


Neurodevelopmental delay up to the age of 4 years in infants born to women with gestational diabetes mellitus: The Japan Environment and Children's Study

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Keywords

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ABSTRACT

Aims/Introduction: This study aimed to investigate the neurodevelopment of infants born to women with gestational diabetes mellitus (GDM).

Materials and Methods: Data from the National Birth Cohort in the Japan Environment and Children's Study from 2011 to 2014 ($n = 81,705$) were used. Japan uses the GDM guidelines of the International Association of Diabetes and Pregnancy Study Groups. The Japanese translation of the Ages and Stages Questionnaires, third Edition, was used to assess neurodevelopment in the following domains: communication skills, gross motor skills, fine motor skills, problem-solving ability, and personal and social skills. The survey was carried out every 6 months from the age of 6 months to 4 years (total of eight times). Generalized estimating equations were used to evaluate the association between maternal GDM and neurodevelopmental delay based on odds ratios (ORs) and 95% confidence intervals (95% CIs).

Results: Neurodevelopmental delays, particularly in problem-solving ability, fine motor skills, and personal and social skills, were significantly higher in infants born to women with GDM than in those born to women without GDM (adjusted OR 1.24, 95% CI 1.12–1.36; adjusted OR 1.15, 95% CI 1.03–1.27; and adjusted OR 1.18, 95% CI 1.04–1.33). Furthermore, stratification showed no significant increase in the adjusted ORs (95% CIs) of girls.

Conclusions: Neurodevelopment was significantly delayed up to 4 years-of-age among boys born to women with GDM.

INTRODUCTION

The Development Origins of Health and Disease hypothesized that future health and the risk of specific diseases are strongly influenced by the environment during the fetal and early post-natal phase¹. A representative study reported that low-birthweight babies have a higher risk of developing metabolic syndromes, such as diabetes, hypertension and hyperlipidemia, in adulthood than normal-birthweight babies^{2,3}. Epigenetics is

one of the mechanisms underlying the Development Origins of Health and Disease hypothesis⁴, and deoxyribonucleic acid (DNA) methylation is reportedly associated with developmental disorders of the brain and nervous system⁵. The first 1,000 days play a crucial role in the growth and development of the child. However, studies on the trajectory of anatomical and functional brain development combined with clinical and epidemiological studies on neurodevelopmental outcomes show a slightly wider crucial period, approximately 3 years after conception^{6,7}. Gestational diabetes mellitus (GDM), which creates an over-

[†]Appendix 1.

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nutritional environment for the fetus, might be one of the risk factors influencing later health of children, particularly leading to neurodevelopmental delay. Hence, it must be assessed accurately.

Gestational diabetes mellitus is a glucose metabolism abnormality diagnosed during pregnancy, and is an obstetric complication that can lead to macrosomia, hypertensive disorders of pregnancy and preterm labor⁸. Because there is an association between maternal body size and GDM⁸, the global incidence of obesity among women of reproductive age has been increasing^{9,10}. Thus, the number of women with GDM has also been increasing, with a reported prevalence of 10.6–11.5%^{11,12}. However, in Japan, the increasing number of underweight women is an issue, and the prevalence of GDM is low (3.9–7.0%)^{13–17}. The associations of maternal obesity with offspring autism spectrum disorder (ASD), attention deficit hyperactivity disorder and cognitive function have been extensively studied in large cohorts, showing modest effect sizes after adjusting for confounding maternal and birth factors⁷. Nevertheless, there are still controversies regarding the neurodevelopment of children born to women with GDM. Some studies have elucidated that children born to women with GDM have poor cognitive function^{18–21}, whereas others have reported good cognitive functions²². A Japanese report published in 1996 showed that children born to pregnant women with impaired glucose tolerance had poorer intellectual development at the age of 3 years²³. However, a meta-analysis has shown that children born to women with GDM are at a higher risk for ASD²⁴. Thus, the effects of GDM on the neurodevelopment of children must be assessed at the age of 4 years.

In a previous study, we investigated the relationship between the body size of pregnant women with GDM and the birth-weight of their babies. We found that the number of infants who are small for gestational age and born to pregnant women with GDM can increase significantly if treatment for appropriate weight gain is not considered²⁵. Therefore, the present study sought to investigate whether infants born to pregnant women with GDM showed delayed neurodevelopment up to the age of 4 years using the Japanese translation of the Ages and Stages Questionnaires, third edition (J-ASQ-3).

MATERIALS AND METHODS

Data collection

The present study used data from the Japanese National Birth Cohort in the Japan Environment and Children's Study (JECS). Participants were recruited from 15 Regional Centers across Japan, which is 45% of the whole birth Study Area, from January 2011 to March 2014^{26,27}. The eligibility criteria for expectant and nursing mothers were as follows: (i) they must live in the study area upon recruitment and will live in Japan continuously for the foreseeable future; (ii) their expected date of delivery must be between 1 August 2011 and mid-2014; and (iii) they must be able to participate in this study without difficulties. The survey used questionnaires and

medical records transcribed by the doctors and medical staff, and data obtained up to 4 years-of-age were utilized. Furthermore, the datasets, *jecs-ta-20190930* and *jecs-qa-20210401*, were applied.

The total number of records was 104,059. Next, 1,992 records of multiple pregnancies were excluded. Finally, 8,729 records were excluded to limit information to full-term pregnancies. Children with diseases affecting neurodevelopment were identified from the medical records transcripts obtained during the 1-month checkups. Those with chromosomal abnormalities ($n = 142$), head and brain abnormalities ($n = 284$), congenital metabolic abnormalities ($n = 239$), and bone dysplasia ($n = 132$) were excluded. In addition, those whose mothers had abnormalities in glucose metabolism ($n = 210$), whose mothers self-reported on the first trimester questionnaire type 1 diabetes mellitus or type 2 diabetes mellitus and whose mothers were treated with insulin without GDM were excluded. Finally, there were 4,759 records of participants with missing J-ASQ-3 data and 5,900 records with missing information about factors that were adjusted. Hence, these data were not included. In total, 81,705 participants were included in the analysis (Figure 1).

GDM definition

In Japan, GDM is diagnosed using the stepwise method²⁸, which is a modified version of the International Association of Diabetes and Pregnancy study groups²⁹. In the initial screening, the random blood glucose level in early pregnancy is assessed. Then, in the second screening, the 50-g glucose challenge test (with a cut-off value of ≥ 140 mg/dL) or a random blood glucose test is carried out at 24–28 weeks of gestation²⁸. Pregnant women with positive screening results should fast overnight and undergo the 75-g oral glucose tolerance test. In the 75-g oral glucose tolerance test, blood samples are collected before as well as 1 and 2 h after glucose loading²⁸. The cut-off plasma glucose level is 92–125 mg/dL before glucose loading, and >180 and >153 mg/dL 1 and 2 h after glucose loading, respectively²⁸. GDM is diagnosed if one of the criteria is met.

Assessment of developmental delays up to the age of 4 years

The ASQ-3 is a screening tool used to evaluate developmental delay in children³⁰. The JECS uses the J-ASQ-3 for assessment at 6 months-of-age (limited 5–6 months range), 12 months-of-age (limited 11–12 months range), 18 months-of-age (limited 17–18 months range), 24 months-of-age (limited 23–25 months range), 30 months-of-age (limited 28–31 months range), 36 months-of-age (limited 34–38 months range), 42 months-of-age (limited 39–44 months range) and 48 months-of-age (limited 45–50 months range). To reduce differences in the timing of developmental assessments, data listed outside of a specific time period were treated as missing values. The J-ASQ-3 questionnaires were mailed and answered by caregivers, primarily mothers. The questionnaire, each with six questions, was divided into five domains, which were as follows: fine motor,

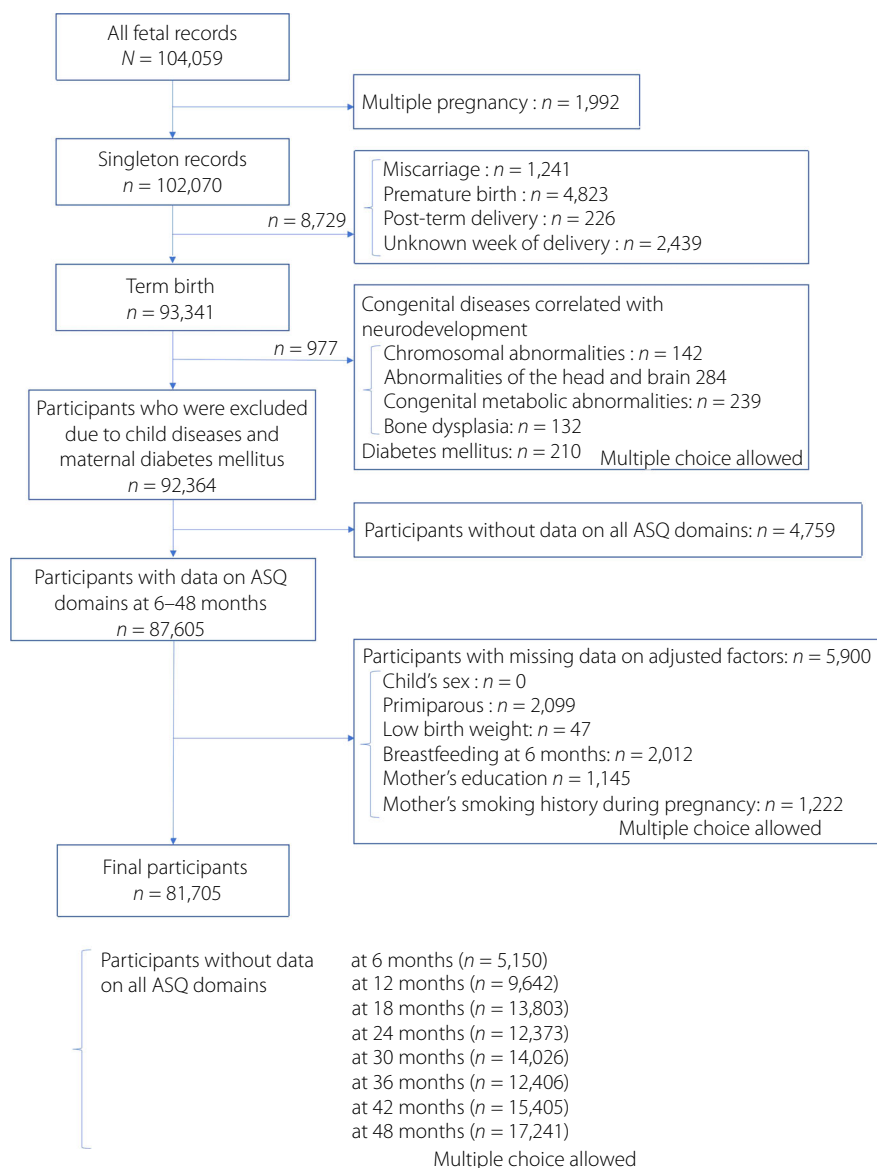


Figure 1 | Flowchart of participant selection. ASQ, Japanese translation of the Ages and Stages Questionnaires.

gross motor, communication, problem-solving ability and personal-social functioning. Each question was scored as follows: 10 for “yes,” 5 for “sometimes” and 0 for “not yet.” The scores for the six questions were summed up to calculate the score of each domain. To define developmental delay, we used the cut-off scores established by Mezawa et al.³¹ who validated the J-ASQ-3 questionnaire.

Variables

Variables were obtained from the medical records transcripts and from the questionnaires administered to mothers during early pregnancy and mid-pregnancy, and after 6 months of delivery. Data about the mother’s age, child’s sex, week and method of delivery, and Apgar score were obtained from the

medical records transcripts at birth. Information about primipara women was obtained from the medical records transcripts during early pregnancy. Data about pre-pregnancy maternal weight, height, smoking history, educational background and household income were collected using the questionnaire administered to mothers during early pregnancy. Household income, educational background and smoking history were categorically changed with the following indicators: household income was categorized as less than or more than 4 million Japanese yen.; educational categories were the graduation of junior high school or high school, and others; and smoking history as the presence or absence of smoking during pregnancy, including even during the first trimester of pregnancy. Information regarding the child’s nutrition was obtained from the

medical records transcripts at 1 month-of-age and the questionnaire administered to mothers at 6 months-of-age.

Statistical analysis

Maternal characteristics and offspring outcomes of women with and without GDM were assessed using the χ^2 -test or analysis of variance. The J-ASQ-3 scores of the offspring were transformed into categorical variables based on the cut-off values of each domain. The odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using generalized estimating equations to assess positive developmental delays (in each domain) of children born to pregnant women with GDM compared with those without GDM. The exposure variable was GDM. The type of model used was binomial logistic regression analysis, and the working correlation matrix was unstructured. The analysis of the data obtained from all participants used a crude model and a model adjusted for the following factors: child's sex, primiparity, breastfeeding at 6 months postpartum, low birth weight (<2,500 g), mother's education and smoking during pregnancy. The analysis of data stratified according to the children's sex used a crude model and a model adjusted for the following factors: primiparity, breastfeeding at 6 months postpartum, low birthweight (<2,500 g), mother's education and smoking during pregnancy.

All data were analyzed using the Statistical Package for the Social Sciences software version 24 (IBM Inc., Armonk, NY, USA), and missing data were excluded in the statistical analysis. Statistical significance was set at $P < 0.05$.

Ethics

The JECS protocol was approved by the institutional review board of Epidemiological Studies of the Ministry of the Environment and by the ethics committees of all participating institutions. The study was carried out in accordance with the principles of the Declaration of Helsinki and its later amendments. Written informed consent was obtained from all participants.

RESULTS

Table 1 shows the perinatal and postnatal characteristics of mothers and children. Of 81,705 participants, 2,162 (2.6%) were diagnosed with GDM. The mean age of mothers at delivery was 31.3 ± 5.0 years. The pre-pregnancy body mass index was 21.2 ± 3.2 kg/m², and the mean weight gain during pregnancy was 10.4 ± 5.0 kg. In total, 41,498 (51%) infants were boys. The mean birth time was 39.5 ± 1.1 weeks, and 14,075 (17%) were born by cesarean section.

Table 2 shows the numbers of ASQ-3 questionnaires less than the cut-off value for each month of age and for each category. Based on the ASQ-3 results at 4 years-of-age, the numbers of participants with a score for each domain below the cut-off value were 2,809 (3.4%) in communication skills, 3,542 (4.3%) in gross motor skills, 4,155 (5.1%) in fine motor skills, 2,209 (2.7%) in problem-solving ability, and 3,463 (4.2%) in personal and social skills. Table 3 shows the ORs (95% CIs) of

Table 1 | Characteristics of mothers and infants

	Participants (<i>n</i> = 81,705)
Mothers	
Age (years)	31.3 ± 5.0
Pre-pregnancy BMI (kg/m ²)	21.2 ± 3.2
Gestational weight gain (kg)	10.4 ± 5.0
Primiparous, <i>n</i> (%)	33,330 (41)
Gestational diabetes mellitus, <i>n</i> (%)	2,162 (2.6)
Smoking during pregnancy, <i>n</i> (%)	13,738 (17)
Maternal educational background, junior high school or high school, <i>n</i> (%)	30,073 (37)
Annual household income of <4,000,000 JPY, <i>n</i> (%)	30,121 (37)
Infants	
Infant sex, male, <i>n</i> (%)	41,498 (51)
Gestational age (weeks)	39.5 ± 1.1
Birthweight (g)	3,064 (5.3)
Low birth weight, <i>n</i> (%)	4,316 (5.3)
Cesarean delivery, <i>n</i> (%)	14,075 (17)
Only breastfeeding at 1 month postpartum, <i>n</i> (%)	44,399 (54)
Breastfeeding at 6 months postpartum, <i>n</i> (%)	60,788 (74)
Weight gain per day up to 1 month-of-age (kg/day)	39.3 ± 11.5
Age in months when the ASQ-3 questionnaire was answered (months)	
6	5.3 ± 0.5
12	11.4 ± 0.5
18	17.4 ± 0.5
24	23.5 ± 0.6
30	29.4 ± 0.6
36	35.6 ± 0.7
42	42.3 ± 0.6
48	48.3 ± 0.6

Data are presented as the mean ± standard deviation or numbers (%). ASQ-3, Japanese translation of the Ages and Stages Questionnaires, third Edition; BMI, body mass index; JPY, Japanese yen.

developmental delay in each domain, which was assessed repeatedly using the questionnaire between 6 months and 4 years-of-age, as shown in Table 2. Notably, the developmental delay in problem-solving ability was significantly higher in infants born to women with GDM than in those born to women without GDM, with a crude and adjusted OR of 1.26 (95% CI 1.14–1.39) and 1.24 (95% CI 1.12–1.36), respectively.

Table 2 | Number of participants below the cut-off value of the Japanese translation of the Ages and Stages Questionnaires questionnaire for each month of age and category

Participants	Age (months)	Communication skill <i>n</i> (%)	Gross motor skills, <i>n</i> (%)	Fine motor skills, <i>n</i> (%)	Problem-solving ability, <i>n</i> (%)	Personal and social skills, <i>n</i> (%)
All (<i>n</i> = 81,705)	6	481 (0.6)	7,869 (9.6)	3,841 (4.7)	8,207 (10.0)	2,798 (3.4)
	12	82 (0.1)	4,038 (4.9)	4,174 (5.1)	3,703 (4.5)	850 (1.0)
	18	1,435 (1.8)	3,069 (3.8)	2,896 (3.5)	2,666 (3.3)	1,616 (2.0)
	24	2,587 (3.2)	3,849 (4.7)	1,403 (1.7)	2,792 (3.4)	1,838 (2.2)
	30	3,152 (3.9)	2,821 (3.5)	3,790 (4.6)	3,698 (4.5)	2,156 (2.6)
	36	2,584 (3.2)	2,914 (3.6)	4,988 (6.1)	4,860 (5.9)	2,125 (2.6)
	42	2,695 (3.3)	2,782 (3.4)	3,338 (4.1)	3,695 (4.5)	2,845 (3.5)
	48	2,809 (3.4)	3,542 (4.3)	4,155 (5.1)	2,209 (2.7)	3,463 (4.2)

ASQ-3, Japanese translation of the Ages and Stages Questionnaires, Third Edition.

The ORs for problem-solving were significant higher even when stratified according to the child's sex. The adjusted ORs with 95% CIs of the fine motor skills and personal and social skills significantly increased to 1.15 (95% CI 1.03–1.27) and 1.18 (95% CI 1.04–1.33), respectively. However, after stratification, the adjusted ORs with 95% CIs (1.16, 95% CI 0.96–1.39 and 1.15, 95% CI 0.92–1.45) of girls were no longer significantly elevated.

DISCUSSION

The primary findings of the current study were as follows. Infants born to women with GDM had a 1.24-fold increased risk of delayed problem-solving skills than those born to women without GDM. Furthermore, there was a sex difference in the neurodevelopmental delay among children born to mothers with GDM. That is, boys had a significantly delayed neurodevelopment than girls (Table 3).

Although several reports examined abnormalities in maternal glucose metabolism and cognitive function in offspring, the present study first focused on GDM and its effects on the five domains of neurodevelopment. In the present study, children born to women with GDM had inferior problem-solving ability, and fine motor and social skills than those born to women without GDM, although the point estimates were 1.24, 1.15 and 1.18, respectively, which were not considerably high. Problem-solving ability can be a predictive factor of adaptive capacity. Hence, there was an association between ASD and problem-solving ability³². ASD is a series of neurodevelopmental disorders defined by persistent social communication deficits, as well as restricted interests, repetitive activities and sensory abnormalities³³. Its symptoms commonly emerge between 12 and 24 months-of-age³⁴. Furthermore, the initial symptoms of autism are deficits in social³⁵ and fine motor skills³⁶, whereas delayed communication skills can be one of the subsequent symptoms. The present study showed that GDM was likely to be a risk factor for ASD development.

The mechanism of cognitive decline in children born to women with GDM has been confirmed in animal studies,

which reported alterations caused by inflammation and DNA methylation^{37,38}. One alteration causes chronic inflammation in the hippocampus of offspring born to mothers with GDM, which persists until young adulthood, thereby destroying the hippocampus³⁸. Furthermore, DNA methylation leads to a decreased expression of synaptophysin in the hippocampus, which is involved in memory and learning³⁹. These alterations have been found to be significant in boys^{39,40}. By contrast, the pathogenesis of ASD arises from a complex interplay of genetic susceptibility and pre-perinatal environmental factors, leading to early changes in brain development³³. An association between the hippocampus and ASD has been reported particularly in boys⁴¹. The fine motor and social skills differed in terms of sex. Furthermore, the development of problem-solving skills was significantly delayed in boys in the current study. Thus, this might provide evidence about the association between GDM and ASD.

Impaired intellectual and behavioral function observed in children born to mothers with diabetes is shown by changes in hippocampal structure and function⁴². Maternal metabolic abnormalities can lead to sex-differentiated changes in the neurodevelopmental process of a growing fetus. In particular, boys are at higher risk of neurodevelopmental disorders^{40,43}. Estrogen promotes hippocampal neurogenesis, and alterations in the hippocampal response to estrogen might be a protective mechanism against intrauterine environment-related changes in the female brain⁴⁰. However, a site-specific analysis of estradiol levels in the hypothalamus of male and female rats from fetal life to adulthood showed significantly fewer sex differences than expected⁴⁴. The causes of sex differences in neurodevelopment are not yet clear. However, the present study hypothesized that neurodevelopmental delays up to 4 years-of-age might indicate alterations in the hippocampus caused by minimal differences in estrogen concentrations. These slowly cause sex differences in neurodevelopment over time, thereby surfacing as symptoms at least at 4 years-of-age.

The insight into what leads to sex differences in neurodevelopment should be considered for brain damage as well as brain

Table 3 | Odds ratios of children born to mothers gestational diabetes mellitus GDM who had scores below the cut-off in each category by the age of 4 years and mothers without gestational diabetes mellitus based on a developmental study using the Japanese translation of the Ages and Stages Questionnaires

Participants	Model	Communication skills		Gross motor skills		Fine motor skills		Problem-solving ability		Personal and social skills	
		OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
All	Crude mode	1.22 (1.02–1.46)	0.032*	1.12 (1.00–1.24)	0.047*	1.17 (1.05–1.30)	0.004**	1.26 (1.14–1.39)	<0.001***	1.21 (1.06–1.37)	0.004**
	Adjusted model 1	1.15 (0.97–1.35)	0.098	1.10 (0.99–1.23)	0.079	1.15 (1.03–1.27)	0.013*	1.24 (1.12–1.36)	<0.001***	1.18 (1.04–1.33)	0.011*
Male	Crude model	1.77 (0.76–4.16)	0.188	1.05 (0.91–1.22)	0.502	1.17 (1.03–1.34)	0.019*	1.25 (1.11–1.41)	<0.001***	1.20 (1.03–1.40)	0.017*
	Adjusted model 2	1.66 (0.56–4.93)	0.360	1.04 (0.89–1.20)	0.649	1.15 (1.01–1.32)	0.039*	1.23 (1.09–1.38)	0.001**	1.18 (1.01–1.37)	0.037*
Female	Crude model	1.07 (0.80–1.42)	0.648	1.19 (1.01–1.39)	0.034*	1.17 (0.98–1.41)	0.088	1.25 (1.07–1.47)	0.006**	1.17 (0.94–1.47)	0.166
	Adjusted model 2	1.06 (0.80–1.41)	0.683	1.17 (1.00–1.37)	0.047*	1.16 (0.96–1.39)	0.121	1.23 (1.05–1.45)	0.010*	1.15 (0.92–1.45)	0.219

In the crude model, the odds ratio of mothers with and without gestational diabetes mellitus was calculated using a generalized estimating equation. In the adjusted model 1, the odds ratio of mothers with and without gestational diabetes mellitus was calculated using generalized estimating equations, and the factors adjusted were child's sex, primiparous, breastfeeding at 6 months, low birthweight (<2,500 g), maternal education and smoking during pregnancy. In the adjusted model 2, the odds ratio of mothers with and without gestational diabetes mellitus was investigated using generalized estimating equations, and the factors adjusted were primiparous, breastfeeding at 6 months, low birthweight (<2,500 g), maternal education and smoking during pregnancy. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. ASQ-3, Japanese translation of the Ages and Stages Questionnaires, third Edition; OR, odds ratio.

protection. Increased rates of umbilical cord knot abnormalities, GDM⁴⁵, preterm deliveries⁴⁶ and pre-eclampsia⁴⁷ have been reported in mothers conceiving a male fetus. In addition, male fetuses are more sensitive to stress during delivery⁴⁸ and have a higher rate of cesarean section⁴⁵. Dynamic macrostructural and microstructural changes in the brain occur from the mid-fetal stage to 2 years after birth⁴⁹. Thus, the fetal brain is still developing in the late trimester, when GDM worsens. Given that male fetuses are more exposed and are weaker to the stressful environment of pregnancy, male infants delivered by mothers with GDM in the present results might have neurodevelopmental delays.

The strength of the present birth cohort study was that it used 104,059 data points and covered 2,162 infants born to mothers with GDM. However, it also had limitations. First, the use of the J-ASQ-3 questionnaire, which includes subjective responses from parents/caregivers, not actual examination, to assess neurodevelopment is a weakness of this study. As the diagnosis was not made by a medical institution, an alternative evaluation by a medical professional is recommended to ensure the reliability of neurodevelopmental delay. By contrast, the ASQ-3 has been validated in several countries, and the results were comparable with those of other countries. Second, this study did not examine the treatment of GDM, blood glucose levels or the timing of GDM diagnosis. A subgroup analysis of what glycemic control method used during pregnancy can improve neurodevelopment and when the offspring of women diagnosed with GDM will present with delayed neurodevelopment must be carried out in the future. Third, neurodevelopment might be influenced by multiple factors, and potential confounders other than the present confounders could influence outcomes. Finally, we carried out statistical processing by treating delay in neurodevelopment from 6 months to 4 years as a single time point. Thus, future research must assess whether there are significant differences at younger time points and whether they will become more or less significant with increasing age. Additionally, when the ASD diagnosis results are added to the J ECS data in the future, the association between GDM and ASD might be further clarified by statistical processing using the risk prediction method. Furthermore, the generalizability of this study is limited to Japanese women. However, the results could be applied to pregnant women with similar body sizes and living environment.

In conclusion, child neurodevelopment, particularly the problem-solving ability, fine motor skills, and personal and social skills domains, was significantly delayed up to 4 years-of-age in boys born to women with GDM.

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DISCLOSURE

The authors declare no conflict of interest.

Approval of the research protocol: The JECS protocol was reviewed and approved by the Ministry of the Environment's Institutional Review Board on Epidemiological Studies and the Ethics Committees of all participating institutions (Ethical Number: No.100910001). This study was also approved by the Ethics Committee of Hokkaido University Center for Environmental Health Sciences (registration number: 21-130; approval date of registry: 26 August 2021).

Informed consent: The JECS was carried out in accordance with the Declaration of Helsinki, and other internationally valid regulations and guidelines for research on human subjects, and written informed consent was obtained from all participants.

Registry and the registration no. of the study/trial: 24 January 2011. University Hospital Medical Information Network ID: UMIN000030786

Animal studies: N/A.

DATA AVAILABILITY STATEMENT

Data are unsuitable for public deposition due to ethical restrictions and the legal framework of Japan. The Act on the Protection of Personal Information (Act No. 57 of May 30, 2003, amendment on September 09, 2015) prohibits the public deposition of data containing personal information. Moreover, the 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, Labor and Welfare restrict the open sharing of epidemiologic data. All inquiries about access to data should be sent to jecs-en@nies.go.jp. Dr Shoji F Nakayama is the person responsible for handling enquiries sent to this e-mail address, JECS Program Office, National Institute for Environmental Studies.

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APPENDIX 1**JAPAN ENVIRONMENT AND CHILDREN'S STUDY (JECS) GROUP**

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