


# Association between pre-pregnancy body mass index and gestational weight gain and perinatal outcomes in pregnant women diagnosed with gestational diabetes mellitus: The Japan Environment and Children's Study

Yoshihiro Saito<sup>1</sup> , Sumitaka Kobayashi<sup>2\*</sup>, Atsuko Ikeda-Araki<sup>2,3</sup>, Sachiko Ito<sup>2</sup>, Chihiro Miyashita<sup>2</sup>, Takashi Kimura<sup>4</sup>, Takumi Hirata<sup>4</sup>, Akiko Tamakoshi<sup>4</sup>, Michinori Mayama<sup>1</sup>, Kiwamu Noshiro<sup>1</sup>, Kinuko Nakagawa<sup>1</sup>, Takeshi Umazume<sup>1</sup>, Kentaro Chiba<sup>1</sup>, Satoshi Kawaguchi<sup>1</sup>, Mamoru Morikawa<sup>1</sup>, Kazutoshi Cho<sup>5</sup>, Hidemichi Watari<sup>1</sup>, Yoshiya Ito<sup>6</sup>, Yasuaki Saijo<sup>7</sup>, Reiko Kishi<sup>2</sup>, the Japan Environment and Children's Study (JECS) group<sup>†</sup>

<sup>1</sup>Department of Obstetrics and Gynecology, Hokkaido University Graduate School of Medicine, Sapporo, Japan, <sup>2</sup>Center for Environmental and Health Sciences, Hokkaido University, Sapporo, Japan, <sup>3</sup>Faculty of Health Sciences, Hokkaido University, Sapporo, Japan, <sup>4</sup>Department of Public Health, Hokkaido University Graduate School of Medicine, Sapporo, Japan, <sup>5</sup>Center for Perinatal Medicine, Hokkaido University Hospital, Sapporo, Japan, <sup>6</sup>Faculty of Nursing, Japanese Red Cross Hokkaido College of Nursing, Kitami, Japan, and <sup>7</sup>Department of Social Medicine, Asahikawa Medical University, Asahikawa, Japan

## Keywords

Body mass index, Gestational diabetes mellitus, Gestational weight gain

## \*Correspondence

Sumitaka Kobayashi  
Tel.: +81-11-706-4748  
Fax: +81-11-706-4725  
E-mail address:  
sukobayashi@cehs.hokudai.ac.jp

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## ABSTRACT

**Aims/Introduction:** We investigated the association between gestational diabetes mellitus (GDM) and perinatal outcomes stratified by pre-pregnancy body mass index (BMI) and/or gestational weight gain (GWG).

**Materials and Methods:** Data from the national birth cohort in the Japan Environment and Children's Study from 2011 to 2014 ( $n = 85,228$ ) were used. Japan uses the GDM guidelines of the International Association of Diabetes and Pregnancy Study Groups. The odds ratios (ORs) of perinatal outcomes were compared between women with and those without GDM.

**Results:** The OR (95% confidence interval) of having a small for gestational age infant in the GDM group with a pre-pregnancy BMI of  $\geq 25.0$  kg/m<sup>2</sup> and insufficient GWG ( $< 2.75$  kg) was 1.78 (1.02–3.12). The OR of having a large for gestational age infant of the same BMI group with excessive GWG ( $> 7.25$  kg) was 2.04 (1.56–2.67). The OR of hypertensive disorders of pregnancy was higher in women with a BMI  $\geq 18.5$  kg/m<sup>2</sup> in the GDM group than in the non-GDM group.

**Conclusions:** Large for gestational age and hypertensive disorders of pregnancy were associated with pre-pregnancy BMI and GWG in either normal weight or overweight/obese women, and the relationship was strengthened when GDM was present. Women with GDM and a BMI of  $\geq 25.0$  kg/m<sup>2</sup> are at risk of having small for gestational age and large for gestational age infants depending on GWG.

## INTRODUCTION

Gestational diabetes mellitus (GDM) is a common obstetric complication that can cause macrosomia, large for gestational

age (LGA) infants, hypertensive disorders of pregnancy (HDP) and preterm birth<sup>1</sup>. Women diagnosed with GDM are more likely to develop obesity<sup>2</sup> and diabetes later in life. The increasing incidence of GDM in developing countries has a role in the global diabetes epidemic<sup>3</sup>. The 2008 Hyperglycemia and Adverse Pregnancy Outcomes<sup>1</sup> study resulted in adjustments to the strict GDM diagnostic criteria that are used in several

<sup>†</sup>The members of Japan Environment and Children's Study (JECS) group are listed in Appendix 1.

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countries, including Japan, since 2010. Japan, however, has witnessed increasing numbers of underweight women (body mass index [BMI]  $<18.5 \text{ kg/m}^2$ ) becoming pregnant<sup>4,5</sup>, along with decreasing birthweights<sup>5,6</sup>.

Nutritional therapy in pregnant women with hyperglycemic disorders provides appropriate nutrition for healthy fetal development, and ensures strict glycemic control and appropriate weight gain<sup>7,8</sup>. The goal of glycemic control and nutritional therapy for all women with GDM is the same regardless of pre-pregnancy BMI and weight gain during pregnancy<sup>9</sup>. In addition, a weight gain less than the recommended weight might be beneficial to prevent excessive birthweight in GDM pregnancies, particularly among overweight and obese women<sup>10</sup>. The results of studies on the association between underweight women with GDM and birthweight have been inconclusive<sup>10</sup>.

Although there are different indicators of appropriate weight gain for each pre-pregnancy BMI, it is possible to make a difference in perinatal outcomes, especially among underweight women, using identical glycemic control and nutritional therapies in all women with GDM.

The purpose of the present study was to investigate the effect of GDM on perinatal outcomes, including fetal growth and the onset of HDP, compared with that of non-GDM in the same pre-pregnancy BMI and gestational weight gain (GWG) categories. The two classification systems that are most often used in Japan<sup>11</sup> for GWG determination were used in the present study, one from the Japanese Ministry of Health, Labor and Welfare (MHLW)<sup>12</sup> and the other, which is used worldwide, from the Institute of Medicine (IOM) in the USA<sup>2</sup>.

## MATERIALS AND METHODS

### Data collection

The study data were collected from the national birth cohort in the Japan Environment and Children's Study (JECS). The purpose of the JECS was to investigate environmental factors that might affect children's health and development<sup>13,14</sup>. Workers with 15 regional centers throughout Japan were responsible for recruiting women in early pregnancy who were living in the respective recruitment areas. The study gathered data from 45% of the births study area from January 2011 through March 2014<sup>13,14</sup>. The eligibility criteria for the participants (expectant mothers) were as follows: (i) they should reside in the study area at the time of recruitment and expect to reside continually in Japan for the foreseeable future; (ii) the expected date of delivery should be between 1 August 2011 and mid-2014; and (iii) they should be capable of participating in the study without difficulty. The participants should be able to comprehend the Japanese language and complete the self-administered questionnaire<sup>13</sup>. Women residing outside the study areas, even if they were receiving care from cooperating healthcare providers within the study areas, were excluded<sup>13</sup>. The women's medical records and a questionnaire given to mothers in the first trimester ( $16.4 \pm 8.0$  gestational weeks) and second or third

trimester ( $27.9 \pm 6.5$  gestational weeks) were abstracted<sup>13</sup>. The dataset jecs-ag-20160424 was used in the present study.

From a potential pool of 104,102 fetal records, 2,452 records were excluded because of uncollected data. An additional 16,422 records were excluded because they had incomplete data or did not meet the entry criteria for the following conditions: maternal height (65 records), maternal weight (2,876), gestational age at birth of  $<37$  or  $\geq 42$  weeks (7,355), congenital anomaly or newborn disease (9,665), type 1 diabetes mellitus (76), type 2 diabetes mellitus (135) and others treated with insulin without GDM (51). Furthermore, duplicate records were excluded. A total of 85,228 participants were included in the final study group (Figure 1).

### Definition of GDM

In Japan, GDM is diagnosed using the modified criteria of the International Association of Diabetes and Pregnancy Study Groups (Table S1)<sup>11,15</sup>. It is diagnosed when at least one value reaches or exceeds any of the following three thresholds in a 75-g oral glucose tolerance test: 92–125 mg/dL for fasting plasma glucose (PG), 180 mg/dL for 1-h PG and 153 mg/dL for 2-h PG<sup>11</sup>. In the JECS, two items were related to GDM in the birth information recorded by physicians or medical staff. Women with GDM were defined as those who were indicated as having "GDM" in the record and those who were not indicated as having "GDM", but provided the "gestational weeks at GDM diagnosis."

### Definition of pre-pregnancy BMI

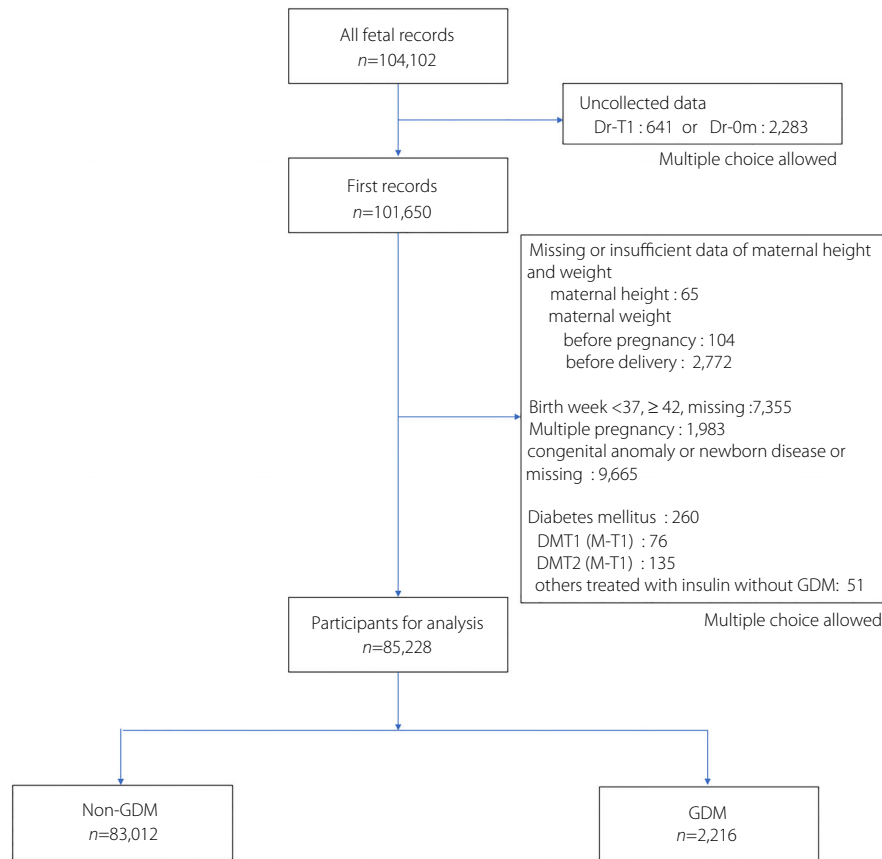
BMI was calculated using the maternal height and weight before pregnancy, and the participants were categorized into one of the three weight groups defined according to BMI, in accordance with the MHLW recommendations as follows: underweight,  $<18.5 \text{ kg/m}^2$ ; normal weight,  $18.5\text{--}24.9 \text{ kg/m}^2$ ; and overweight/obese,  $\geq 25.0 \text{ kg/m}^2$ <sup>12</sup>. The IOM divides women into four groups: underweight,  $<18.5 \text{ kg/m}^2$ ; normal weight,  $18.5\text{--}24.9 \text{ kg/m}^2$ ; overweight,  $25.0\text{--}29.9 \text{ kg/m}^2$ ; and obese,  $\geq 30.0 \text{ kg/m}^2$ .

### Definition of GWG

GWG was calculated by comparing prenatal maternal weight with weight measured at the time of labor. The recommended weight gains for the three MHLW groups were as follows: underweight, 9.0–12.0 kg; normal weight, 7.0–12.0 kg; and overweight/obesity, approximately 5.0 kg (Figure 2a)<sup>13</sup>. The recommended weight gain for the four IOM groups were as follows: underweight, 12.5–18.0 kg; normal weight, 11.5–16.0 kg; overweight, 7.0–11.5 kg; and obese, 5.0–9.0 kg (Figure 2b)<sup>2</sup>. Because the range for weight gain in the IOM overweight group was up to 4.5 kg, we chose "approximately 5.0 kg (2.75–7.25 kg)" as the metric for overweight/obese in the MHLW classification, which is consistent with the IOM range.

### Perinatal outcomes

Low birthweight and macrosomia were defined as  $<2,500 \text{ g}$  and  $\geq 4,000 \text{ g}$ , respectively. Small for gestational age (SGA) and



**Figure 1** | Flowchart of the selected participants. DMT1, type 1 diabetes; DMT2, type 2 diabetes; Dr-0m, medical records provided by a doctor or medical staff at birth; Dr-T1, medical records provided by a doctor or medical staff in the first trimester; GDM, gestational diabetes mellitus; M-T1, self-administered questionnaires for mothers in the first trimester.

LGA infants had birthweights of <10th or >90th percentile, respectively, according to the Japanese birthweight standard (2010)<sup>16</sup>. Polyhydramnios and HDP were collected from birth information recorded by doctors or medical staff. HDP, measured after 20 gestational weeks, was defined as a systolic blood pressure of  $\geq 140$  mmHg and diastolic blood pressure of  $\geq 90$  mmHg<sup>17</sup>. The short-term prognoses of infants were assessed using the 5-min Apgar score or umbilical arterial blood power of hydrogen.

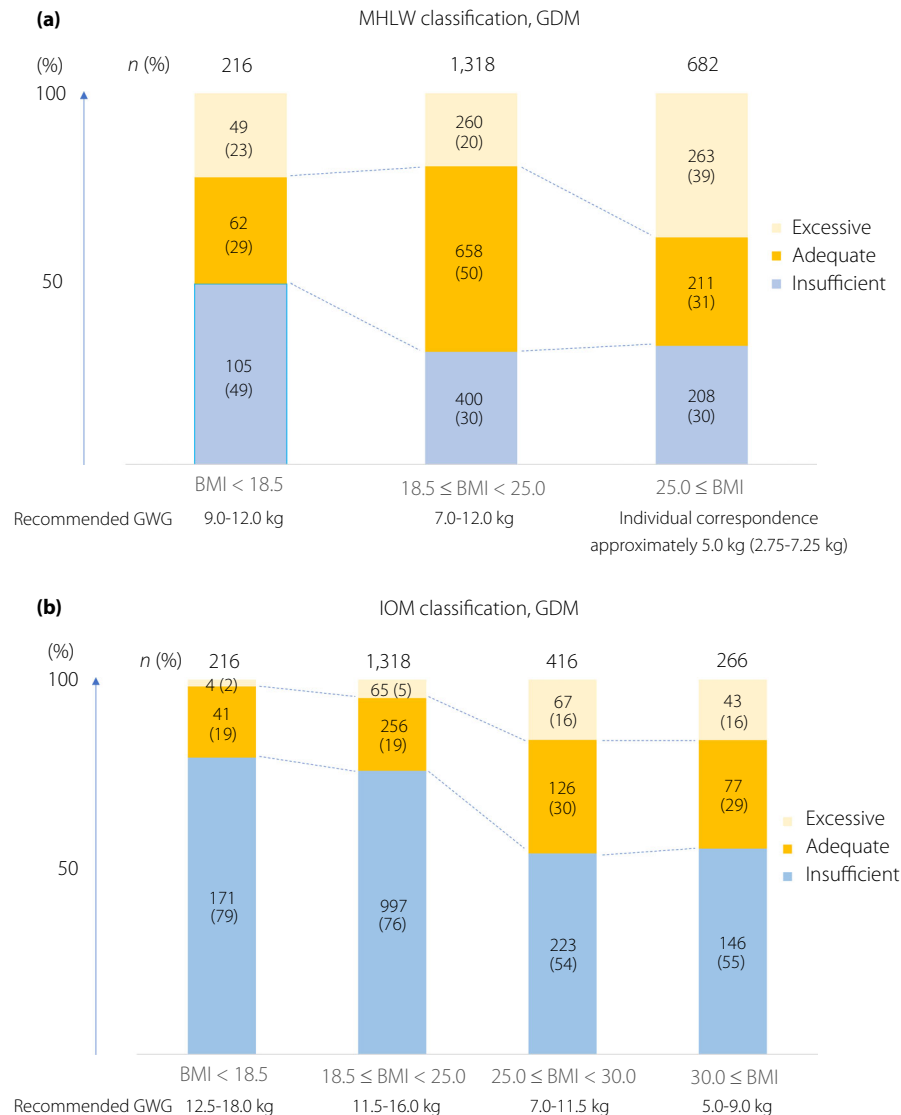
**Variables**

Multiple factors were abstracted from the mothers’ or their partners’ questionnaire for comparison between the GDM and non-GDM groups. These included the maternal age, parity, gestational age (weeks) when GDM was diagnosed, insulin treatment, length of labor, cesarean delivery status, maternal smoking during pregnancy, partner smoking during pregnancy, drinking during pregnancy, annual household income, maternal educational background, nutritional support and hypertensive disorders before pregnancy. Smoking and drinking history during pregnancy were collected by a questionnaire survey, which

asked about smoking and drinking history, spanning the period from the very beginning of pregnancy until before the pregnancy became apparent.

**Statistical analysis**

Maternal characteristics and perinatal outcomes for the GDM and non-GDM groups were evaluated using the  $\chi^2$ -test or analysis of variance. First, the participants were stratified by pre-pregnancy BMI or GWG according to the MHLW and IOM classifications, respectively. For each of the same strata, the odds ratios (OR) of SGA, LGA, macrosomia and HDP in the GDM group compared with the non-GDM group were calculated using a logistic regression model. Macrosomia and HDP were adjusted for maternal age, fetal sex, maternal smoking and GWG (stratified by pre-pregnancy BMI) or pre-pregnancy BMI (stratified by GWG). SGA was adjusted for maternal age, maternal smoking, HDP and pre-pregnancy BMI or GWG, because SGA and LGA were defined using birthweight, gestational age and fetal sex<sup>16</sup>. LGA was adjusted for maternal age, maternal smoking and pre-pregnancy BMI or GWG. Finally, pre-pregnancy BMI and GWG were combined and stratified,



**Figure 2** | (a) Cumulative bar chart of the participants' gestational weight gain (GWG) stratified by pre-pregnancy body mass index (BMI) in the Japanese Ministry of Health, Labor and Welfare (MHLW) classification. (b) Cumulative bar chart of the participants' GWGs stratified by pre-pregnancy BMI in the Institute of Medicine (IOM) classification. GDM, gestational diabetes mellitus.

and the relationship between GDM and each perinatal outcome was expressed as an OR using logistic regression analysis. All data were analyzed using JMP Pro 14.0 (SAS Institute, Cary, NC, USA), and missing data were excluded from the statistical analysis. A *P*-value of <0.05 showed statistical significance.

#### Ethical approval

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

#### RESULTS

Of the 85,228 participants in the present study, 2,216 (2.6%) developed GDM. Their classifications according to the MHLW and IOM criteria are presented in Figure 2. Fewer women had excessive GWG according to the IOM classification, and the divisions of the women were more balanced across all categories in the MHLW classification than in the IOM classification.

Table 1 shows the maternal characteristics and perinatal outcomes of all participants according to the non-GDM and GDM groups. Pre-pregnancy BMI was significantly higher in the GDM group ( $23.7 \pm 5.1 \text{ kg/m}^2$ ) than in the non-GDM group ( $21.1 \pm 3.2 \text{ kg/m}^2$ ,  $P < 0.001$ ), but the GWG was 25% lower in the GDM group ( $7.9 \pm 5.1 \text{ kg}$ ) than in the non-GDM

**Table 1** | Maternal characteristics and perinatal outcomes: Gestational versus non-gestational diabetes

	Non-GDM <i>n</i> = 83,012 (97.4%)	GDM <i>n</i> = 2,216 (2.6%)	<i>P</i> -value
Maternal characteristics			
Age (years)	31.0 ± 5.0	33.3 ± 5.0	<0.001***
Primiparous, <i>n</i> (%)	32,341 (39)	857 (39)	0.645
Pre-pregnancy BMI (kg/m <sup>2</sup> )	21.1 ± 3.2	23.7 ± 5.1	<0.001***
Gestational weight gain (kg)	10.5 ± 4.3	7.9 ± 5.1	<0.001***
Gestational week at GDM diagnosis (weeks)	(–)	24.9 ± 7.7	(–)
Insulin treatment, <i>n</i> (%)	(–)	253 (11)	(–)
Labor duration (min)	510 ± 437	488 ± 455	0.037*
Cesarean delivery, <i>n</i> (%)	14,012 (17)	599 (28)	<0.001***
Smoking (mother) during pregnancy, <i>n</i> (%)	14,837 (18)	419 (19)	0.246
Smoking (partner) during pregnancy, <i>n</i> (%)	40,057 (48)	1,000 (45)	0.001**
Drinking during pregnancy, <i>n</i> (%)	40,161 (48)	970 (44)	<0.001***
Annual household income <4,000,000 JPY, <i>n</i> (%)	30,635 (37)	784 (35)	0.043*
Maternal educational background, junior high school or high school, <i>n</i> (%)	29,688 (36)	817 (37)	0.353
Nutritional support, <i>n</i> (%)	7,535 (9)	1,567 (71)	<0.001***
Hypertensive disorder before pregnancy, <i>n</i> (%)	770 (1)	70 (3)	<0.001***
Hypertensive disorders of pregnancy, <i>n</i> (%)	2,084 (3)	151 (7)	<0.001***
Perinatal outcomes			
Infant sex, male, <i>n</i> (%)	42,098 (51)	1,141 (52)	0.471
Gestational age (days)	276.3 ± 7.8	274.4 ± 8.2	<0.001***
Birthweight (g)	3,064 ± 363	3,080 ± 400	0.031*
Low birthweight (<2,500 g), <i>n</i> (%)	4,288 (5)	129 (6)	0.168
Macrosomia (≥4,000 g), <i>n</i> (%)	718 (1)	36 (2)	<0.001***
SGA (<10% percentile)	5,241 (6)	150 (7)	0.4173
LGA (>90% percentile)	7,351 (9)	311 (14)	<0.001***
Polyhydramnios, <i>n</i> (%)	241 (0)	22 (1)	<0.001***
Non-reassuring fetal status, <i>n</i> (%)	1,855 (2)	71 (3)	0.002**
Still birth, <i>n</i> (%)	30 (0)	1 (0)	0.827
Apgar score (5 min) <7, <i>n</i> (%)	268 (0)	14 (1)	0.016*
UmA-pH <7.0, <i>n</i> (%)	141 (0)	1 (0)	0.139

Data are presented as the mean ± standard deviation or number (%). The non-gestational diabetes mellitus (GDM) group was compared with the GDM group using the  $\chi^2$ -test or independent *t*-test. \**P* < 0.05; \*\**P* < 0.01; \*\*\**P* < 0.001. BMI, body mass index; JPY, Japanese yen; LGA, large for gestational age; SGA, small for gestational age; UmA-pH, umbilical cord artery pH.

group (10.5 ± 4.3 kg, *P* < 0.001). Women with GDM were significantly older than those without GDM (33.3 ± 5.0 vs 31.0 ± 5.0 years, *P* < 0.001). Cesarean section rates were 10% higher in the GDM group (27.7%) than in the non-GDM group (17.2%, *P* < 0.001). There were no significant differences in educational background, as well as prevalence rates of low birthweight, SGA, umbilical arterial blood power of hydrogen, and stillbirths between the two groups.

Table 2 shows the association between GDM and perinatal outcomes stratified by pre-pregnancy BMI using the MHLW classification. All ORs were compared between the GDM and the non-GDM, same pre-pregnancy BMI groups. The highest percentage of SGA was 12% in the underweight GDM group, but the OR of SGA was slightly elevated (1.30, 95% confidence interval [CI] 0.92–1.83) in the overweight/obese GDM group compared with the overweight/obese non-GDM group. The incidence of LGA positively correlated with BMI, and the ORs

of LGA in the normal weight and overweight/obese GDM groups were significantly higher than those in the normal weight and overweight/obese non-GDM groups (1.56, 95% CI 1.30–1.87 and 1.67, 95% CI 1.37–2.04, respectively). The incidence of HDP was similar to that of LGA, with significantly higher ORs of HDP in the normal weight and overweight/obese participants in the GDM groups than in those in the non-GDM groups (2.19, 95% CI 1.67–2.87 and 2.24, 95% CI 1.75–2.87, respectively). Notably, in all the stratified groups, GWG was much smaller among those with GDM than among those without GDM.

Table 3 shows the association between GDM and perinatal outcomes stratified by GWG using the MHLW classification. No significant difference in the incidence of SGA infants was observed between the GDM and non-GDM groups, despite the weight gain during pregnancy. However, the OR of having a LGA infant significantly increased in the adequate and excessive

**Table 2** | Association between gestational diabetes mellitus and perinatal outcomes stratified by pre-pregnancy body mass index using the Ministry of Health, Labor and Welfare, Japan classification

Pre-pregnancy BMI (kg/m <sup>2</sup> )	GDM		n	GWG (kg) <sup>†</sup>	SGA		LGA		Macrosomia		HDP	
	No	Yes			n (%) <sup>‡</sup>	OR (95% CI)	n (%) <sup>‡</sup>	OR (95% CI)	n (%) <sup>‡</sup>	OR (95% CI)	n (%) <sup>‡</sup>	OR (95% CI)
<18.5 (Underweight)	No	13,464	1,292 (10)	11.1 ± 5.6	Reference	657 (5)	Reference	40 (0)	Reference	220 (2)	Reference	
	Yes	216	26 (12)	9.6 ± 4.0	1.00 (0.65–1.54)	13 (6)	1.46 (0.82–2.60)	0 (0)	(–)	4 (2)	1.18 (0.90–1.54)	
18.5–24.9 (Normal weight)	No	61,292	3,624 (6)	10.7 ± 3.7	Reference	5,338 (9)	Reference	493 (1)	Reference	1,329 (2)	Reference	
	Yes	1,318	82 (6)	8.9 ± 4.4	0.82 (0.65–1.04)	149 (11)	1.56 (1.30–1.87)***	19 (1)	2.14 (1.35–3.42)**	59 (4)	2.19 (1.67–2.87)***	
≥25.0 (Overweight/obese)	No	8,256	325 (4)	8.0 ± 5.1	Reference	1,356 (16)	Reference	185 (2)	Reference	535 (6)	Reference	
	Yes	682	42 (6)	5.5 ± 5.9	1.30 (0.92–1.83)	149 (22)	1.67 (1.37–2.04)***	17 (2)	1.30 (0.78–2.18)	88 (13)	2.24 (1.75–2.87)***	

Logistic regression models are adjusted for maternal age, smoking, hypertensive disorders of pregnancy (HDP) and gestational weight gain (GWG) when the perinatal outcomes are small for gestational age (SGA). Logistic regression models are adjusted for maternal age, smoking and GWG when the perinatal outcomes are large for gestational age (LGA). Logistic regression models are adjusted for maternal age, smoking, infant sex and GWG when the perinatal outcomes are macrosomia and HDP. Odds ratio (OR) and 95% confidence interval (95% CI) is in comparison with the reference group. \* $P < 0.05$ ; \*\* $P < 0.01$ ; \*\*\* $P < 0.001$ . BMI, body mass index; GDM, gestational diabetes mellitus. <sup>†</sup>Mean ± standard deviation. <sup>‡</sup>Percent (%) represents  $n_{\text{case}} / n_{\text{all}} \times 100$ .

weight gain GDM group compared with the adequate and excessive weight gain non-GDM group (1.31, 95% CI 1.06–1.62 and 1.74, 95% CI 1.43–2.12, respectively). The OR of HDP was significantly increased in all the GDM groups compared with non-GDM groups (1.68, 95% CI 1.16–2.43 for insufficient; 2.13, 95% CI 1.58–2.86 for adequate; and 1.54, 95% CI 1.13–2.11 for excessive GWG). The incidence of macrosomia was exceptionally low in the insufficient GWG group, and no significant difference in the OR of macrosomia was observed between the GDM and non-GDM groups.

In Table 4, pre-pregnancy BMI and GWG were combined and subdivided into nine groups. Each group was further stratified into GDM and non-GDM groups, and the number (%) and OR (95% CI) of each outcome for GDM compared with non-GDM were calculated for each group. In the pre-pregnancy underweight and insufficient GWG group, the incidence of SGA infants was significantly higher (16% in the non-GDM group and 17% in the GDM group) than in any of the other subgroups. However, in the overweight/obese and insufficient GWG group, the OR of having a SGA infant was 1.78 (95% CI 1.02–3.12) in the GDM group compared with that in the non-GDM group. In the pre-pregnancy underweight group, the incidence rates of LGA, macrosomia and HDP were low in all GWG subgroups, and no significant difference was observed in the relationship between GDM and non-GDM. The incidence rate of LGA infants significantly increased in the normal pre-pregnancy weight and excessive GWG with GDM (24%), and pre-pregnancy overweight/obese and excessive GWG with GDM (33%) groups. The OR of having a LGA infant in the GDM group compared with the non-GDM group was 1.91 (95% CI 1.42–2.56) for the normal weight and excessive GWG group, and 2.04 (95% CI 1.56–2.67) for the overweight/obesity and excessive GWG group. The incidence of HDP in the GDM group was increased to 14% in the pre-pregnancy overweight/obese subgroups with adequate and excessive GWG. The ORs of HDP in the pre-pregnancy overweight/obese with adequate and excessive GWG subgroups with GDM were higher at 2.66 (95% CI 1.73–4.10) and 1.84 (95% CI 1.26–2.68), respectively, than those in the same subgroups without GDM.

In the present study, identical analyses were carried out using the IOM classification, and the association between GDM and perinatal outcomes was similar to the outcome obtained using the MHLW classification (Tables S2–S4).

## DISCUSSION

The present study had the following main findings: (i) the strongest relationship between GDM and SGA was found in the subgroup of participants who were overweight/obese pre-pregnancy and had insufficient GWG (OR 1.78, 95% CI 1.02–3.12; Table 4); and (ii) LGA and HDP were strongly related to pre-pregnancy BMI and GWG in women with either pre-pregnancy normal weight or overweight/obese, and GDM further strengthened the relationship (Tables 2–4).

**Table 3** | Association between gestational diabetes mellitus and perinatal outcomes stratified by gestational weight gain using the Ministry of Health, Labor and Welfare, Japan classification

GWG	GDM	n	Pre-pregnancy BMI (kg/m <sup>2</sup> ) <sup>†</sup>	SGA		LGA		Macrosomia		HDP	
				n (%) <sup>‡</sup>	OR (95% CI)	n (%) <sup>‡</sup>	OR (95% CI)	n (%) <sup>‡</sup>	OR (95% CI)	n (%) <sup>‡</sup>	OR (95% CI)
Insufficient	No	12,720	21.1 ± 3.8	1,427 (11)	Reference	521 (4)	Reference	41 (0)	Reference	261 (2)	Reference
	Yes	713	23.9 ± 5.8	71 (10)	1.07 (0.82–1.40)	47 (7)	0.99 (0.71–1.38)	2 (0)	0.50 (0.12–2.11)	39 (5)	1.68 (1.16–2.43)**
Adequate	No	40,776	20.9 ± 2.8	2,688 (7)	Reference	2,798 (7)	Reference	199 (0)	Reference	774 (2)	Reference
	Yes	931	22.9 ± 4.5	53 (6)	0.93 (0.70–1.23)	109 (12)	1.31 (1.06–1.62)*	14 (2)	1.66 (0.93–2.96)	57 (6)	2.13 (1.58–2.86)***
Excessive	No	29,516	21.4 ± 3.4	1,126 (4)	Reference	4,032 (14)	Reference	478 (2)	Reference	1,049 (4)	Reference
	Yes	572	24.6 ± 5.1	26 (5)	1.41 (0.94–2.12)	155 (28)	1.74 (1.43–2.12)***	20 (4)	1.33 (0.83–2.14)	55 (10)	1.54 (1.13–2.11)**

Logistic regression models are adjusted for maternal age, smoking, hypertensive disorders of pregnancy (HDP) and pre-pregnancy body mass index (BMI) when the perinatal outcomes are small for gestational age (SGA). Logistic regression models are adjusted for maternal age, smoking and pre-pregnancy BMI when the perinatal outcomes are large for gestational age (LGA). Logistic regression models are adjusted for maternal age, smoking, infant sex and pre-pregnancy BMI when the perinatal outcomes are macrosomia and HDP. Odds ratio (OR) and 95% confidence interval (95% CI) is in comparison with the reference group. \**P* < 0.05; \*\**P* < 0.01; \*\*\**P* < 0.001. GDM, gestational diabetes mellitus; GWG, gestational weight gain.

<sup>†</sup>Mean ± standard deviation. <sup>‡</sup>Percent (%) represents  $n_{\text{case}} / n_{\text{all}} \times 100$ .

The incidence of SGA infants has been reported to increase in women with GDM when strict glycaemic control is applied<sup>18–20</sup>. Similarly, as shown in Table 4, a significantly increased OR of having a SGA infant was observed in overweight/obese women with GDM and insufficient GWG compared with those without GDM. The high OR of having a SGA infant in the overweight/obese and insufficient GWG GDM group might be caused by their much lower average GWG (−1.0 ± 3.5 kg). In all the groups stratified by pre-pregnancy BMI, the smaller GWG in the GDM group might be owing to dietary restrictions for patients with GDM. In particular, the incidence of SGA infants in the GDM subgroup with a BMI of ≥25.0 kg/m<sup>2</sup> and insufficient GWG should be noted. However, the highest incidence of SGA infants was observed in the pre-pregnancy underweight group with insufficient GWG, consistent with SGA being more affected by underweight and insufficient GWG<sup>21</sup>.

It might be beneficial for underweight women diagnosed with GDM to increase their GWG to reduce their risk of having a SGA infant. Infants born with SGA are considered as having a high risk for future cardiovascular events and other health risks<sup>22,23</sup>. Using the MHLW classification, we found that the incidence of SGA infants in the present study was 17% (18/105) among the pre-pregnancy underweight women with insufficient GWG who developed GDM, and 10% (6/62) for this subgroup with adequate weight gain. Therefore, an adequate GWG of ≥9.0 kg is important to reduce the incidence of SGA infants among underweight women with GDM.

In the present study, we found that the incidence rates of LGA, macrosomia and HDP were lower in the pre-pregnancy underweight group, and observed no relationship between

GDM and these outcomes in that group. This emphasizes the need for guidance on appropriate weight gain to prevent the occurrence of SGA infants in the underweight group. However, LGA and HDP strongly correlated with GDM in the pre-pregnancy overweight/obese group, and special attention should be paid to the occurrence of LGA (33%) and HDP (14%) in this group with excessive GWG. Previous studies reported that for LGA and HDP, pre-pregnancy BMI and GWG strongly correlated<sup>24,25</sup>, but GDM further strengthened the relationship<sup>24</sup>. Table 3 shows that HDP is affected by GDM, even among those with insufficient GWG, which suggests that GDM is a strong risk factor of HDP.

Among overweight/obese women, adequate weight control is particularly important, because an increased OR of having a SGA infant was observed in the GDM group when GWG was insufficient compared with the non-GDM group, and the ORs of LGA infants and HDP increased with excessive GWG. The OR of macrosomia in the GDM group significantly increased among those with normal weight and adequate GWG compared with that in the non-GDM group. However, the incidence of macrosomia was low in other subgroups, and the relationship among BMI, GWG and macrosomia was unclear.

The present study showed a lower prevalence of GDM (3.9–7.0%) than those reported in previous studies<sup>26–30</sup>. Those studies might have overestimated the prevalence, because Morikawa *et al.*<sup>26,27</sup> included women with diabetes mellitus, and the study by Iwama *et al.*<sup>28</sup> was a multicenter study involving relatively large hospitals that treated high-risk pregnancies. In a large previous study of secondary and tertiary centers in Japan, 13,037 (5.5%) of 237,941 women were diagnosed with GDM, including 13.3% of preterm births<sup>29</sup>. In a population-based Japanese study

**Table 4** | Association between gestational diabetes mellitus and perinatal outcomes stratified by both pre-pregnancy body mass index and gestational weight gain using the Ministry of Health, Labor and Welfare, Japan classification

Pre-pregnancy BMI (kg/m <sup>2</sup> )	GWG	GDM	n <sub>all</sub>	SGA		LGA		Macrosomia		HDP	
				n <sub>case</sub> (%) <sup>†</sup>	OR (95% CI)	n <sub>case</sub> (%) <sup>†</sup>	OR (95% CI)	n <sub>case</sub> (%) <sup>†</sup>	OR (95% CI)	n <sub>case</sub> (%) <sup>†</sup>	OR (95% CI)
<18.5 (Underweight)	Insufficient	No	3,499	546 (16)	Reference	68 (2)	Reference	6 (0)	Reference	51 (1)	Reference
		Yes	105	18 (17)	1.07 (0.63–1.82)	5 (5)	2.38 (0.94–6.04)	0 (0)	(–)	2 (2)	1.21 (0.29–5.05)
	Adequate	No	5,192	486 (9)	Reference	207 (4)	Reference	8 (0)	Reference	71 (1)	Reference
		Yes	62	6 (10)	1.07 (0.46–2.53)	3 (5)	1.32 (0.41–4.26)	0 (0)	(–)	1 (2)	1.11 (0.15–8.12)
	Excessive	No	4,773	260 (5)	Reference	382 (8)	Reference	26 (1)	Reference	98 (2)	Reference
		Yes	49	2 (4)	0.73 (0.18–3.04)	5 (10)	1.32 (0.52–3.37)	0 (0)	(–)	1 (2)	0.99 (0.14–7.26)
18.5–24.9 (Normal weight)	Insufficient	No	8,149	828 (10)	Reference	332 (4)	Reference	26 (0)	Reference	151 (2)	Reference
		Yes	400	34 (9)	0.80 (0.56–1.15)	16 (4)	0.89 (0.53–1.52)	1 (0)	0.72 (0.10–5.31)	16 (4)	2.05 (1.21–3.46)**
	Adequate	No	33,096	2,063 (6)	Reference	2,275 (7)	Reference	156 (0)	Reference	568 (2)	Reference
		Yes	658	35 (5)	0.80 (0.56–1.13)	71 (11)	1.58 (1.22–2.04)***	12 (2)	3.71 (2.05–6.72)***	27 (4)	2.27 (1.52–3.40)***
	Excessive	No	20,047	733 (4)	Reference	2,731 (14)	Reference	311 (2)	Reference	610 (3)	Reference
		Yes	260	13 (5)	1.33 (0.75–2.33)	62 (24)	1.91 (1.42–2.56)***	6 (2)	1.50 (0.66–3.40)	16 (6)	1.96 (1.17–3.28)*
≥25.0 (Overweight/obese)	Insufficient	No	1,072	53 (5)	Reference	121 (11)	Reference	9 (1)	Reference	59 (6)	Reference
		Yes	208	19 (9)	1.78 (1.02–3.12)*	26 (13)	1.13 (0.72–1.78)	1 (0)	0.54 (0.07–4.32)	21 (10)	1.81 (1.06–3.09)*
	Adequate	No	2,488	139 (6)	Reference	316 (13)	Reference	35 (1)	Reference	135 (5)	Reference
		Yes	211	12 (6)	0.93 (0.51–1.72)	35 (17)	1.34 (0.91–1.98)	2 (1)	0.61 (0.15–2.57)	29 (14)	2.66 (1.73–4.10)***
	Excessive	No	4,696	133 (3)	Reference	919 (20)	Reference	141 (3)	Reference	341 (7)	Reference
		Yes	263	11 (4)	1.44 (0.76–2.70)	88 (34)	2.04 (1.56–2.67)***	14 (5)	1.70 (0.96–3.00)	38 (14)	1.84 (1.26–2.68)**

Logistic regression models are adjusted for maternal age, smoking and hypertensive disorders of pregnancy (HDP) when the perinatal outcomes are small for gestational age (SGA). Logistic regression models are adjusted for maternal age and smoking when the perinatal outcomes are large for gestational age (LGA). Logistic regression models are adjusted for maternal age, smoking and infant sex when the perinatal outcomes are macrosomia and HDP. Odds ratio (OR) and 95% confidence interval (95% CI) is in comparison with the reference group. \**P* < 0.05; \*\**P* < 0.01; \*\*\**P* < 0.001. BMI, body mass index; CI, gestational diabetes mellitus; GWG, gestational weight gain. <sup>†</sup>Percent (%) represents n<sub>case</sub> / n<sub>all</sub> × 100.



of 46,365 women, the prevalence of GDM, including preterm birth, was reported to be 3.9%, which is closer to the present study<sup>30</sup>. However, the present study found a 2.6% prevalence of GDM among those with only term births. Preterm births and miscarriages were excluded from this study, and GDM is considered a risk factor of preterm birth<sup>1</sup>. A meta-analysis of 5,349,476 pregnant women worldwide using the International Association of Diabetes and Pregnancy Study Groups diagnostic criteria found a 10.6% prevalence of GDM (95% CI 10.5–10.6)<sup>31</sup>, whereas it was 11.5% (95% CI 10.9–12.1) in 20 countries across Asia<sup>32</sup>. One of the reasons for the low prevalence of GDM in Japan is that only few pregnant women are overweight/obese. Another reason for the low prevalence might be that the participants in the present study included relatively healthy women. In the present study, the prevalence of need for insulin therapy in participants was 11% (Table 1), whereas previous studies, including studies carried out in Japan, have reported between 9 and 59% of women with GDM required insulin therapy<sup>33–37</sup>. In general, high-risk GDM women are referred to high-risk perinatal centers. Thus, high-risk GDM women might be lost to follow up, resulting in the possibility of fewer high-risk GDM women with low need for insulin therapy. The J ECS is reportedly a very similar population to Japan's 2013 Vital Statistics Survey<sup>14</sup>. However, the GDM subpopulation might be controversial in the J ECS, and further research with an appropriate study design is required to clarify the prevalence of GDM.

The IOM classification system, which was designed on the basis of the body size of American women, appears to be inappropriate for the physique of Japanese women. When establishing an optimal GWG for Japanese women using the IOM classification, the lower end of the range for their pre-pregnant BMI values should be used<sup>6,38</sup>. The optimal GWG in the IOM classification is based not only on BMI, but also on height. The mean height in the J ECS was  $158.1 \pm 5.4$  cm, which is similar to the IOM's definition of short height, which is 157 cm<sup>2,38</sup>. Therefore, on the basis of these findings, the weight gain index for pregnant Japanese women with GDM should be based on the MHLW classification.

The present study had the following strengths. First, data from a Japanese national study that included 13,680 pregnant women with a low pre-pregnancy BMI ( $<18.5$  kg/m<sup>2</sup>) can be valuable for other populations worldwide. The 15 regional Centers in the J ECS birth cohort provide uniform care standards for obstetric patients based on Japan's standard obstetric practice guidelines established in 2008<sup>11</sup> and the Japanese Clinical Practice Guideline for Diabetes<sup>8</sup>. Second, the present study used both the MHLW and IOM classification systems. Because similar results were obtained using both classification systems, the findings relative to GDM in this study should be reliable.

However, the present study had several limitations as well. First, the appropriate GWG for the overweight/obese group of the MHLW classification, approximately 5 kg, was applied to the IOM recommended range of 4.5 kg for overweight women.

As the overweight/obese group accounted for two-thirds of the overweight women in this study, the 4.5 kg range was preferred to the 4 kg range for the obese group in the IOM recommendation. No significant change was observed in the results when the range was set at 4 kg. However, the definition of this range is temporary and illogical, so it is not universal. Second, "overt diabetes"<sup>39</sup> might have been counted as GDM in the J ECS. Its prevalence in Japan is not yet known, but it is expected to be low and should not affect these results. Third, the present study did not include data for 75-g oral glucose tolerance test PG levels; therefore, assessing perinatal outcomes related to PG levels is difficult. Fourth, this study has limited generalizability beyond Japanese women; however, the present findings might be useful in studying other groups with statures similar to those of Japanese women. Fifth, perinatal outcomes were studied only among term women with GDM. Because insufficient GWG among women with GDM increased the incidence of preterm birth by 3.5-fold compared with sufficient GWG<sup>40</sup>, the impact of insufficient GWG on pre-pregnancy underweight women with GDM and preterm birth needs to be determined. Finally, as the prevalence of GDM is lower than previously reported, the results need to be interpreted in the light of the possibility that participants in J ECS are a more environmentally and health-conscious population, and should be investigated further.

LGA and HDP were strongly associated with pre-pregnancy BMI and GWG in the pre-pregnancy normal weight and overweight/obese women, and the relationship was further strengthened by GDM. In GDM patients with a pre-pregnancy BMI of  $\geq 25.0$  kg/m<sup>2</sup>, the incidence rates of SGA and LGA infants relied on GWG. This result was similar regardless of whether the MHLW or IOM classification system was used.

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## DISCLOSURE

The authors declare no conflict of interest.

Approval of the research protocol: The J ECS protocol was approved by the institutional review board of the Japan National Institute for Environmental Studies (registration number: 2017-002) and by the Ethics Committees of all participating institutions. This study was also approved by the Ethics Committee of the Hokkaido University Center for Environmental Health Sciences (Registration number: 21-130; Approval date of registry: August 26, 2021).

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

Registry and the registration no. of the study/trial: Not applicable because JECS is not a clinical trial.

Animal studies: Not applicable.

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## APPENDIX 1

### JAPAN ENVIRONMENT AND CHILDREN'S STUDY (JECS) GROUP

Members of the JECS Group as of 2021: Michihiro Kamijima (principal investigator, Nagoya City University, Nagoya, Japan), Shin Yamazaki (National Institute for Environmental Studies, Tsukuba, Japan), Yukihiro Ohya (National Center for Child Health and Development, Tokyo, Japan), Reiko Kishi (Hokkaido University, Sapporo, Japan), Nobuo Yaegashi (Tohoku University, Sendai, Japan), Koichi Hashimoto (Fukushima Medical University, Fukushima, Japan), Chisato Mori (Chiba University, Chiba, Japan), Shuichi Ito (Yokohama City University, Yokohama, Japan), Zentarō Yamagata (University of Yamagata, Yonezawa, Japan), Hidekuni Inadera (University of Toyama, Toyama, Japan), Takeo Nakayama (Kyoto University, Kyoto, Japan), Hiroyasu Iso (Osaka University, Suita, Japan), Masayuki Shima (Hyogo College of Medicine, Nishinomiya, Japan), Youichi Kurozawa (Tottori University, Yonago, Japan), Narufumi Sugauma (Kochi University, Nankoku, Japan), Koichi Kusu-hara (University of Occupational and Environmental Health, Kitakyushu, Japan) and Takahiko Katoh (Kumamoto University, Kumamoto, Japan).

## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1** | Methods for diagnosing gestational diabetes mellitus in Japan.

**Table S2** | Association between gestational diabetes mellitus and perinatal outcomes stratified by pre-pregnancy body mass index using the Institute of Medicine classification.

**Table S3** | Association between gestational diabetes mellitus and perinatal outcomes stratified by gestational weight gain using the Institute of Medicine classification.

**Table S4** | Association between gestational diabetes mellitus and perinatal outcomes stratified by both pre-pregnancy body mass index and gestational weight gain using the Institute of Medicine classification.