Maternal low birth weight and hypertensive disorders of pregnancy

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Short running title

Maternal birth weight and HDP

Abstract

Objectives

To investigate the association between maternal own low birth weight (<2,500 g) and subsequent risks for hypertensive disorders of pregnancy (HDP) and preeclampsia.

Study design

A multicenter retrospective study was conducted using clinical data from 12 primary maternity care units from 2012 to 2018. A total of 17,119 women with information about their own birth weight, who delivered at term, were subdivided into four groups according to maternal birth weights [(<2,500, 2,500–3,499, 3,500–3,999, and ≥4,000) g].

Main outcome measures

Multivariate regression analyses were conducted to evaluate the risks for HDP and preeclampsia among women born with low birth weight compared with women born with a birth weight of 2,500–3,499 g. We evaluated these risks, stratified by pre-pregnancy BMI or their infants' birth weight categories.

Results

Maternal low birth weight was an independent risk factor for HDP after adjustment for several covariates, but not for preeclampsia. A 100-g increase in maternal birth weight was associated with a 3% risk reduction for HDP. Additionally, women born with low birth weight had the highest risk for HDP among those with a pre-pregnancy BMI of ≥25 kg/m^2. Conversely,

women born with high birth weight (≥4,000 g) had the highest risk for preeclampsia if they complicate with fetal growth restrictions.

Conclusion

Women born with low birth weight had an increased risk for HDP. Collection of information on maternal birth weight may facilitate the prediction of HDP and patients' self-awareness of such risk, allowing the modification of lifestyle factors associated with HDP.

Keywords

Cardiovascular disease, Developmental Origins of Health and Disease, Hypertensive disorders of pregnancy, Low birth weight, Preeclampsia

Abbreviations

ART, assisted reproductive technology; BMI, body mass index; HDP, hypertensive disorders of pregnancy; SGA, small for gestational age.

Introduction

According to the annual report of the Ministry of Health, Labor and Welfare in Japan, the prevalence of low birth weight (<2,500 g) has been on the rise in Japan (1). Approximately 1 in 10 infants were born with low birth weight in 2016, which is almost double that in 1975 (1). This increase can be attributed to some factors, including inadequate pregnancy weight gain, increased number of underweight women, and increased rate of preterm birth (2).

Since David Barker's initial discovery in the late 80s (3), there has been growing evidence of the association between women born with low birth weight and increased risks for non-communicable diseases (e.g., cardiovascular disease and diabetes mellitus) later in life (4). Although the underlying biological mechanisms for this association is yet to be elucidated, epigenetic modifications attributed to various conditions (e.g., hypoxia, oxidative stress, inflammatory cytokines, and hyperglycemia) during fetal and neonatal period negatively affect their subsequent health (5, 6).

Furthermore, several studies in the early 2000s demonstrated that women born with low birth weight or born small for gestational age (SGA) had significantly increased risks for hypertensive disorders of pregnancy (HDP) or preeclampsia (7-12). Pregnancy is known as a stress marker that could unmask underlying susceptibility to non-communicable diseases, and

the development of HDP during pregnancy can act as a predictor of such diseases even as early as 20–40 years of age (13-15).

However, many researchers demonstrated that the prevalence of HDP and preeclampsia differs according to race, ethnicity, and country (16, 17). Moreover, the definitions of HDP and preeclampsia have changed since 20 years. In addition, although the two major causes of low birth weight are preterm birth and fetal growth restrictions, the etiology of these two are considerably different (2). The ratio of preterm birth to fetal growth restrictions among women born with low birth weight has changed since two decades by the advancement in perinatal care management, patient awareness, and lifestyle changes including diet and physical activity (18). Few studies have evaluated and verified the association between maternal low birth weight and subsequent risk for HDP using recent clinical data. Thus, further research is required to revalidate this association reported mainly 20 years ago.

Here, in this retrospective study, we sought to investigate the association between maternal low birth weight and subsequent risks for HDP and preeclampsia using recent Japanese clinical data derived from 12 primary maternal care units.

Methods

A multicenter retrospective study was conducted using clinical data from 12 primary maternity care units located in Aichi and Gifu prefectures in Japan. These maternity care units basically care for low- to moderate-risk pregnancies through the initial management of maternal, fetal, and neonatal problems. Women who delivered at term ($37^{0/7}$ to $41^{6/7}$ weeks) at these units from January 2012 to December 2018 were included in this study (Figure 1). Exclusion criteria were women who had preterm birth, post-term birth, stillbirth, multiple birth, major congenital and chromosomal abnormalities, and incomplete medical records on their own birth weight and HDP.

Information on maternal and neonatal demographic characteristics and pregnancy complications were collected from the electronic medical records system at each unit. The clinical data of this study were extracted by system engineers, who were blinded to the research purpose, at the Kishokai Medical Corporation. Identifying information (e.g., name, patient number, and address) was anonymized before analysis. The maternal and neonatal information included maternal own birth weight, maternal age at delivery, gestational age at delivery, mode of delivery, parity, pre-pregnancy body mass index (BMI), pregnancy weight gain, assisted reproductive technology (ART), smoking during pregnancy, alcohol consumption during pregnancy, duration of education, HDP, preeclampsia, infant sex, and infant birth weight and height. Information on maternal own birth weight was based on self-reports obtained through

a self-administered questionnaire, not on birth registry in public institutions. Women who could not recall their own birth weight were therefore excluded from this study. Data on parity, pre-pregnancy BMI, ART, smoking during pregnancy, alcohol consumption during pregnancy, and duration of education were also based on self-reports.

HDP was defined as hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg) during pregnancy (19). Preeclampsia was defined as hypertension and either proteinuria (≥0.3 g/day, or ≥1+ on a urine dipstick) or end-organ dysfunction or uteroplacental dysfunction (19). Light-for-dates, appropriate-for-dates, and heavy-for-dates were defined as birth weight below the 10^{th} percentile, within the 10–90^{th} percentile, and over the 90^{th} percentile for gestational age, respectively, according to a sex-specific Japanese neonatal anthropometric chart in 2000 (20).

To determine whether maternal birth weight affects the development of subsequent HDP and preeclampsia, univariate and multivariate logistic regression analyses were performed. All eligible women were subdivided into four groups according to maternal birth weight (<2,500 g, 2,500–3,499 g, 3,500–3,999 g, and ≥4,000 g). In this study, low and high birth weights were defined as <2,500 g and ≥4,000 g, respectively. The prevalence of HDP and preeclampsia was determined in each group. Crude odds ratios (ORs) and 95% confidence

intervals (CIs) were evaluated by univariate logistic regression models. Women with a birth weight of 2,500–3,499 g were selected as the reference group. We then evaluated the adjusted ORs after adjusting for covariates including seven factors (maternal age, parity, pre-pregnancy BMI, pregnancy weight gain, ART, smoking during pregnancy, and duration of education), which were previously reported to be associated with HDP (21). In addition, we evaluated the adjusted ORs for the 100-g increase in maternal birth weight.

Next, we performed additional analyses to identify women at a high risk for subsequent HDP and preeclampsia, comparing these risks, stratified by maternal pre-pregnancy BMI category (<18.5 kg/m^2, 18.5–25 kg/m^2, and ≥25 kg/m^2) or their infants' birth weight category (light-for-dates, appropriate-for-dates, and heavy-for-dates).

Maternal and neonatal characteristics were compared using Chi-square test or Fisher's exact test for the categorical variables and one-way ANOVA or Kruskal-Wallis test for the continuous variables according to normal or non-normal distributions. Statistical significance was defined as a *p*-value <0.05. All statistical analyses were performed with SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and SPSS 26 (SPSS Inc., Chicago, IL, USA).

The use of data in this study was authorized by Kishokai Medical Corporation

Executive Committee (approval number 2016–009), and this study protocol was approved by the Institutional Ethics Board of Nagoya University (approval number 2015–0415). The need for signed informed consent was waived because all data were anonymized and retrospectively collected from the existing medical records.

Results

A total of 43,883 women delivered at term at the 12 primary maternity care units from 2012 to 2018 (Figure 1). After excluding 26,764 women, the remaining 17,119 were eligible for this study. The women were divided into 4 groups according to their birth weight category (<2,500 g [n = 1,084, 6.3%], 2,500–3,499 g [n = 12,893, 75.3%], 3,500–3,999 g [n = 2,688, 15.7%], and ≥4,000 g [n = 454, 2.7%]). Supplementary Table 1 shows the baseline characteristics of women with complete data (n = 17,119) and without complete data (n = 26,534).

Table 1 shows the maternal and neonatal characteristics, stratified by maternal birth weight category. There was a negative trend in the prevalence of HDP and light-for-dates infants with increasing birth weight category. There was no significant correlation between the prevalence of preeclampsia and maternal birth weight category.

Table 2 shows the crude and adjusted odds ratios for HDP, stratified by maternal birth

191 weight category. Univariate and multivariate analyses were performed to determine whether
192 low and high birth weights are independent risk factors for HDP. The adjusted odds ratios for
193 birth weights of <2,500 g and ≥4,000 g were 1.42 (1.00–2.01) and 0.59 (0.29–1.22),
194 respectively, compared with birth weight of 2,500–3,499 g for the reference group. A 100-g
195 increase in maternal birth weight was associated with a 3% reduction in the risk for HDP
196 (adjusted OR, 0.97; 95% CI, 0.95–0.99).
197
198 Table 3 shows the crude and adjusted odds ratios for preeclampsia, stratified by
199 maternal birth weight category. Univariate and multivariate analyses were performed to
200 determine whether low and high birth weights are independent risk factors for preeclampsia.
201 The adjusted odds ratios for birth weights of <2,500 g and ≥4,000 g were 1.69 (0.93–3.05) and
202 0.52 (0.13–2.16), respectively, compared with birth weight of 2,500–3,499 g for the reference
203 group. A 100-g increase in maternal birth weight was associated with a 2% reduction in the
204 risk for preeclampsia (adjusted OR, 0.98; 95% CI, 0.94–1.02), but this was not statistically
205 significant.
206
207 An additional analysis was performed to identify women at a high risk for HDP and
208 preeclampsia, comparing these risks according to pre-pregnancy BMI category (<18.5 kg/m^2,
209 18.5–25 kg/m^2, and ≥25 kg/m^2) and maternal birth weight category (<2,500 g, 2,500–3,499 g,

3,500–3,999 g, and ≥4,000 g) (Figure 2). The women with pre-pregnancy BMI of ≥25 kg/m^2 had higher risks for HDP and preeclampsia. Among these women, those born with low birth weight experienced the highest risk for HDP (17.6%). Regarding preeclampsia, we could not find any significant relationships between pre-pregnancy BMI category and maternal birth weight.

An additional analysis was performed to identify high risk women for HDP and preeclampsia, comparing these risks according to their infants' birth weight category (light-for-dates, appropriate-for-dates, and heavy-for-dates) and maternal birth weight category (<2,500 g, 2,500–3,499 g, 3,500–3,999 g, and ≥4,000 g) (Figure 3). The women whose infants were categorized as light-for-dates had a higher risk for HDP and preeclampsia along with the increase of maternal birth weight. Interestingly, women born at ≥4,000 g had the highest risk for preeclampsia among women whose infants were categorized as light-for-dates.

Discussion

In this multicenter retrospective study, we sought to investigate the association between maternal low birth weight and subsequent risks for HDP and preeclampsia using Japanese clinical data. The main findings of this study showed that maternal low birth weight (<2,500 g) was an independent risk factor for HDP after adjustment of several covariates, but not for

preeclampsia. In addition, women born with low birth weight had the highest risk for HDP among those with a pre-pregnancy BMI of ≥25 kg/m^2. Conversely, women born with high birth weight (≥4,000 g) had the highest risk for preeclampsia among women who delivered light-for-dates infants. These findings indicate that collecting information on maternal own birth weight may facilitate prediction of HDP and patients' self-awareness of such risk, allowing them to reduce or modify the lifestyle factors associated with HDP.

Our findings are consistent with previous studies, demonstrating that women born with low birth weight or SGA had 1.5–2.0 fold increased risks for HDP and preeclampsia (7-12, 22, 23). We also found a negative trend in the risk of HDP with increasing maternal birth weight, and a 100-g increase in maternal birth weight was significantly associated with a 3% reduction in the risk of HDP.

Compared with previous reports, the odds ratio for HDP among women born with low birth weight in this study was lower, and there was no statistically significant association between maternal low birth weight and preeclampsia (p=0.09). Although this is also in line with a previous study (12), possible explanations for the lack of association between maternal low birth weight and preeclampsia were: (1) the pathophysiological difference between HDP and preeclampsia; (2) differences in race and country, and (3) the potential risk for developing

248 preeclampsia may be different between women born at preterm without growth restrictions and
249 women born at term with growth restrictions, despite comparable birth weights.
250
251 Firstly, HDP not only refers to preeclampsia, but also to gestational hypertension,
252 superimposed preeclampsia, and chronic hypertension, indicating a heterogeneous
253 pathophysiology (24). It has been suggested that maternal constitutional factors (e.g., obesity,
254 diabetes mellitus, and diet) strongly affect the development of clinical symptoms of HDP,
255 especially superimposed preeclampsia and chronic hypertension, while immunogenic
256 maladaptation (attributed to defective remodeling of the uterine spiral arteries) is the main
257 cause of preeclampsia (24, 25). Based on Baker's hypothesis, women born with low birth
258 weight may have a predisposition to metabolic syndrome and tend to be affected by maternal
259 constitutional factors (23, 26). These women may resultantly show an increased risk for HDP,
260 but not for preeclampsia. Secondly, a previous study demonstrated that the association between
261 maternal birth weight and subsequent risk for preeclampsia significantly differed according to
262 race, country, or study population (7). Finally, the two major causes of low birth weight are
263 preterm birth and fetal growth restrictions (2). In recent Japan, approximately one-third of the
264 causes are due to preterm birth, and two-thirds are due to fetal growth restrictions (18, 27). A
265 well-designed observational study demonstrated that women born with SGA had a significantly
266 increased risk for HDP (OR 1.8; 95% CI, 1.1–2.8); however, women born at preterm did not

have a significantly increased risk (OR 1.5, 95% CI, 0.96–2.5) after adjusting for several covariates (8). Therefore, the differential effect between preterm birth and fetal growth restrictions during pregnancy on subsequent risks for HDP or preeclampsia may affect our results. Unfortunately, we could not collect data on gestational age at maternal birth; thus, we could not distinguish women born preterm from women born with growth restrictions in this study population.

In general, the etiology of HDP and fetal growth restrictions overlaps, and these two disorders are closely connected with each other (28, 29). Thus, it is expected that women who delivered light-for-dates infants show a higher rate of HDP. However, interestingly, women born with a weight of <2,500 g did not have higher risks for HDP and preeclampsia among those who delivered light-for-dates infants; instead, women born with a birth weight of ≥4,000 g had higher risks for these disorders. Although the underlying mechanism remains unclear, a possible explanation for this may be associated with the degree of placental dysfunction which induces fetal growth restrictions or HDP. From the viewpoint of fetal programming, women born with low birth weight are more likely to deliver light-for-dates infants because of their genetic or shared environmental factors in the etiology of light-for-dates infants, but this situation is less likely to be attributed to placental dysfunction (30). In contrast, delivery of light-for-dates infants among women born with a birth weight of ≥4,000 g may be largely

attributed to placental dysfunction, indicating increased risks for HDP and preeclampsia (31).

The strength of this study is that it was carried out using recent Japanese clinical data based on self-reports, with a large sample size. The prevalence of HDP and preeclampsia differs according to race, ethnicity, and guidelines (17); hence, this study made it possible to revalidate the consistency of the association among the Japanese population. Second, most previous reports demonstrated an association between women born with SGA and HDP or preeclampsia; however, little evidence exists regarding the association between maternal low birth weight (<2,500 g) and such diseases. The prevalence of low birth weight in Japanese males and females was 10.6% and 8.3%, respectively, in 2016, which is approximately double of that reported in 1975 (5.5% and 4.7%, respectively) (1). Our study may facilitate awareness of the recent trend of growing numbers of low birth weight infants not only in developing countries but also in some developed countries such as Japan, Spain, and Korea (32). Furthermore, the pathophysiology of HDP and cardiovascular disease share many features; therefore, lifestyle-modifying interventions during pregnancy may improve their long-term cardiovascular health (33, 34).

Several limitations of this study should be acknowledged. First, we could not collect information on gestational age at maternal birth. As a result, we could not assess whether the

infants were SGA or not and whether low birth weight was due to preterm birth or SGA. Even though the birth weight is the same, the pathophysiologic mechanisms of preterm birth (inflammation, uterine distension, and activation of the fetal hypothalamus-pituitary-adrenal axis) and that of term SGA (placental dysfunction, undernutrition, oxidative stress, anti-angiogenic imbalance, and hypoxia) were considerably different. Thus, these two disorders may have differential effects on the fetal environment (e.g., metabolism and postnatal growth) (35). According to a recent report, approximately two-thirds of cases were due to term SGA, and one-third were due to preterm birth, which is considerably different from a previous study thirty years ago, which demonstrated that preterm birth accounts for up to 85% of low birth weight (18). Second, the information on birth weight was based on self-declaration, not on birth registry in public institutions. Thus, our results need to be considered with caution due to recall bias and the possibility of inaccuracy of their birth weights. In addition, we obtained information on their birth weights from approximately 40% of women who delivered at these units. Therefore, we cannot exclude the possibility of a selection bias. To solve the statistical problem of missing data on self-reported maternal birth weight, we estimated adjusted odds ratios by multivariate logistic analysis after missing data were replaced with substituted values using multiple imputation. The adjusted odds ratios for HDP and preeclampsia for birth weights of <2,500 g were 1.45 (1.10–1.92) and 1.27 (0.75–2.16), respectively, compared with birth weight of 2,500–3,499 g for the reference group. This result was consistent with previous

results without multiple imputation. Finally, we could not collect maternal information on the history of HDP or preeclampsia; therefore, this factor could not be incorporated into covariates of the multivariate regression analyses.

In conclusion, we demonstrated that maternal low birth weight is associated with the development of HDP, but not preeclampsia. Collecting information on maternal birth weight may play an important role in better perinatal management, including patients' self-awareness of such risk, allowing the improvement of their long-term cardiovascular health.

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Disclosures

The authors have no potential conflicts of interest to disclose.

Data availability

The data that support the findings of this study are available from the corresponding author, (TU), upon reasonable request, and with the permission of Kishokai Medical Corporation.

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Figure legends

Figure 1. Flow diagram of the study population. Data on 43,883 women who delivered at term were collected. A total of 17,119 women were eligible for this study after excluding 26,764 women, and they were divided into 4 groups according to their birth weight. HDP, hypertensive disorders of pregnancy. * indicates items not mutually exclusive.

Figure 2. Rates of HDP (A) and preeclampsia (B) stratified by pre-pregnancy BMI category (<18.5 kg/m^2, 18.5–25 kg/m^2, and ≥25 kg/m^2) and maternal birth weight category (<2,500 g, 2,500–3,499 g, 3,500–3,999 g, and ≥4,000 g). HDP, hypertensive disorders of pregnancy; BMI, body mass index.

Figure 3. Rates of HDP (A) and preeclampsia (B) stratified by their infants' birth weight category (light-for-dates, appropriated-for-dates, and heavy-for-dates) and maternal birth weight category (<2,500 g, 2,500–3,499 g, 3,500–3,999 g, and ≥4,000 g).
HDP, hypertensive disorders of pregnancy; LFD, light-for dates; AFD, appropriate-for-dates; and HFD, heavy-for-dates.

Table 1. Maternal and neonatal characteristics stratified by maternal birth weight.

Maternal birth weight category	<2,500 g n = 1,084	2,500–3,499 g n = 12,893	3,500–3,999 g n = 2,688	≥4,000 g n = 454	*p*-value
Maternal characteristics					
Maternal own birth weight (g)	2,181 ± 317	3,005 ± 248	3,660 ± 136	4,138 ± 187	<0.05
Maternal age (years)	30.2 ± 4.9	30.7 ± 4.7	31.4 ± 4.7	32.0 ± 4.7	<0.05
Gestational age at delivery (weeks)	39.5 ± 1.1	39.6 ± 1.1	39.7 ± 1.1	39.7 ± 1.1	<0.05
Cesarean section	203/1,084 (18.7)	2,004/12,888 (15.5)	459/2,686 (17.1)	87/454 (19.2)	<0.05
Primipara	586/1,084 (54.1)	7,043/12,893 (54.6)	1,390/2,686 (51.7)	218/454 (48.0)	<0.05
Pre-pregnancy BMI (kg/m^2)	20.7 ± 3.2	20.7 ± 2.9	21.3 ± 3.1	21.5 ± 3.3	<0.05
Pregnancy weight gain (kg)	10.2 ± 3.7	10.4 ± 3.5	10.8 ± 3.7	11.3 ± 4.1	<0.05
Assisted reproductive technology	57/983 (5.8)	706/11,701 (6.0)	179/2,448 (7.3)	30/402 (7.5)	0.07
Smoking during pregnancy	13/1,072 (1.2)	129/12,762 (1.0)	35/2,652 (1.3)	6/451 (1.3)	0.49
Alcohol consumption during pregnancy	1/1,066 (0.1)	42/12,728 (0.3)	6/2,650 (0.2)	4/443 (0.9)	0.06
Duration of education (years)					<0.05
<9 years	23/776 (3.0)	162/9,066 (1.8)	49/1,921 (2.6)	1/316 (0.3)	
9–12 years	245/776 (31.6)	2,177/9,066 (24.0)	466/1,921 (24.3)	92/316 (29.1)	
13–15 years	240/776 (30.9)	2,969/9,066 (32.7)	620/1,921 (32.3)	105/316 (33.2)	
≥16 years	268/776 (34.5)	3,758/9,066 (41.5)	786/1,921 (40.9)	118/316 (37.3)	
Hypertensive disorders of pregnancy	62/1,084 (5.7)	514/12,893 (4.0)	107/2,688 (4.0)	15/454 (3.3)	<0.05
Preeclampsia	16/1,084 (1.5)	150/12,893 (1.2)	37/2,688 (1.4)	4/454 (0.9)	0.59
Neonatal characteristics					
Male	538/1,084 (49.6)	6,591/12,891 (51.1)	1,393/2,686 (51.9)	241/454 (53.1)	0.53
Birth weight (g)	2,956 ± 353	3,059 ± 352	3,226 ± 364	3,333 ± 388	<0.05

Height (cm)	49.4 ± 1.7	49.7 ± 1.6	50.3 ± 1.6	50.4 ± 1.7	<0.05
Light-for-dates infants	144/1,082 (13.3)	939/12,887 (7.3)	74/2,684 (2.8)	11/454 (2.4)	<0.05
Appropriate-for-dates infants	880/1,082 (81.3)	10,761/12,887 (83.5)	2,059/2,684 (76.7)	305/454 (67.2)	<0.05
Heavy-for-dates infants	58/1,082 (5.4)	1,187/12,887 (9.2)	551/2,684 (20.5)	138/454 (30.4)	<0.05

BMI, body mass index. Data are presented as mean ± standard deviation or n (%).

Table 2. Risk of HDP according to maternal birth weight category.

Maternal birth weight	Crude OR (95% CI)	Adjusted OR (95% CI)
<2,500 g	1.46 (1.11–1.92)	1.42 (1.00–2.01)
2,500–3,499 g	1.0 (reference)	1.0 (reference)
3,500–3,999 g	1.00 (0.81–1.23)	0.89 (0.68–1.16)
≥4,000 g	0.82 (0.49–1.39)	0.59 (0.29–1.22)
100-g increase	0.98 (0.97–1.00)	0.97 (0.95–0.99)

Multivariate analyses were performed after adjustment for each covariate including maternal age, parity, pre-pregnancy body mass index, pregnancy weight gain, assisted reproductive technology, smoking during pregnancy, and duration of education. Results were reported as odds ratios and 95% CI, with maternal birth weight of 2,500–3,499 g as the reference group. OR, odds ratio; CI, confidence interval.

Table 3. Risk of preeclampsia according to maternal birth weight category.

Maternal birth weight	Crude OR (95% CI)	Adjusted OR (95% CI)
<2,500 g	1.27 (0.76–2.14)	1.69 (0.93–3.05)
2,500–3,499 g	1.0 (reference)	1.0 (reference)
3,500–3,999 g	1.19 (0.83–1.70)	1.17 (0.76–1.82)
≥4,000 g	0.76 (0.28–2.05)	0.52 (0.13–2.16)
100-g increase	0.99 (0.96–1.03)	0.98 (0.94–1.02)

Multivariate analyses were performed after adjustment for each covariate including maternal age, parity, pre-pregnancy body mass index, pregnancy weight gain, assisted reproductive technology, smoking during pregnancy, and duration of education. Results were reported as odds ratios and 95% CI, with maternal birth weight of 2,500–3,499 g as the reference group. OR, odds ratio; CI, confidence interval.

Supplementary Table 1. Baseline characteristics of women with and without complete data.

Variable	With complete data (n = 17,119)	Without complete data (n = 26,534)	*p*-value
Maternal characteristics			
Maternal own birth weight (g)	3,086 ± 441	3,100 ± 481	0.71
Maternal age (years)	30.8 ± 4.7	30.9 ± 4.7	<0.05
Gestational age at delivery (weeks)	39.6 ± 1.1	39.6 ± 1.1	<0.05
Cesarean section	2,753/17,112 (16.1)	4,454/25,978 (17.1)	<0.05
Primipara	9,237/17,119 (54.0)	13,244/26,534 (49.9)	<0.05
Pre-pregnancy BMI (kg/m^2)	20.8 ± 3.0	20.9 ± 3.0	<0.05
Pregnancy weight gain (kg)	10.5 ± 3.6	10.7 ± 3.7	<0.05
Assisted reproductive technology	972/15,534 (6.3)	997/12,966 (7.7)	<0.05
Smoking during pregnancy	183/16,937 (1.1)	372/14,862 (2.5)	<0.05
Alcohol consumption during pregnancy	53/16,887 (0.3)	74/14,654 (0.5)	<0.05
Duration of education (years)			<0.05
<9 years	235/12,079 (1.9)	392/10,084 (3.9)	
9–12 years	2,980/12,079 (24.7)	3,122/10,084 (31.0)	
13–15 years	3,934/12,079 (32.6)	3,137/10,084 (31.1)	
≥16 years	4,930/12,079 (40.8)	3,433/10,084 (34.0)	
Hypertensive disorders of pregnancy	698/17,119 (4.1)	1,227/23,870 (5.1)	
Preeclampsia	207/16,628 (1.2)	416/23,839 (1.7)	
Neonatal characteristics			
Male	8,763/17,115 (51.2)	13,467/26,533 (50.8)	0.37
Birth weight (g)	3,086 ± 364	3,079 ± 364	0.05
Height (cm)	49.8 ± 1.7	49.7 ± 1.8	<0.05
Light-for-dates infants	1,168/17,107 (6.8)	1,809/26,484 (6.8)	1.00
Appropriate-for-dates infants	14,005/17,107 (81.9)	21,755/26,484 (82.1)	0.46
Heavy-for-dates infants	1,934/17,107 (11.3)	2,920/26,484 (11.0)	0.37

BMI, body mass index. Data are presented as mean ± standard deviation or n (%).