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SHORT REPORT

Association between maternal gestational diabetes mellitus and high-sensitivity C-reactive protein levels in 8-year-old children: The Yamanashi Adjunct Study of the Japan Environment and Children's Study (JECS)

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ABSTRACT

Gestational diabetes mellitus (GDM) is one of the most common pregnancy-related complications; it is associated with adverse pregnancy outcomes and metabolic disorders in offspring, consistent with the concept of the developmental origins of health and disease. This cohort study of women without diabetes (n = 761), who were part of the Yamanashi Adjunct Study of the Japan Environment and Children's Study, aimed to explore the associations between maternal GDM and their offspring's level of high-sensitivity C-reactive protein (hsCRP), a biomarker of inflammatory and cardiovascular diseases. We analyzed the associations between GDM and the offspring's hsCRP levels using a multiple logistic regression model. A mother with GDM significantly increased the risk for high hsCRP level by 4.07-fold (≥2.0 mg/L) in the child. As such, maternal GDM was significantly associated with increased serum hsCRP levels in 8-year-old children.

INTRODUCTION

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy[1]; it is one of the most common pregnancy-related complications, and is associated with adverse pregnancy outcomes[2–5]. Consistent with the concept of developmental origins of health and disease[6,7], several studies showed that children born from mothers with GDM are at high risk for obesity and metabolic disorders in adulthood[8,9]. As such, the screening and diagnosis of GDM are essential during postnatal care, as well as maternal care.

High-sensitivity C-reactive protein (hsCRP) is an inflammatory biomarker that is well-known for its use in the assessment of major cardiovascular risk and hypertension in adults[10,11]. In children, some studies have shown a relationship between high serum hsCRP levels and obesity or metabolic disorders[12,13]. However, the association between maternal GDM and the child's serum hsCRP level remains unknown. Therefore, the present investigation examined the associations between GDM and high serum hsCRP levels in children using a prospective birth cohort study in Japan.

MATERIALS AND METHODS

Additional details related to the MATERIAL AND METHODS are included in the Supporting Information section.

Study design

The present study was part of the Japan Environment and Children's Study (JECS) and the Yamanashi Adjunct Study.

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

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The JECS is an ongoing prospective nationwide birth cohort study in Japan, which mainly aims to investigate the associations between environmental factors and children's health and development. Pregnant women were recruited from 15 Regional Centers between January 2011 and March 2014. The study protocol was approved by the institutional review board of the Ministry of the Environment and the Ethics Committees of all participating institutions, and the study was carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants. Details of the study design have been described previously[14–17].

Statistical analysis

We investigated the associations between children's serum hsCRP levels at 8 years old and the presence of GDM in the mother using an univariate or a multiple logistic regression model with adjustments for potential confounders.

Statistical analyses were carried out using EZR version 1.54 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria)[18]. All statistical tests were two-tailed, and statistical significance was set at $P < 0.05$.

RESULTS

Characteristics

A total 950 8-year-old children were born from mothers included in the Yamanashi Adjunct Study of JECS. After excluding 188 participants due to missing data/records of hsCRP levels and one participant due to missing data/records of GDM diagnosis, 761 participants were eligible for inclusion in the present analysis (Figure 1). A total of 30 participants (3.9%) were born from mothers with GDM (Table 1). The median maternal age at pregnancy and pre-pregnancy body mass index were 32 years (75% confidence interval [CI] 29–36 years) and 20.3 kg/m^2 (75% CI 19.1–22.3 kg/m^2), respectively.

Association between GDM and high serum hsCRP levels (≥2 mg/L) in 8-year-old children

We analyzed whether serum hsCRP levels were high (≥2.0 mg/L) in 8-year-old children born from mothers with GDM. Maternal GDM was significantly associated with an increase of hsCRP levels in 8-year-old children in both the univariate and multivariate analyses, with odds ratios of 3.86 (75% CI 1.26–11.8) and 4.07 (75% CI 1.30–12.8), respectively (Table 2).

DISCUSSION

Elevated CRP levels, which is a response to increased cytokine secretion from the adipose tissues in obese individuals[19], has been used as a marker of cardiovascular risk[20–24], diabetes and metabolic syndrome in adults[25,26]. Although hsCRP remains unproven as an independent risk factor for future cardiovascular diseases in children, a previous study showed an association of elevated serum hsCRP levels with the risk of obesity or metabolic disorders in children[13]. Large prospective studies will be required to establish the clinical relevance of findings in the present study by exploring whether the elevated serum hsCRP levels are associated with changes in disease end-points in the future.

The present study suggests that maternal GDM stimulates their children's inflammation represented by serum hsCRP levels, independent of obesity. Deoxyribonucleic acid methylation in a gene set related to immune response was reportedly

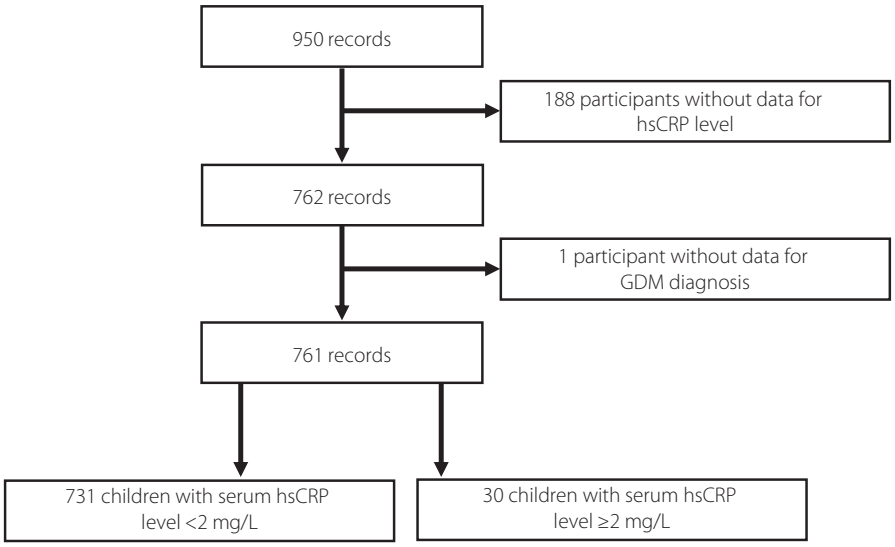

Figure 1 | Inclusion flowchart for the analysis of children in the Yamanashi Adjunct Study of the Japan Environment and Children's Study (JECS). This study included 761 children from the Yamanashi Adjunct Study of the Japan Environment and Children's Study. GDM, gestational diabetes; hsCRP, high-sensitivity C-reactive protein.

Table 1 | Characteristics of the 8-year-old children in the Yamanashi Adjunct Study of the Japan Environment and Children's Study

Characteristic	All cases	Serum hsCRP level	
		<2 mg/L	≥2 mg/L
	n = 761	*n* = 731	*n* = 30
Born from a mother with GDM, *n* (%)	32 (4.2)	28 (3.8)	4 (13.3)
BMI percentile ≥95%, *n* (%)	28 (3.7)	26 (3.6)	2 (6.7)
Sex (boys), *n* (%)	374 (49.2)	359 (49.1)	15 (50.0)
Median maternal age at pregnancy, years (25–75% CI)	32 (29–36)	32 (29–36)	31 (29–35)
Older pregnancy (≥35 years)	259 (34.0)	251 (34.3)	8 (26.7)
Median maternal BMI pre-pregnancy, kg/m^2 (25–75% CI)	20.3 (19.1–22.3)	20.3 (19.1–22.3)	20.0 (19.0–22.1)
Underweight (<18.5 kg/m^2), *n* (%)	121 (15.9)	118 (16.1)	3 (10.0)
Obese (≥25 kg/m^2), *n* (%)	62 (8.2)	60 (8.2)	2 (6.7)
Low birthweight infant, *n* (%)	93 (12.2)	88 (12.0)	5 (16.7)
Large baby, *n* (%)	10 (1.3)	10 (1.4)	0 (0.0)
Premature birth, *n* (%)	59 (7.8)	59 (8.1)	0 (0.0)

The presented values do not include missing data. BMI, body mass index; CI, confidence interval; GDM, gestational diabetes mellitus; hsCRP, high-sensitivity C-reactive protein; JECS, Japan Environment and Children's Study.

Table 2 | Univariate and multivariate analysis for elevated high-sensitivity C-reactive protein (≥2 mg/L) in 8-year-old children born from the Yamanashi Adjunct Study of the Japan Environment and Children's Study participants

Analysis method	Birth from a mother with GDM OR (95% CI)	*P*-value
Univariate analysis	3.86 (1.26–11.8)	<0.05
Multivariate analysis[†]	4.07 (1.30–12.8)	<0.05

GDM, gestational diabetes mellitus; hsCRP, high-sensitivity C-reactive protein; JECS, Japan Environment and Children's Study; OR, odds ratio.
[†]Adjusted for obesity (body mass index percentile ≥95%), sex and older pregnancy (maternal age at pre-pregnancy ≥35 years).

altered in the liver of mice born from high-fat diet-fed mice compared with those born from standard diet-fed mice[27]. In humans, GDM was associated with deoxyribonucleic acid methylation in some inflammation-related genes in chorionic villi and cord blood[28]. Then, the alternation of deoxyribonucleic acid methylation is a possible mechanism by which maternal GDM affects offspring's inflammation.

The present study had several limitations. First, information on race, blood pressure, passive smoking status, plasma glucose and insulin concentration were lacking, all of which have been reported as confounders for the offspring of mothers with impaired glucose metabolism[8]. Second, information of sex and maternal age at pre-pregnancy was obtained through a self-administered structured questionnaire; measurement errors in these variables might have produced some residual confounding.

In summary, the present observation showed that, in Japan, maternal GDM is significantly associated with increased serum hsCRP levels in 8-year-old children. This result implies that the prevention of GDM might reduce the risk of future metabolic disorders in the children, as well as reduce maternal adverse pregnancy outcomes.

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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, and the Ethics Committee, University of Yamanashi.

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

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.

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SUPPORTING INFORMATION

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

Supplementary Material