011) Trends in the prevalence of developmental disabilities in US children, 1997–2008. Pediatrics 127:1034–1042. https://doi.org/10.1542/peds.2010-2989
4. Simeonsson RJ, Sharp MC (1992) Developmental delays. In: Hockelman RA, Friedman SB, Nelson NM et al (ed) Primary pediatric care. Mosby-Year Book, St Louis, pp 867–870
5. Gottlieb CA, Maemner MJ, Cappa C, Durkin MS (2009) Child disability screening, nutrition, and early learning in 18 countries with low and middle incomes: data from the third round of UNICEF’s Multiple Indicator Cluster Survey (2005–06). Lancet 374:1831–1839. https://doi.org/10.1016/S0140-6736(09)61871-7
6. Marchi J, Berg M, Dencker A, Olander KE, Begley C (2015) Risks associated with obesity in pregnancy, for the mother and baby: a systematic review of reviews. Obes Rev 16:621–638. https://doi.org/10.1111/obr.12288
7. Goldstein RF, Abell SK, Ranasinha S et al (2017) Association of gestational weight gain with maternal and infant outcomes: a systematic review and meta-analysis. JAMA 317:2207–2225. https://doi.org/10.1001/jama.2017.3635
8. Pigatti Silva F, Souza RT, Caccuri JG et al (2019) Role of Body Mass Index and gestational weight gain on preterm and adverse perinatal outcomes. Sci Rep 11(9):13093. https://doi.org/10.1038/s41598-019-49704-x
9. Institute of Medicine and National Research Council Committee to reexamine IOM pregnancy weight guidelines; Rasmussen K, Yaktine AL, editors (2009) Weight gain during pregnancy: an evidence-based reevaluation of Japanese guidelines for gestational weight gain to multicultural guidelines. Washington (DC), US: National Academ Press. https://doi.org/10.17226/12584
10. Press release from The Ministry of Labour Health and Welfare (2006) Optimal weight gain during pregnancy (in Japanese) [Cited on June 15, 2021]. https://www.mhlw.go.jp/houdou/2006/02/dl/h0201-3a4.pdf
11. Shindo R, Aoki M, Yamamoto Y, Misumi T, Miyagi E, Aoki S (2019) Optimal gestational weight gain for underweight pregnant women in Japan. Sci Rep 9:18129. https://doi.org/10.1038/s41598-019-45550-y
12. Enomoto K, Aoki S, Toma R, Fujiwara K, Sakamaki K, Hirahara F (2016) Pregnancy outcomes based on pre-pregnancy body mass index in Japanese women. PLoS ONE 11:e0157081. https://doi.org/10.1371/journal.pone.0157081
13. Hinkle SN, Sharma AJ, Kim SY, Schieve LA (2013) Maternal prepregnancy weight status and associations with children’s development and disabilities at kindergarten. Int J Obes (Lond) 37:1344–1351. https://doi.org/10.1038/ijo.2013.128
14. Duffany KO, McVeigh KH, Kershaw TS, Lipskind HS, Ickovics JR (2016) Maternal obesity: risks for developmental delays in early childhood. Matern Child Health J 20:219–230. https://doi.org/10.1007/s10895-015-1821-z
15. Windham GC, Anderson M, Lyall K et al (2019) Maternal pre-pregnancy body mass index and gestational weight gain in relation to autism spectrum disorder and other developmental disorders in offspring. Autism Res 12:316–327. https://doi.org/10.1002/aur.2057
16. Michikawa T, Nitta H, Nakayama SF et al (2018) Baseline profile of participants in the Japan Environment and Children’s Study (JECS. J Epidemiol 28:99–104. https://doi.org/10.2188/jjea.je20170018
17. Ishitsuka K, Nakayama SF, Kishi R et al (2017) Japan Environment and Children’s Study: backgrounds, activities, and future directions in global perspectives. Environ Health Prev Med 22:61. https://doi.org/10.1186/s12199-017-0667-y
18. Kawamoto T, Nitta H, Murata K et al (2014) Rationale and study design of the Japan environment and children’s study (JECS). BMC Public Health 14:25. https://doi.org/10.1186/1471-2458-14-25
19. Squires J, Bricker D (2009) Ages and Stages Questionnaires®, Third Edition (ASQ-3™). A parent-completed child-monitoring system. Brookes Publishing Co., Baltimore, US
20. McDonald S, Kehler H, Bayrampour H, Fraser-Lee N, Tough S (2016) Risk and protective factors in early child development: results from the All Our Babies (AOB) pregnancy cohort. Res Dev Disabil 58:20–30. https://doi.org/10.1016/j.ridd.2016.08.010
21. Demirci A, Kartal M (2018) Sociocultural risk factors for developmental delay in children aged 3–60 months: a nested case-control study. Eur J Pediatr 177:691–697. https://doi.org/10.1007/s00431-018-3109-y
22. Westgard C, Alnasser Y (2017) Developmental delay in the Amazon: the social determinants and prevalence among rural communities in Peru. PLoS ONE 12:e0186263. https://doi.org/10.1371/journal.pone.0186263
23. Sandin S, Lichtenstein P, Kuja-Halkola R, Larsson H, Hultman CM, Reichenberg A (2014) The familial risk of autism. JAMA 311:1770–1777. https://doi.org/10.1001/jama.2014.4144
24. Colvert E, Tick B, McEwen F et al (2015) Heritability of autism spectrum disorder in a UK population-based twin sample. JAMA Psychiatry 72:415–423. https://doi.org/10.1001/jamapsychiatry.2014.3028
25. Fujiwara K, Aoki S, Kurasa K, Okuda M, Takahashi T, Hirahara F (2014) Associations of maternal pre-pregnancy underweight with small-for-gestational-age and spontaneous preterm birth, and optimal gestational weight gain in Japanese women. J Obstet Gynecol Res 40:988–994. https://doi.org/10.1111/jog.12283
26. Morisaki N, Nagata C, Jwa SC, Sago H, Saito S, Oken E, Fujikawa T (2017) Pre-pregnancy BMI-specific optimal gestational weight gain for women in Japan. J Epidemiol 27:492–498. https://doi.org/10.1016/j.jej.2016.09.013
27. Maruyama S, Nakamura S (2015) The decline in BMI among Japanese women after World War II. Econ Hum Biol 18:125–138. https://doi.org/10.1016/j.ehb.2015.05.001
28. Ogawa K, Morisaki N, Sago H, Fujiwara T, Horikawa R (2018) Association between women’s perceived ideal gestational weight gain during pregnancy and pregnancy outcomes. Sci Rep 8:11574. https://doi.org/10.1038/s41598-018-29936-z
29. Nomura K, Nagashima K, Suzuki S, Itoh H (2019) Application of Japanese guidelines for gestational weight gain to multiple pregnancy outcomes and its optimal range in 101,336 Japanese women. Sci Rep 9:17310. https://doi.org/10.1038/s41598-018-35309-8
30. Gardner RM, Lee BK, Magnusson C, Rai D, Frisell T, Karlsson H et al (2015) Maternal body mass index during early pregnancy, gestational weight gain, and risk of autism spectrum disorders: results from a Swedish total population and discordant sibling study. Int J Epidemiol 44:870–883. https://doi.org/10.1093/ije/dyv081
31. Kubota K, Itoh H, Tasaka M, et al; Hamamatsu Birth Cohort (HBC) Study Team (2013) Changes of maternal dietary intake, bodyweight and fetal growth throughout pregnancy in pregnant
Japanese women. J Obstet Gynaecol Res 39:1383–1390. https://doi.org/10.1111/jog.12070
32. Uno K, Takemi Y, Hayashi F, Hosokawa M (2016) Nutritional status and dietary intake among pregnant women in relation to pre-pregnancy body mass index in Japan. Nihon Koshu Eisei Zasshi 63:738–749. Japanese
33. Vohr BR, Poggi Davis E, Wanke CA, Krebs NF (2017) Neurodevelopment: the impact of nutrition and inflammation during preconception and pregnancy in low-resource settings. Pediatrics 139(Suppl 1):S38–S49. https://doi.org/10.1542/peds.2016-2828f
34. Molloy AM, Kirke PN, Brody LC, Scott JM, Mills JL (2008) Effects of folate and vitamin B12 deficiencies during pregnancy on fetal, infant, and child development. Food Nutr Bull 29(2 suppl):S101-S111; discussion S112-S115. https://doi.org/10.1177/15648265080292S114
35. Wachs TD, Georgieff M, Cusick S, McEwen BS (2014) Issues in the timing of integrated early interventions: contributions from nutrition, neuroscience, and psychological research. Ann N Y Acad Sci 1308:89–106. https://doi.org/10.1111/nyas.12314
36. Sussman D, Ellegood J, Henkelman M (2013) A gestational ketogenic diet alters maternal metabolic status as well as offspring physiological growth and brain structure in the neonatal mouse. BMC Pregnancy Childbirth 13:198. https://doi.org/10.1186/1471-2393-13-198
37. Sussman D, Germann J, Henkelman M (2015) Gestational ketogenic diet programs brain structure and susceptibility to depression & anxiety in the adult mouse offspring. Brain Behav 5:e00300. https://doi.org/10.1002/brb3.300
38. Agarwal PK, Xie H, Suthyapalan Rema AS et al (2020) Evaluation of Ages and Stages Questionnaire (ASQ 3) as a developmental screener at 9, 18, and 24 months. Early Hum Dev 147:105081. https://doi.org/10.1016/j.earlhumdev.2020.105081
39. Fauls JR, Thompson BL, Johnston LM (2020) Validity of the Ages and Stages Questionnaire to identify young children with gross motor difficulties who require physiotherapy assessment. Dev Med Child Neurol 62:837–844. https://doi.org/10.1111/dmcn.14480
40. Ga HY, Kwon JY (2011) A comparison of the Korean ages and stages questionnaires and Denver developmental delay screening test. Ann Rehabil Med 35:369–374. https://doi.org/10.5535/arm.2011.35.3.369
41. Romero Otalvaro AM, Grañana N, Gaeto N et al (2018) ASQ-3: validation of the Ages and Stages Questionnaire for the detection of neurodevelopmental disorders in Argentine children. Arch Argent Pediatr 116:7–13. https://doi.org/10.5546/aap.2018.en
42. Yue A, Jiang Q, Wang B et al (2019) Concurrent validity of the Ages and Stages Questionnaire and the Bayley Scales of Infant Development III in China. PLoS ONE 14:e0221675. https://doi.org/10.1371/journal.pone.0221675
43. Mezawa H, Aoki S, Nakayama SF et al (2019) Psychometric profile of the Ages and Stages Questionnaires. Japanese translation Pediatr Int 61:1086–1095. https://doi.org/10.1111/ped.13990

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