JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
ORIGINAL ARTICLE

Association of glycated hemoglobin at an early stage of pregnancy with the risk of gestational diabetes mellitus among non-diabetic women in Japan: The Japan Environment and Children's Study

Tetsuo Sekine[1], Kyoichiro Tsuchiya[1,*], Hiroyuki Uchinuma[1], Sayaka Horiuchi[2], Megumi Kushima[2], Sanae Otawa[2], Hiroshi Yokomichi[3], Kunio Miyake[3], Yuka Akiyama[3], Tadao Ooka[3], Reiji Kojima[3], Ryoji Shinohara[2], Shuji Hirata[4], Zentaro Yamagata[2,3], The Japan Environment and Children's Study Group[†], Michihiro Kamijima, Shin Yamazaki, Yukihiro Ohya, Reiko Kishi, Nobuo Yaegashi, Koichi Hashimoto, Chisato Mori, Shuichi Ito, Zentaro Yamagata, Hidekuni Inadera, Takeo Nakayama, Hiroyasu Iso, Masayuki Shima, Youichi Kurozawa, Narufumi Suganuma, Koichi Kusuhara, Takahiko Katoh

[1]Third Department of Internal Medicine, Interdisciplinary Graduate School of Medicine and Engineering, University of Yamanashi, Yamanashi, Japan, [2]Center for Birth Cohort Studies, University of Yamanashi, Chuo City, Yamanashi, Japan, [3]Department of Health Sciences, School of Medicine, University of Yamanashi, Chuo City, Yamanashi, Japan, and [4]Department of Obstetrics and Gynecology, University of Yamanashi, Yamanashi, Japan

Keywords
Cohort studies, Hyperglycemia, Pregnancy outcome

***Correspondence**
Kyoichiro Tsuchiya
Tel.: +81-55-273-9682
Fax: +81-55-273-9685
E-mail address:
tsuchiyak@yamanashi.ac.jp

J Diabetes Investig 2022; 13: 687–695

doi: 10.1111/jdi.13701

ABSTRACT

Aims/Introduction: Gestational diabetes mellitus (GDM) is one of the most common complications of pregnancy and is associated with adverse pregnancy outcomes. This study aimed to explore the associations between glycated hemoglobin (HbA1c) levels at the early stage of pregnancy and the GDM risk among non-diabetic women in a nationwide study in Japan. In addition, the relationship between GDM and adverse pregnancy outcomes was also analyzed.

Materials and Methods: This cohort study (n = 89,799) used data from the Japan Environment and Children's Study. We stratified the participants into four groups according to HbA1c levels at an early stage of pregnancy. We investigated the association of HbA1c at an early stage of pregnancy with the risk of GDM, and of GDM with the risk of some representative adverse pregnancy outcomes, using the multiple logistic regression model with adjustment for potential confounders.

Results: The adjusted odds ratio for GDM per 0.1 percentage point increase in HbA1c (%) was 1.20. The adjusted odds ratio for developing GDM was significantly increased in women from the HbA1c 5.0–5.4% category. GDM significantly increased the adjusted odds ratio for adverse pregnancy outcomes, such as hypertensive disorders of pregnancy, polyhydramnios and premature birth.

Conclusions: High-normal HbA1c levels at the early stage of pregnancy are significantly associated with GDM risk in women in Japan. GDM was significantly associated with adverse pregnancy outcomes.

INTRODUCTION

Gestational diabetes mellitus (GDM) occurs when resistance to circulating insulin results in hyperglycemia, an impaired glucose metabolism first detected during pregnancy. It is one of the most common pregnancy-related complications and is associated with adverse pregnancy outcomes[1–4]. Additionally, GDM increases the lifetime risk of developing type 2 diabetes for both mothers and children[5–9]. Therefore, GDM screening and diagnosis are essential in prenatal care. The American Diabetes Association recommends testing for glycated hemoglobin

[†]A comprehensive list of consortium members appears in the Acknowledgments section of the paper.

Received 10 August 2021; revised 8 October 2021; accepted 20 October 2021

(HbA1c) before conception[10], as this measure can be used in the triage for GDM risk stratification. Preconception counseling usually discusses the importance of maintaining serum glucose levels as close to normal as possible, ideally with a HbA1c level of <6.0%. However, type 2 diabetes among East Asian people has been widely characterized primarily by β-cell dysfunction with evident responses immediately after the ingestion of glucose or a meal. Its association with adiposity is substantially lower compared that of white people[11]. In a study of Taiwanese women without pre-existing diabetes, elevated HbA1c levels even within the normal range were considered to be associated with an increased risk of GDM and adverse outcomes[12]. This finding suggests that Asian women with relatively high HbA1c values, even those within the normal range, might be more likely to develop GDM than women from different populations. However, no published study has examined the association of HbA1c levels with GDM risk in a large cohort of Asian participants.

Therefore, the present study aimed to explore the associations between HbA1c levels at the early stages of pregnancy and the risk of GDM among non-diabetic women in the nationwide study in Japan, the Japan Environment and Children's Study (JECS). Additionally, the associations between GDM and adverse pregnancy outcomes were supplementally analyzed.

MATERIAL AND METHODS

Additional details of the Material and Methods are included in the Supporting information section.

Study design

The JECS is an ongoing prospective nationwide birth cohort study in Japan. The main aim of the JECS was to investigate the associations of environmental factors with children's health and development. Pregnant women were recruited at 15 Regional Centers between January 2011 and March 2014. Questionnaires were completed, and maternal venous blood samples were obtained from participants during the first trimester and the second or third trimester[13]. Details of the study design and a summary of the baseline profiles of participants have been described previously[13–16]. In this study, we analyzed the 'jecs-ta 20190930' dataset released by the Program Office in October 2019. The dataset included information on 104,062 fetal records. The study was conducted in accordance with the Declaration of Helsinki.

Statistical analysis

Continuous variables were reported as medians and 95% confidence intervals (CIs). Categorical variables were described as numbers and percentages. We investigated the associations of HbA1c levels at an early stage of pregnancy with the risk of GDM among non-diabetic Japanese women using the multiple logistic regression model with adjustment for potential confounders (older pregnancy, pre-pregnancy body mass index [BMI], gestational weeks during the HbA1c level measurements, history of GDM, polycystic ovarian syndrome (PCOS), cesarean section, large babies, premature births, miscarriages and stillbirths, multiple pregnancies, alcohol status, smoking status, blood pressure at the early stage of pregnancy, and mother's own birthweight). Additionally, the associations between GDM and the risk of representative adverse pregnancy/infant outcomes, such as hypertensive disorder of pregnancy (HDP), polyhydramnios and premature birth, were investigated. All analyses used the multiple logistic regression model. The associations between GDM and HDP were adjusted for older pregnancy, pre-pregnancy BMI, primipara, multiple pregnancies, blood pressure at the early stage of pregnancy, and history of HDP, renal disease, hypertension, hypothyroidism, autoimmune disease and anti-phospholipid antibody syndrome. The associations between GDM and polyhydramnios were adjusted for older pregnancy, pre-pregnancy BMI, fetal malformation and multiple pregnancies. The associations between GDM and premature birth were adjusted for age, pre-pregnancy BMI, multiple pregnancies, placenta previa, placental abruption, premature rupture of membranes, HDP, history of premature birth, fetal growth restriction, polyhydramnios, fetal distress, uterine malformation, smoking status, household income, and highest educational attainment of the mother and father.

Data were analyzed by multiple logistic regression models as appropriate using EZR version 1.53 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria)[17]. Statistical significance was set at 0.05 and all statistical tests were two-tailed. Only the main outcomes were presented for the adjusted odds ratio (OR) and *P*-values due to the JECS rule.

RESULTS

Characteristics

A total of 104,062 fetal records with a median gestational age of 12 weeks (95% CI 8–26 weeks) were recruited between January 2011 and March 2014. We excluded 14,263 participants due to missing data/records for the GDM diagnosis (n = 2,377), diabetes history (n = 209), missing data/records of HbA1c levels and/or a method for HbA1c measurement (n = 11,607), and HbA1c level ≥6.5% (n = 70). Then, 89,799 participants were eligible for the present analysis (Figure 1). Women with anemia or iron preparations, which might affect HbA1c levels, were not excluded. The median age, pre-pregnancy BMI and gestational age during HbA1c level measurements were 31 years (95% CI 22–39 years), 20.5 kg/m^2 (95% CI 17.4–27.6 kg/m^2) and 15 weeks (95% CI 11–21 weeks; Table 1). The number of older pregnancies, obesity and GDM diagnoses were 21,625 (24.1%), 9,772 (10.9%) and 2,397 (2.7%), respectively. In each HbA1c category, the higher the HbA1c category, the higher the older pregnancies, obesity, GDM diagnosis, prevalence of GDM history, and delivery of large babies,

premature births, miscarriages and stillbirths (Table 1). In contrast, the higher the HbA1c category, the lower the underweight, gestational weeks during the HbA1c level measurements and prevalence of a PCOS history.

Association of HbA1c levels at the early stage of pregnancy with GDM

Next, we analyzed how much various known GDM risk factors contribute to its diagnosis in all participants or in each HbA1c category. In each HbA1c category analysis, stillbirth history in ≤4.9% and 6.0–6.4%, and PCOS history and multiple pregnancies in 6.0–6.4% were excluded because they were unable to be calculated. To analyze all participants, the adjusted OR [95% CI] for GDM per 0.1 percentage point (1.1 mmol/mol) increase in HbA1c was 1.20 [1.18–1.22] (Table 2). In each HbA1c category, a significant increase in the adjusted OR for GDM was observed, even in the HbA1c category 5.0–5.4% (1.11, 95% CI 1.05–1.17) and HbA1c categories 5.5–5.9% (1.24, 95% CI 1.15–1.33) and 6.0–6.4% (1.54, 95% CI 1.20–1.98). Furthermore, women from the HbA1c category 5.0–5.4% had a significantly higher adjusted OR for the occurrence of GDM (1.32, 95% CI 1.10–1.58) compared with that of those in the HbA1c category ≤4.9% (Table 3). Similarly, the frequency of occurrence for each GDM confounder showed differences in older pregnancy, BMI at pre-pregnancy, history of GDM, PCOS, cesarean section, large babies, multiple pregnancies and mother's own birthweight (Table 4). In particular, the frequency of older pregnancies (40.6 vs 23.6%), obesity (31.3 vs 10.3%), GDM history (4.5 vs 0.2%) and the mother's own low birthweight (LBW; 7.3 vs 4.9%) remarkably increased in GDM versus non-GDM, respectively.

Association between GDM and adverse pregnancy outcomes

We then assessed whether GDM increased the risk of known adverse pregnancy outcomes in this cohort. In HDP analysis, anti-phospholipid antibody syndrome was excluded because it

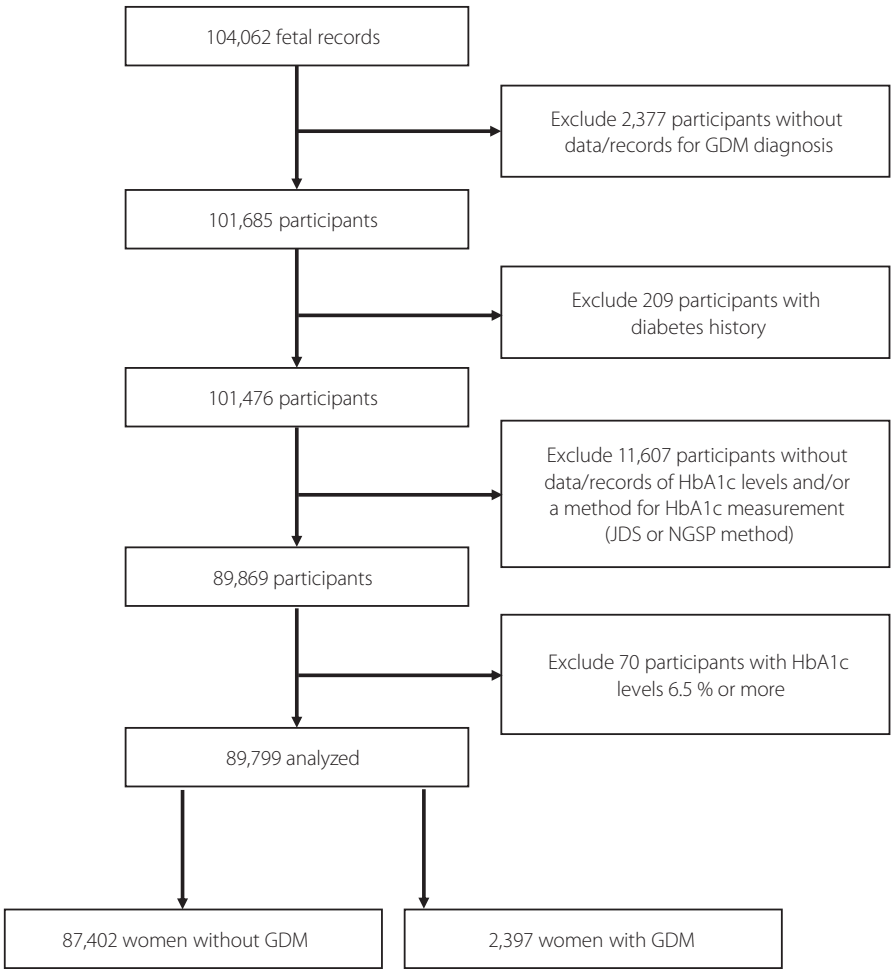

Figure 1 | Participants inclusion flowchart regarding the analysis of the gestational diabetes (GDM) risk during pregnancy. The study included 89,799 pregnant women from the data of the Japan Environment and Children's Study (JECS). HbA1c, glycated hemoglobin; JDS, Japan Diabetes Society; NGSP, National Glycohemoglobin Standardization Program.

Table 1 | Characteristics of study participants

Characteristic	All cases	HbA1c category, % (mmol/mol)			
		≤4.9 (≤30)	5.0–5.4 (31–36)	5.5–5.9 (37–41)	6.0–6.4 (42–47)
	n = 89,799 (100%)	*n* = 17,589 (19.6%)	*n* = 56,544 (63.0%)	*n* = 15,325 (17.1%)	*n* = 341 (0.4%)
Age, median (95% CI) (years)	31 (22–39)	29 (21–38)	31 (23–39)	33 (24–40)	34 (25–41)
Older pregnancy (≥35 years)	21,625 (24.1)	2,783 (15.8)	13,259 (23.5)	5,424 (35.4)	159 (46.6)
BMI at pre-pregnancy, Median, kg/m^2 (95% CI)	20.5 (17.4–27.6)	20.2 (17.3–25.7)	20.5 (17.4–27.1)	21.1 (17.6–30.2)	27.1 (18.7–37.5)
Underweight (<18.5 kg/m^2)	13,900 (15.5)	3,196 (18.2)	8,751 (15.5)	1,939 (12.7)	14 (4.1)
Obesity (≥25 kg/m^2)	9,772 (10.9)	1,188 (6.8)	5,607 (9.9)	2,770 (18.1)	207 (60.9)
Gestational weeks during the HbA1c level measurement median (95% CI)	15 (11–21)	17 (12–21)	15 (11–20)	14 (11–20)	14 (10–20)
Diagnosis of GDM, *n* (%)	2,397 (2.7)	227 (1.3)	1,194 (2.1)	849 (5.5)	127 (37.2)
History, *n* (%)					
GDM	316 (0.4)	28 (0.2)	144 (0.3)	124 (0.8)	20 (5.9)
PCOS	727 (0.8)	154 (0.9)	466 (0.8)	106 (0.7)	1 (0.3)
Large babies	556 (0.7)	70 (0.5)	320 (0.7)	155 (1.1)	11 (3.6)
Premature births	2,997 (3.9)	440 (3.1)	1,916 (4.0)	627 (4.7)	14 (4.7)
Miscarriages	17,169 (19.4)	3,097 (17.9)	10,745 (19.3)	3,250 (21.5)	77 (22.8)
Stillbirths	647 (0.7)	100 (0.6)	410 (0.7)	132 (0.9)	5 (1.5)
Multiple pregnancy	1,733 (1.9)	379 (2.2)	1,037 (1.8)	307 (2.0)	10 (2.9)
Alcohol status, *n* (%)					
Quit drinking on knowing they were pregnant	40,538 (46.5)	8,339 (48.9)	25,517 (46.5)	6,553 (44.1)	129 (40.3)
Current drinking	2,356 (2.7)	455 (2.7)	1,441 (2.6)	447 (3.0)	13 (4.1)
Smoking status, *n* (%)					
Past smokers	20,972 (23.8)	3,964 (23.0)	13,210 (23.8)	3,706 (24.6)	92 (28.1)
Quit smoking on knowing they were pregnancy	11,481 (13.0)	2,785 (16.2)	7,076 (12.7)	1,573 (10.4)	47 (14.3)
Current smokers	4,078 (4.6)	820 (4.8)	2,489 (4.5)	734 (4.9)	35 (10.7)
Mother's own birthweight (yes/no)					
Low birthweight (<2,500 g)	3,899 (5.0)	707 (4.7)	2,450 (4.9)	723 (5.4)	19 (6.9)
High birthweight (≥4,000 g)	1,799 (2.3)	362 (2.4)	1,128 (2.3)	294 (2.2)	15 (5.5)

Values presented exclude missing data. BMI, body mass index; CI, confidence interval; GDM, gestational diabetes; HbA1c, glycated hemoglobin; PCOS, polycystic ovarian syndrome.

was unable to be calculated. GDM significantly increased the adjusted OR for HDP (1.41, 95% CI 1.17–1.69), polyhydramnios (2.99, 95% CI 2.06–4.33) and premature birth (1.23, 95% CI 1.01–1.49; Table S1).

DISCUSSION

The global prevalence of hyperglycemia in pregnancy using the International Association of Diabetes and Pregnancy Study Groups' criteria has been estimated at 17%, with regional estimates varying between 10% in North America and 25% in South-East Asia[18]. However, among women in Asian countries, the prevalence of GDM in Japanese women was relatively low[19,20]. Although the reasons are not well understood, it is likely to involve multiple factors, including ethnic-specific genetic, lifestyle, social–cultural and other environmental factors; a possible explanation might be attributed to wide dissemination of general health checkups in Japan in the past decades, which could provide opportunities for lifestyle management. Further investigations are required to clarify the country-specific risks for GDM/diabetes among Asian countries.

In a prospective study enrolling 1,989 pregnant Taiwanese women, the optimal cut-off HbA1c value that maximized the

Table 2 | Multivariable-adjusted odds ratios for gestational diabetes in each category of glycated hemoglobin in the early stage of pregnancy

Risk factor	All cases	HbA1c category, % (mmol/mol)			
		≤4.9 (≤30)	5.0–5.4 (31–36)	5.5–5.9 (37–41)	6.0–6.4 (42–46)
HbA1c levels at the early stage of pregnancy (per 0.1% [1.1 mmol/mol])	1.20† (1.18–1.22) <0.0001	1.10†,‡ (0.95–1.27) 0.21	1.11† (1.05–1.17) <0.001	1.24† (1.15–1.33) <0.0001	1.54†,§ (1.20–1.98) <0.001

Values represent adjusted odds ratio (95% confidence interval) and *P*-values. †Adjusted for older pregnancy (aged ≥35 years), body mass index at pre-pregnancy (three groups: <18.5, <25 [reference] and ≥25 kg/m^2), gestational weeks during the glycated hemoglobin (HbA1c) levels measurement, history of gestational diabetes, polycystic ovarian syndrome, large babies, premature births, miscarriages, stillbirths, caesarean section, multiple pregnancy, alcohol status (three groups; no-drinking [reference], quit drinking on knowing about pregnancy and current drinking), smoking status (four groups; never smoker [reference], past smoker, quit smoking on knowing about pregnancy and current smoker), systolic blood pressure (four groups; <120 [reference], <140, <160, and ≥160 mmHg), diastolic blood pressure (four groups: <70 [reference], <90, <110, ≥110 mmHg) and mother's own birthweight (three groups; <2,500, <4,000 [reference] and ≥4,000 g). ‡The factor of stillbirths history was excluded because adjustment was unable to be calculated. §The factors of multiple pregnancy, and history of polycystic ovarian syndrome and stillbirths were excluded because they were unable to be calculated in adjustment.

Table 3 | Multivariable-adjusted odds ratios for gestational diabetes in groups of glycated hemoglobin at the early stage of pregnancy

	HbA1c category, % (mmol/mol)			
	≤4.9 (≤30)	5.0–5.4 (31–36)	5.5–5.9 (37–41)	6.0–6.4 (42–46)
Adjusted OR for GDM†	Ref	1.32 (1.10–1.58) <0.01	2.75 (2.27–3.34) <0.0001	19.6 (13.9–27.8) <0.0001

Values represent adjusted odds ratio (OR), 95% confidence interval and *P*-values. †Adjusted for older pregnancy (aged ≥35 years), body mass index at pre-pregnancy (three groups: <18.5, <25 [reference] and ≥25 kg/m^2), gestational weeks during the glycated hemoglobin (HbA1c) levels measurement, history of gestational diabetes (GDM), polycystic ovarian syndrome, large babies, premature births, miscarriages, stillbirths, cesarean section, multiple pregnancy, alcohol status (three groups: no-drinking [reference], quit drinking at realizing pregnancy and current drinking), smoking status (four groups: never smoker [reference], past smoker, quit smoking at realizing pregnancy and current smoker), systolic blood pressure (four groups: <120 [reference], <140, <160 and ≥160 mmHg), diastolic blood pressure (four groups: <70 [reference], <90, <110 and ≥110 mmHg) and mother's own birthweight (three groups: <2,500, <4,000 [reference] and ≥4,000 g).

total sensitivity and specificity for GDM diagnosis was 5.7% (sensitivity of 45.2% and specificity of 84.1%)[12]. The present study including 89,799 participants showed that HbA1c levels at an early stage of pregnancy are significantly associated with GDM risk. Notably, even the HbA1c category 5.0–5.4%, which is regarded as within a normal range, had a significantly higher adjusted OR for developing GDM than that of the ≤4.9% HbA1c category. This observation suggests that pregnant women in Japan with HbA1c levels ≥5.0% might need to be considered as at risk for GDM.

The American College of Obstetricians and Gynecologists suggested the screening obese women for pre-existing diabetes or GDM by the first trimester, in contrast to the 24–28 weeks screening recommended for low-risk women[21,22]. Early screening and diagnosis of GDM leads to an early treatment by critical periods of fetal growth and development, which prevents the fetus from being exposed to hyperglycemia. According to the previous studies, the treatment of GDM diagnosed at 24–28 weeks led to decreased adverse pregnancy outcomes; for example, cesarean section, large babies, shoulder dystocia and HDP, so that earlier treatment in the first trimester might further decrease pregnancy complications[4,23]. However, there are no clinical guidelines in Asian countries, including Japan, showing an optimal marker at an early stage of pregnancy to predict and assess the risk of subsequent GDM. The present study also proposed HbA1c levels as a useful marker at an early stage of pregnancy for GDM risk assessment.

Similarly, with HbA1c levels at an early stage of pregnancy, the risk for GDM is significantly affected by clinical history, such as GDM, PCOS and cesarean section. It suggests that the risk for GDM needs to be evaluated while taking clinical history and HbA1c levels into consideration. Among them, GDM history was identified to markedly increase the frequency in GDM (4.5%) than in non-GDM (0.2%). In clinical settings, women with a GDM history might need careful monitoring and proactive care management during pregnancy, even if HbA1c levels are normal or low at the early stage of pregnancy. Furthermore, one-third to half of women with a GDM history

Table 4 | Frequency of occurrence for each gestational diabetes confounders

Risk factors	GDM	
	−	+
Older pregnancy (age ≥35 years), *n* (%)	20,651 (23.6)	974 (40.6)
BMI at pre-pregnancy, *n* (%)		
Underweight (<18.5 kg/m^2)	13,676 (15.7)	224 (9.4)
Obesity (≥25 kg/m^2)	9,023 (10.3)	749 (31.3)
History, *n* (%)		
GDM	208 (0.2)	108 (4.5)
PCOS	693 (0.8)	34 (1.4)
Cesarean section	7,690 (8.9)	361 (15.3)
Large babies	526 (0.7)	30 (1.5)
Premature births	2,895 (3.9)	102 (5.2)
Miscarriages	16,615 (19.3)	554 (23.4)
Stillbirths	632 (0.7)	15 (0.6)
Multiple pregnancy, *n* (%)	1,650 (1.9)	83 (3.5)
Smoking status, *n* (%)		
Past smokers	20,343 (23.7)	629 (26.7)
Quit smoking on knowing they were pregnant	11,184 (13.0)	297 (12.6)
Current smokers	3,951 (4.6)	127 (5.4)
Mother's own birthweight, *n* (%)		
Low birthweight (<2,500 g)	3,746 (4.9)	153 (7.3)
High birthweight (≥4,000 g)	1,750 (2.3)	49 (2.3)

Values presented exclude missing data. BMI, body mass index; GDM, gestational diabetes; PCOS, polycystic ovarian syndrome.

have been reported to develop type 2 diabetes within 3–5 years[24], and 70% will develop type 2 diabetes if followed up for >10 years[6]. Irrespective of HbA1c levels, women with a GDM history should be carefully monitored after delivery and during pregnancy. Future studies are necessary to clarify the association between HbA1c levels at early pregnancy and the development of type 2 diabetes after delivery.

The present study suggests that the higher HbA1c group shows a higher tendency of drinking and smoking habits with lower tendency of quitting them. Some previous studies showed that pregnant women who smoked had a significantly higher risk of GDM in Korea[25] and China[26]. In contrast, a meta-analysis for 84 observational studies in Asian countries has shown that drinking before pregnancy is found to be a protective factor for GDM, with an odds ratio of 0.79[27]. It suggests that, unlike smoking, moderate alcohol consumption might be associated with a reduced risk of GDM. Therefore, the higher tendency of drinking and smoking habits observed in higher HbA1c categories is not likely to consistently affect the risk for GDM in the present study. However, chronic drinking can worsen lifestyle management, which might affect risks for metabolic disorders. Furthermore, a report showed that ethanol consumption 2 weeks before pregnancy resulted in a decrease in the number of viable fetuses and abnormal fetal development, and these effects were accompanied by impaired maternal glucose homeostasis and hepatic steatosis during pregnancy[28]. Further evidence is required to elucidate the optimal amount and timing of alcohol consumption during pre-pregnancy to reduce GDM risk.

Consistent with previous studies, the present study using the JECS cohort showed that GDM significantly increased the risk of representative adverse pregnancy outcomes, such as HDP, polyhydramnios and premature birth[3,29,30]. A previous study on HDP using the JECS showed a similar trend to that of the present study[31]. However, the adjusted ORs were slightly different (1.41, 95% CI 1.17–1.69 and 2.08, 95% CI 1.51–2.86 in the present and previous study, respectively), likely because of population differences arising from the selected exclusion criteria and covariates. Stated differently, the present study confirmed that GDM was a risk factor for adverse pregnancy outcomes, even in modern Japanese medical practice, where the diagnosis and treatment of GDM are now well established. Previous studies suggest that GDM risk might be reduced by diet, exercise and lifestyle counseling. These interventions have been shown to be particularly effective when introduced in the first or early second trimester[32]. Therefore, the importance of screening using HbA1c levels at early pregnancy to prevent the development of GDM and adverse pregnancy outcomes was suggested.

As shown in reports from the USA[33] and Norway[34], after adjustment with pre-pregnancy BMI, mothers' LBW is

significantly associated with their risk for GDM. The present study showed that the mother's own LBW was more frequent in GDM (7.3%) than it was in non-GDM (4.9%), suggesting that environmental factors acting early in life, such as fetal life and newborn, also had profound effects for the development of GDM in Asian women. Although our understanding of the biological mechanisms underlying the effects of LBW on the development of GDM is far from complete, some early metabolic changes have been proposed. LBW has been associated with endothelial[35] and β-cell[36] dysfunction, dyslipidemia[37,38], insulin resistance[37,39], and impaired glucose tolerance[39,40] in adulthood. Recently *in vivo* studies suggested that these metabolic changes were programmed *in utero*[35,41–43]. These metabolic changes, impaired glucose tolerance and dyslipidemia, whether resulting from what was programmed *in utero* or other factors, can lead to the development of GDM. As observed in Western countries, including the USA[44], France[45] and Germany[46], the average birthweight in Japan has been decreasing every year. In the 1990s, the average birthweight in Japan was approximately 3,300 g; however, it has since decreased to approximately 3,000 g, and the prevalence of LBW in Japan has increased to 10%[47,48]. Therefore, future studies on the association of a woman's own birthweight with her subsequent risk for GDM should be carried out in Japan.

The present study had several limitations. First, information on race, family history of diabetes and urine glucose, which are reported as confounders for GDM[49,50], is lacking. Second, non-significant ORs associated with relatively wide CIs do not necessarily indicate the true absence of ORs. Third, most information was obtained through a self-administered structured questionnaire used in JECS, and measurement error in these variables might have resulted in some degree of residual confounding. Fourth, women with anemia or iron supplementation, which might affect HbA1c levels, were not excluded.

In summary, the present observations indicate that high-normal HbA1c levels in the early stage of pregnancy are significantly associated with the risk of GDM in women in Japan. Additionally, GDM was significantly associated with adverse pregnancy outcomes. The risk for GDM is strongly affected by history of GDM, previous studies suggest that the risk of GDM might be reduced by diet, exercise and lifestyle counseling. These interventions have been shown to be particularly effective when introduced in the first or early second trimester[32]. The present observations will help identify pregnant women in Japan, and possibly in other Asian countries, for early preventive interventions for GDM.

ACKNOWLEDGMENTS

We are grateful to all the participants of the JECS and to all individuals involved in data collection. This study was funded by the Ministry of the Environment, Japan. The findings and conclusions of this article are solely the responsibility of the authors and do not represent the official views of the above government. The members of the JECS Group as of 2021 are follows: 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), Zentaro Yamagata (University of Yamanashi, Chuo, 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 Suganuma (Kochi University, Nankoku, Japan), Koichi Kusuhara (University of Occupational and Environmental Health, Kitakyushu, Japan) and Takahiko Katoh (Kumamoto University, Kumamoto, Japan).

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, and the Ethics Committee, University of Yamanashi.

Informed consent: Written informed consent was obtained from all participants.

Approval date of Registry and the Registration No. of the study/trial: The study protocol was approved by the Institutional Review Board of the Ministry of the Environment (No. 2020-016, approved on 18 February 2021) and the Ethics Committees of all participating institutions (No. 745, approved on 5 April 2021).

Animal studies: N/A.

REFERENCES

1. Saravanan P, Magee LA, Banerjee A, *et al*. Gestational diabetes: opportunities for improving maternal and child health. *Lancet Diabetes Endocrinol* 2020; 8: 793–800.
2. Landon MB, Spong CY, Thom E, *et al*. A multicenter, randomized trial of treatment for mild gestational diabetes. *N Engl J Med* 2009; 361: 1339–1348.
3. The HAPO study cooperative research group. Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med* 2008; 358: 1991–2002.
4. Crowther CA, Hiller JE, Moss JR, *et al*. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. *N Engl J Med* 2005; 352: 2477–2486.
5. Dabelea D. The predisposition to obesity and diabetes in offspring of diabetic mothers. *Diabetes Care* 2007; 30: S169–S174.

6. Kim C, Newton KM, Knopp RH. Gestational diabetes and the incidence of type 2 diabetes: a systematic review. *Diabetes Care* 2002; 25: 1862–1868.
7. Dabelea D, Pettitt DJ. Intrauterine diabetic environment confers risks for type 2 diabetes mellitus and obesity in the offspring, in addition to genetic susceptibility. *J Pediatr Endocrinol Metab* 2001; 14: 1085–1091.
8. Silverman BL, Metzger BE, Cho NH, *et al*. Impaired glucose tolerance in adolescent offspring of diabetic mothers: relationship to fetal hyperinsulinism. *Diabetes Care* 1995; 18: 611–617.
9. Buchanan TA, Xiang AH, Page KA. Gestational diabetes mellitus: risks and management during and after pregnancy. *Nat Rev Endocrinol* 2012; 8: 639–649.
10. American Diabetes Association. 14. Management of diabetes in pregnancy: standards of medical care in diabetes—2021. *Diabetes Care* 2021; 44: S200–S210.
11. Yabe D, Seino Y, Fukushima M, *et al*. β cell dysfunction versus insulin resistance in the pathogenesis of type 2 diabetes in East Asians. *Curr Diab Rep* 2015; 15: 36.
12. Ho Y-R, Wang P, Lu M-C, *et al*. Associations of mid-pregnancy HbA1c with gestational diabetes and risk of adverse pregnancy outcomes in high-risk Taiwanese women. *PLoS One* 2017; 12: e0177563.
13. Kawamoto T, Nitta H, Murata K, *et al*. Rationale and study design of the Japan environment and children's study (JECS). *BMC Public Health* 2014; 14: 25.
14. Michikawa T, Nitta H, Nakayama SF, *et al*. Baseline profile of participants in the Japan Environment and Children's Study (JECS). *J Epidemiol* 2018; 28: 99–104.
15. Sasaki H, Arata N, Tomotaki A, *et al*. Time course of metabolic status in pregnant women: the Japan Environment and Children's Study. *J Diabetes Investig* 2020; 11: 1318–1325.
16. Iwai-Shimada M, Nakayama SF, Isobe T, *et al*. Questionnaire results on exposure characteristics of pregnant women participating in the Japan Environment and Children Study (JECS). *Environ Health Prev Med* 2018; 23: 45.
17. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. *Bone Marrow Transplant* 2013; 48: 452–458.
18. Gunderson EP, Chiang V, Pletcher MJ, *et al*. History of gestational diabetes mellitus and future risk of atherosclerosis in mid-life: the coronary artery risk development in young adults study. *J Am Heart Assoc* 2014; 3: e000490.
19. Pu J, Zhao B, Wang EJ, *et al*. Racial/Ethnic differences in gestational diabetes prevalence and contribution of common risk factors. *Paediatr Perinat Epidemiol* 2015; 29: 436–443.
20. Hedderson MM, Darbinian JA, Ferrara A. Disparities in the risk of gestational diabetes by race-ethnicity and country of birth. *Paediatr Perinat Epidemiol* 2010; 24: 441–448.
21. Practice Bulletin No. 137: Gestational diabetes mellitus. *Obstet Gynecol* 2013; 122: 406–416.
22. American College of Obstetricians and Gynecologists. ACOG committee opinion #315: obesity in pregnancy. *Obstet Gynecol* 2005; 106: 671–675.
23. Landon MB, Rice MM, Varner MW, *et al*. Mild gestational diabetes mellitus and long-term child health. *Diabetes Care* 2015; 38: 445–452.
24. Mestman JH, Anderson GV, Guadalupe V. Follow-up study of 360 subjects with abnormal carbohydrate metabolism during pregnancy. *Obstet Gynecol* 1972; 39: 421–425.
25. Kim MK, Han K, You SY, *et al*. Prepregnancy smoking and the risk of gestational diabetes requiring insulin therapy. *Sci Rep* 2020; 10: 13901.
26. Leng J, Shao P, Zhang C, *et al*. Prevalence of gestational diabetes mellitus and its risk factors in Chinese pregnant women: a prospective population-based study in Tianjin, China. *PLoS One* 2015; 10: e0121029.
27. Lee KW, Ching SM, Ramachandran V, *et al*. Prevalence and risk factors of gestational diabetes mellitus in Asia: a systematic review and meta-analysis. *BMC Pregnancy Childbirth* 2018; 18: 494.
28. Lee YJ, Kim JY, Lee DY, *et al*. Alcohol consumption before pregnancy causes detrimental fetal development and maternal metabolic disorders. *Sci Rep* 2020; 10: 10054.
29. Vink JY, Poggi SH, Ghidini A, *et al*. Amniotic fluid index and birth weight: Is there a relationship in diabetics with poor glycemic control? *Am J Obstet Gynecol* 2006; 195: 848–850.
30. Bryson CL. Association between gestational diabetes and pregnancy-induced hypertension. *Am J Epidemiol* 2003; 158: 1148–1153.
31. Kyozuka H, Yasuda S, Murata T, *et al*. Adverse obstetric outcomes in early-diagnosed gestational diabetes mellitus: The Japan Environment and Children's Study. *J Diabetes Investig* 2021. https://doi.org/10.1111/jdi.13569
32. Koivusalo SB, Rönö K, Klemetti MM, *et al*. Gestational diabetes mellitus can be prevented by lifestyle intervention: the Finnish gestational diabetes prevention Study (RADIEL). *Diabetes Care* 2016; 39: 24–30.
33. Innes KE. Association of a woman's own birth weight with subsequent risk for gestational diabetes. *JAMA* 2002; 287: 2534–2541.
34. Egeland GM, Skjarven R, Irgens LM. Birth characteristics of women who develop gestational diabetes: population based study. *BMJ* 2000; 321: 546–547.
35. McAllister AS, Atkinson AB, Johnston GD, *et al*. Relationship of endothelial function to birth weight in humans. *Diabetes Care* 1999; 22: 2061–2066.
36. Hoet JJ, Ozanne S, Reusens B. Influences of pre- and postnatal nutritional exposures on vascular/endocrine systems in animals. *Environ Health Perspect* 2000; 108: 563–568.
37. Mi J, Law C, Zhang K-L, *et al*. Effects of infant birthweight and maternal body mass index in pregnancy on

components of the insulin resistance syndrome in China. *Ann Intern Med* 2000; 132: 253–260.
38. Barker DJ. Maternal and fetal origins of coronary heart disease. *J R Coll Physicians Lond* 1994; 28: 544–551.
39. Crowther NJ, Cameron N, Trusler J, *et al*. Association between poor glucose tolerance and rapid post natal weight gain in seven-year-old children. *Diabetologia* 1998; 41: 1163–1167.
40. Phillips DI. Birth weight and the future development of diabetes. A review of the evidence. *Diabetes Care* 1998; 21: B150–B155.
41. Petry CJ. Long-term effects on offspring of intrauterine exposure to deficits in nutrition. *Hum Reprod Update* 2000; 6: 578–586.
42. Barker DJP. In utero programming of cardiovascular disease. *Theriogenology* 2000; 53: 555–574.
43. Clark PM. Programming of the hypothalamo-pituitary-adrenal axis and the fetal origins of adult disease hypothesis. *Eur J Pediatr* 1998; 157: S7–S10.
44. Donahue SMA, Kleinman KP, Gillman MW, *et al*. Trends in birth weight and gestational length among singleton term births in the United States. *Obstet Gynecol* 2010; 115: 357–364.
45. Diouf I, Charles MA, Blondel B, *et al*. Discordant time trends in maternal body size and offspring birthweight of term deliveries in France between 1972 and 2003: data from the French National Perinatal Surveys. *Paediatr Perinat Epidemiol* 2011; 25: 210–217.
46. Schiessl B, Beyerlein A, Lack N, *et al*. Temporal trends in pregnancy weight gain and birth weight in Bavaria 2000–2007: slightly decreasing birth weight with increasing weight gain in pregnancy. *J Perinat Med* 2009; 37: 374–379.
47. Fukuoka H, Sata F. Molecular mechanism of developmental origins of health and disease (DOHaD). *Nippon Eiseigaku Zasshi* 2016; 71: 185–187 (Japanese).
48. Sata F. Developmental origins of health and disease (DOHaD) and epidemiology. *Nippon Eiseigaku Zasshi* 2016; 71: 41–46 (Japanese).
49. Getahun D, Fassett MJ, Jacobsen SJ. Gestational diabetes: risk of recurrence in subsequent pregnancies. *Am J Obstet Gynecol* 2010; 203:467.e1–467.e6.
50. Kim C, Liu T, Valdez R, *et al*. Does frank diabetes in first-degree relatives of a pregnant woman affect the likelihood of her developing gestational diabetes mellitus or nongestational diabetes? *Am J Obstet Gynecol* 2009; 201:576.e1–576.e6.

SUPPORTING INFORMATION

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

Table S1 | Multivariable-adjusted odds ratios for adverse pregnancy outcomes.