Gestational weight gain mediates the effects of energy intake on birth weight among singleton pregnancies in the Japan Environment and Children’s Study

Marina Minami¹, Naw Awn J-P¹, Shuhei Noguchi¹, Masamitsu Eitoku¹*, Sifa Marie Joelle Muchanga¹, Naomi Mitsuda¹, Kaori Komori¹, Kahoko Yasumitsu-Lovell¹, Nagamasa Maeda², Mikiya Fujieda³, Narufumi Suganuma¹ and the Japan Environment and Children’s Study (JECS) Group

Abstract

Background: Extra energy intake is commonly recommended for pregnant women to support fetal growth. However, relevant data regarding variations in energy intake and expenditure, body mass index and gestational weight gain (GWG) are frequently not considered. This study aimed to investigate how energy intake during pregnancy and gestational weight gain (GWG) are associated with birth weight.

Methods: Early pregnant women were recruited into a Japanese nationwide prospective birth cohort study between 2011 and 2014. We analysed data of 89,817 mother-child pairs of live-born non-anomalous singletons after excluding births before 28 weeks or after 42 weeks. Energy intake during pregnancy was estimated from self-administered food frequency questionnaires (FFQ) and was stratified into low, medium, and high. Participants completed the FFQ in mid-pregnancy (mean 27.9 weeks) by recalling food consumption at the beginning of pregnancy. Effects of energy intake on birth weight and mediation by GWG were estimated using the Karlson–Holm–Breen method; the method separates the impact of confounding in the comparison of conditional and unconditional parameter estimates in nonlinear probability models. Relative risks and risk differences for abnormal birth size were calculated.

Results: Mean daily energy intake, GWG, and birth weight were 1682.1 (533.6) kcal, 10.3 (4.0) kg, and 3032.3 (401.4) g, respectively. 6767 and 9010 women had small-for-gestational-age and large-for-gestational-age infants, respectively. Relative to low energy intake, moderate and high intakes increased adjusted birth weights by 13 g and 24 g, respectively: 58 and 69% of these effects, respectively, were mediated by GWG. Compared with the moderate energy intake group, the low energy intake group had seven more women per 1000 women with a small-for-gestational-age birth, whereas the high energy intake group had eight more women per 1000 women with a large-for-gestational-age birth.

Conclusion: GWG mediates the effect of energy intake on birth weight. All pregnant women should be given adequate nutritional guidance for optimal GWG and fetal growth.

*Correspondence: meitoku@kochi-u.ac.jp

¹ Department of Environmental Medicine, Kochi Medical School, Kochi University, Nankoku, Kochi 783-8505, Japan

Full list of author information is available at the end of the article

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Background

Fetal growth and birth weight are determined by a complex interaction among several maternal, pregnancy-related, and fetal-related factors. Extreme prepregnancy body mass indexes (BMIs), insufficient or excessive gestational weight gain (GWG), imbalanced nutrition, alcohol consumption and smoking, maternal diabetes and hypertension, multiple pregnancies, and preterm birth have all been associated with abnormal size of newborns [1–5].

Appropriate GWG has been investigated based on pre-pregnancy BMI, and several organisations have proposed GWG guidelines [6, 7] for pregnant women to lower their risk of giving birth to newborns of abnormal size or birth weight. Similarly, the energy requirements for pregnant women have been investigated based on their pre-pregnancy BMI and stage of pregnancy [8, 9]. Findings indicated that additional energy is needed during pregnancy to support fetal growth, the incremental increases in the sizes of the maternal tissues, and changes in maternal energy metabolism. Thus, recommendations have been published [10, 11] for the intake of extra energy to meet the increased demand, depending on pre-pregnancy body weight and the intensity of physical activity. However, the relationship between maternal energy intake and fetal growth is unclear. Some investigators [12–14] found no associations between energy intake and fetal growth and birth weight. However, they do document positive associations between GWG and maternal energy intake and birth weight. Awareness of gaining weight may influence the food consumption of a pregnant woman and hence the newborn birth weight [15]; however, it is more likely that energy consumed during pregnancy is deposited in the maternal and fetal tissues and perceived as GWG [8, 9]. Thus, it is plausible that the effects of energy intake on fetal growth and birth weight may be mediated by GWG, which has not been investigated previously.

Therefore, the present study aimed to investigate how energy intake during pregnancy and GWG are associated with birth weight and distinguish between the direct association of energy intake and indirect association mediated by GWG. Furthermore, we aimed to evaluate how different levels of energy intake affect birth size (determined by weight for gestational age at birth) in a cohort of singleton pregnancies from the Japan Environment and Children’s Study (JECS) [16].

Methods

Study participants

The JECS aims to explore environmental factors that affect the health and development of children and is being by the Environment, Japan. The detailed methodology and baseline profile of the study participants have been reported previously [16, 17]. Briefly, approximately 100,000 early pregnant women who live in 15 designated Study Areas across Japan were recruited between January 2011 and March 2014. They will be followed until the participating children reach 13 years of age. Participants were considered eligible if they met the following criteria: (1) they resided in a Study Area at the time of recruitment and were expected to reside continually in Japan, (2) they were expected to give birth after August 1, 2011, and (3) they were capable of understanding the Japanese language and completing a self-administered questionnaire.

This study uses the jecs-ag-20,160,424 dataset (released in June 2016) from the JECS, which comprises information from 104,102 fetal records. Therefore, formal sample size calculation was not performed in the present study. We restricted this study to 97,182 pregnancies resulting in live singleton births with no major birth defects. Then, we excluded participants based on predetermined exclusion criteria related to our exposure and outcome variables (Fig. 1): births before 28 weeks or after 42 weeks; missing or implausible daily energy intake (we used commonly applied values of < 500 or > 3500 kcal/day to define implausible daily energy intake [18, 19]); missing birth weight; implausible data on GWG (i.e. body weight recorded instead of GWG); and missing parity or newborn sex.

Exposure and outcome assessment

Nutritional information during pregnancy was obtained via a validated food frequency questionnaire (FFQ) [20, 21]. The FFQ was administered twice during pregnancy. The first time was in the first trimester to investigate the pre-pregnancy food frequency. The second FFQ conducted in mid-pregnancy (after week 22) was used in this study. The participants completed the FFQ by recalling their food consumption at the beginning of pregnancy (i.e., the point at which they realised that they were pregnant) and recording the quantity of each food item and the frequency with which it was consumed. Frequency categories ranged from ‘almost never’ to ‘7 or more times per day’ (or ‘10 glasses per day’ for beverages). Daily

Keywords: Birth weight, Energy intake, Fetal development, Gestational weight gain, Pregnancy, Small for gestational age
total energy intake was estimated using a food composition table that was developed based on the Standardised Tables of Food Composition in Japan (2010 edition) [22].

Anthropometric measurements of newborns, including birth weight (in grams) and gestational age at birth (in weeks), were extracted from medical records transcripts. Gestational age was calculated from the first day of the last menstrual period or by using ultrasound examinations of the fetus during the first trimester. Birth size was defined as small-for-gestational-age (SGA), appropriate-for-gestational-age (AGA), and large-for-gestational-age (LGA) for birth weights below the 10th percentile, 10th to 90th percentile, or above the 90th percentile, respectively, according to the Japanese parity and sex-specific neonatal birth weight chart for gestational age at birth [23].

**Mediator and other covariates**

Demographic, medical condition, and pregnancy-related data were collected through self-administered standard questionnaires or from medical records. GWG (mediator variable) was calculated by subtracting the self-reported pre-pregnancy body weight from the last measured weight closest to childbirth. Pre-pregnancy BMI was calculated by dividing the self-reported pre-pregnancy body weight (in kilograms) by the square of the height (in metres). The following information was also obtained: socioeconomic and lifestyle information, such as education, alcohol consumption, and smoking; occupation during pregnancy; physical activity levels (metabolic equivalent of a task measured as minutes per day) [24]; medical history of chronic diseases (diabetes, hypertension, heart disease, and kidney disease); nausea and vomiting during pregnancy; and receipt of health guidance.

**Statistical analysis**

Daily energy intake during pregnancy was stratified into three levels (low, moderate, and high) comprising approximately equal numbers of participants. The tertiles were the 33.4 and 67.9 percentiles, corresponding to the energy intake values of 1412 kcal and 1856 kcal, respectively. GWG was analysed as a continuous variable. Birth weight was studied as a continuous variable and birth size in categories (SGA, AGA, and LGA). Pre-pregnancy BMI was stratified as ‘underweight’ (<18.5 kg/m²), ‘normal weight’ (18.5–24.9 kg/m²), and ‘overweight and obese’ (≥25 kg/m²). Because the Japanese physique is small and underweight by global standards, the Ministry of Health, Labour and Welfare (MHLW) has provided a guideline for pregnancy weight gain, calculated from the Japanese average and by pre-pregnancy BMI category. The participants were grouped into ‘low’,
The participants were categorised into three age groups: ≤25, 26–35, and ≥36 years. Maternal educational attainment was stratified into three groups: ‘high school or less’, ‘vocational school/college’, and ‘university or higher education’. Considering that activity level may vary across job types, occupation during pregnancy was categorised as ‘unemployed’ (including students and women not classifiable by occupation), ‘low physical job’ (e.g. managers, engineers, and clerks), ‘moderate physical job’ (e.g. sales, services, and security workers), and ‘high physical job’ (e.g. manufacturing process workers, farmers, construction workers, carrying workers, and cleaners). Physical activity during pregnancy was grouped into three levels (low, moderate, and high) with approximately equal numbers of participants in each group. Other variables, such as alcohol consumption and smoking during pregnancy, chronic diseases, nausea and vomiting during pregnancy, and receipt of health guidance, were dichotomised as present (yes) or absent (no). Non-smoking and non-drinking women also included those who quit before or after they realised that they were pregnant.

Descriptive statistics of the participants were calculated for the entire study population and according to the levels of energy intake. The mean and standard deviation for continuous variables and numbers and percentages for categorical variables are reported. Since our primary aim was to examine how energy intake during pregnancy and GWG are associated with birth weight, we performed a mediation analysis. Figure 2 illustrates the conceptual framework of our study. We assumed energy intake preceding GWG in our analyses. The following points were the reasons for this assumption. First, the participants completed the FFQ by recalling their food consumption from conception (although FFQ was administered during mid-pregnancy). Second, the rate of weight gain is slower in the first trimester compared to the second or third [27] (although we used the total GWG). We compared the coefficients of the exposure (energy intake during pregnancy) derived from models with and without the mediator (GWG) (Fig. 2a) by employing the Karlson–Holm–Breen method using a linear regression model [28]. The Karlson–Holm–Breen method allowed, in a single command, the separation of the total effect of energy intake (c) into direct (ć) and indirect effects mediated by GWG (c – ć) while controlling for potential confounding variables. Based on the literature [1–5, 29, 30] and considering the causal relationship with exposure and outcome variables (Fig. 2b), the following factors were considered potential confounders and controlled for in the mediation analysis: maternal age (years), parity, educational level, pre-pregnancy BMI (kg/m²), type of occupation and physical activity level during pregnancy, alcohol consumption and smoking during pregnancy, the presence of chronic diseases, receipt of health guidance, and nausea and vomiting during pregnancy. To increase the precision of the estimates, newborn sex and gestational age (weeks) were also adjusted. Next, we evaluated the associations between levels of energy intake (moderate energy intake as the referent) and birth size using a multinomial logistic regression model. The crude and adjusted relative risk ratios (RRR), adjusted risk differences, and corresponding 95% confidence intervals (CIs) for SGA and LGA births were reported. The same factors included in the mediation analysis, except newborn sex and gestational age, were included in the adjusted model. Additionally, we examined the characteristics of the women according to their inclusion status in our analysis. All statistical analyses were performed using Stata/MP version 15.1 (StataCorp., College Station, TX, USA). Statistical significance was defined as a two-sided P-value < 0.05.

Ethics statement
This study was conducted according to the principles expressed in the Declaration of Helsinki. All procedures involving human participants were approved by the Japan Ministry of the Environment’s Institutional Review Board on Epidemiological Studies (No. 100910001) and the Ethics Committees of all participating institutions. Written informed consent was obtained from all participants.

Results
Of the 97,182 eligible pregnancies reviewed, 7365 were excluded because they met the predetermined exclusion criteria. Thus, 89,817 (92.4%) mother-child pairs of live-born non-anomalous singletons remained for analyses (Fig. 1). The mean (standard deviation) that participants completed FFQ was 27.9 (6.5) weeks. The mean birth weight in the low, moderate, and high energy intake groups and in the entire study population were 3016 (402.9) g, 3034.7 (399.6) g, 3046.4 (401.1) g, and 3032.3 (401.4) g, respectively. Of the 89,817 women assessed, 6767 (7.5%) and 9010 (10.0%) gave birth to SGA and LGA infants, respectively. The proportions of SGA births were...
8.1, 7.4, and 7.2%, and those of LGA births were 9.7, 9.8, and 10.6%, respectively, in the low, moderate, and high energy intake groups.

Table 1 reports descriptive statistics of participants according to the levels of energy intake. Younger, nulliparous women who did not exceed high school, and women who had extreme pre-pregnancy BMIs, reported less activity, and gained less weight during pregnancy were more prevalent in the low energy intake group than in the other groups. In contrast, parous women who reported being active during pregnancy and gained greater weight were more frequent in the high energy intake group.

Table 2 presents the estimated linear regression coefficients for the association between energy intake during pregnancy and birth weight and the portion of the associations mediated by GWG. It shows that, relative to the low energy intake group, mean birth weights were increased by 13.43 g and 23.76 g in the moderate and high energy intake groups, respectively. The results also show that GWG mediated a significant portion of the effect of energy intake on birth weight; the proportion mediated by GWG was 58.4 and 68.5% in the moderate

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**Table 1** Descriptive statistics of participants according to the levels of energy intake.

**Table 2** Estimated linear regression coefficients for the association between energy intake during pregnancy and birth weight and the portion of the associations mediated by GWG.

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**Fig. 2** Schematic illustration of the conceptual framework. a Direct and indirect effects of energy intake during pregnancy on birth weight. b Directed acyclic graph for the association between energy intake during pregnancy and birth weight. The dotted lines represent the research question and the solid lines the covariates adjusted for.
| Participant (Number) | Energy intake level<sup>a</sup> | All (89,817) | Low (30,035) | Moderate (30,914) | High (28,868) |
|----------------------|--------------------------------|-------------|--------------|------------------|---------------|
|                      | Mean (SD)                      |             |              |                  |               |
| Energy intake, kcal/d|                                | 1682.1(536.6)| 1144.9(200.2)| 1623.3(126.5)    | 2304.1(382.5) |
| Maternal age, year   |                                | 31.2(5.0)   | 30.6(5.2)    | 31.4(4.9)        | 31.6(4.9)     |
| Pre-pregnancy BMI, kg/m<sup>2</sup> |                         | 21.2(3.3)   | 21.3(3.4)    | 21.2(3.2)       | 21.3(3.3)     |
| GWG, kg              |                                | 10.3(4.0)   | 10.0(4.1)    | 10.3(3.9)        | 10.6(4.0)     |
| Gestational age, weeks |                              | 38.9(1.4)   | 38.9(1.4)    | 38.9(1.4)        | 38.8(1.4)     |
| Birth weigh          |                                | 3032.3(401.4)| 3016.1(402.9)| 3034.7(399.6)    | 3046.4(401.1) |
|                      | Number (%)                     |             |              |                  |               |
| Maternal age         |                                |             |              |                  |               |
| Up to 25 years       |                                | 11,952(13.3)| 5103(17.0)   | 3650(11.8)       | 3199(11.1)    |
| 26–35 years          |                                | 58,970(65.7)| 19,237(64.1)| 20,643(66.8)     | 19,090(66.1)  |
| 36 or more years     |                                | 18,892(21.0)| 5694(19.0)   | 6619(21.4)       | 6579(22.8)    |
| Missing              |                                | 3           | 1            | 2                | 0             |
| Pre-pregnancy BMI, kg/m<sup>2</sup> |                         |             |              |                  |               |
| Underweight, < 18.5  |                                | 14,451(16.1)| 5006(16.7)   | 5006(16.2)       | 4439(15.4)    |
| Normal weight, 18.5–24.9 |                        | 65,772(73.2)| 21,609(72.0)| 22,829(73.9)     | 21,334(73.9)  |
| Overweight and obese, ≥25 |                          | 9551(10.6)  | 3400(11.3)   | 3074(9.9)        | 3077(10.7)    |
| Missing              |                                | 43(0.1)     | 20(0.1)      | 5(0.0)           | 18(0.1)       |
| GWG<sup>b</sup>      |                                |             |              |                  |               |
| Low                  |                                | 15,917(17.7)| 5942(19.8)   | 5471(17.7)       | 4504(15.6)    |
| Appropriate          |                                | 41,932(46.7)| 13,958(46.5)| 14,631(47.3)     | 13,343(46.2)  |
| High                 |                                | 30,238(33.7)| 9566(31.9)   | 10,162(32.9)     | 10,510(36.4)  |
| Missing              |                                | 1730(1.9)   | 569(1.9)     | 650(2.1)         | 511(1.8)      |
| Parity               |                                |             |              |                  |               |
| Nullipara            |                                | 36,240(40.4)| 14,055(46.8)| 12,334(39.9)     | 9851(34.1)    |
| Multipara            |                                | 53,577(59.7)| 15,980(53.2)| 18,580(60.1)     | 19,017(65.9)  |
| Educational level    |                                |             |              |                  |               |
| High school or less  |                                | 32,419(36.1)| 12,225(40.7)| 10,396(33.6)     | 9798(33.9)    |
| Vocational school/College |                       | 37,680(42.0)| 12,015(40.0)| 13,099(42.4)     | 12,566(43.5)  |
| University or higher |                                | 19,395(21.6)| 5668(18.9)   | 7311(23.7)       | 6416(22.2)    |
| Missing              |                                | 323(0.4)    | 127(0.4)     | 108(0.4)         | 88(0.3)       |
| Occupation during pregnancy<sup>c</sup> |                  |             |              |                  |               |
| Non-employed         |                                | 29,422(32.8)| 9461(31.5)   | 10,290(33.3)     | 9671(33.5)    |
| Low physical job     |                                | 33,884(37.7)| 11,021(36.7)| 12,065(39.0)     | 10,798(37.4)  |
| Moderate physical job |                                | 18,254(20.3)| 6608(22.0)   | 5855(18.9)       | 5791(20.1)    |
| High physical job    |                                | 3971(4.4)   | 1500(5.0)    | 1313(4.3)        | 1158(4.0)     |
| Missing              |                                | 4286(4.8)   | 1445(4.8)    | 1391(4.5)        | 1450(5.0)     |
| Physical activity level (MET-min/d) |             |             |              |                  |               |
| Low                  |                                | 30,351(33.8)| 10,704(35.6)| 10,507(34.0)     | 9140(31.7)    |
| Moderate             |                                | 27,981(31.2)| 9362(31.2)   | 9970(32.3)       | 8649(30.0)    |
| High                 |                                | 27,312(30.4)| 8547(28.5)   | 9089(29.4)       | 9676(33.5)    |
| Missing              |                                | 4173(4.7)   | 1422(4.7)    | 1348(4.4)        | 1403(4.9)     |
| Smoking during pregnancy |                               |             |              |                  |               |
| Yes                  |                                | 4052(4.5)   | 1549(5.2)    | 1184(3.8)        | 1319(4.6)     |
| No                   |                                | 85,049(94.7)| 28,217(94.0)| 29,508(95.5)     | 27,324(94.7)  |
| Missing              |                                | 716(0.8)    | 269(0.9)     | 222(0.7)         | 225(0.8)      |
and high energy intake groups, respectively. Table 3 presents relative risk ratios and risk differences for SGA and LGA births. Compared with the moderate energy intake group, the risk of SGA birth was significantly higher in the low energy intake group (adjusted RRR: 1.12, 95% CI: 1.04–1.19), whereas the risk of LGA birth was significantly higher in the high energy intake group (adjusted RRR: 1.09, 95% CI: 1.03–1.16). It also shows that, compared with the moderate energy intake group, the low energy intake group had seven more women per 1000 women with an SGA birth, whereas the high energy intake group had eight more women per 1000 women with an LGA birth. Table 4 shows the characteristics of women according to their inclusion status in the analyses. The included and excluded groups largely resembled each other; however, the excluded group had a higher proportion of younger women, those who did not exceed high school, and those who engaged in a job that required moderate physical activity. A higher proportion of the excluded women gained more weight than recommended but had a higher proportion of SGA births than that for the included women.

**Discussion**

The relationship between maternal energy intake and birth weight is often overlooked because it is mediated by GWG. In this Japanese cohort of non-anomalous singleton pregnancies, energy intake during pregnancy was positively associated with birth weight. Specifically, we observed absolute mean birth weight increases of 19 g and 30 g when moving from low energy intake to moderate and high energy intakes, respectively. This association persisted after adjusting for pre-pregnancy BMI, smoking during pregnancy, gestational age, and other established confounding factors. Notably, a significant portion of the association was mediated by GWG. Previous studies [12–14] have not investigated this relationship, and GWG may have obscured the associations between energy intake and fetal growth and birth weight in those studies. Moreover, the characteristics of participants and the method of handling energy intake values may partly explain the differences in findings between studies. Factors such as pre- and peri-conceptional nutritional status of participating women, different dietary patterns and energy composition, and the exclusion or inclusion
of preterm births into the study might determine the observed association between maternal energy intake and birth weight. Measuring energy intake as ordinal categories, as done in this study, allows effects that would have been smaller and not obvious on continuous measurement to be captured. Mediation analysis showed that GWG mediated a significant portion of the associations between energy intake and birth weight. This mediating role of GWG can be understood from the biological relationships between GWG and energy intake and birth weight. Energy intake during pregnancy is deposited in maternal and fetal tissues and is recognised as GWG [8, 9]. A GWG of 12.5 kg, for example, equates to approximately 0.9 kg of protein, 3.8 kg of fat, and 7.8 kg of water [8], and is a reflection of fetal weight together with the incremental increases in the sizes of the maternal tissues and volumes of amniotic fluid and blood [9].

During pregnancy, energy intake in both extremes increases the risk of abnormal fetal size. In our cohort, when compared with the moderate energy intake group, the low intake group had seven more women per 1000 women with an SGA birth, whereas the high intake group had eight more women per 1000 women with an LGA birth. We observed that, compared with the moderate energy intake group, the mean daily energy intakes in the low and high intake groups were 478 kcal lower and 681 kcal higher, respectively. One could argue that this difference is clinically significant. Pre- and peri-conception nutritional statuses influence the development of the placenta and mechanisms for balancing energy

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**Table 2** Estimated linear regression coefficients for the associations between energy intake during pregnancy and birth weight, and for the effects mediated by GWG

| Energy intake level | Birth weight | 95% CI |
|--------------------|--------------|--------|
| **Low**            | Coefficients * | 95% CI |
| Total effect       | 13.43        | 7.99–18.86 |
| Direct effect      | 5.59         | 0.15–11.02 |
| Indirect effect    | 7.84         | 5.92–9.76 |
| Proportion mediated by GWG | 58.4% | |
| **Moderate**       |               |        |
| Total effect       | 23.76        | 18.20–29.32 |
| Direct effect      | 7.50         | 1.92–12.38 |
| Indirect effect    | 16.27        | 14.31–18.23 |
| Proportion mediated by GWG | 68.5% | |
| **High**           |               |        |
| Total effect       | 23.76        | 18.20–29.32 |
| Direct effect      | 7.50         | 1.92–12.38 |
| Indirect effect    | 16.27        | 14.31–18.23 |

CI: confidence interval, GWG: gestational weight gain

Mediation analysis was performed by employing the Karlson–Holm–Breen method using a linear regression model. The model was adjusted for maternal age, parity, pre-pregnancy body mass index, educational level, type of occupation during pregnancy, physical activity level during pregnancy, alcohol consumption and smoking during pregnancy, nausea and vomiting during pregnancy, presence of chronic disease, receipt of health guidance, female sex, and gestational age (weeks)

* Regression coefficients can be interpreted as, for example, mean birth weight was increased by 13.43 g when moving from low to moderate energy intake

| Energy intake level | Birth weight | 95% CI |
|--------------------|--------------|--------|
| **Low**            | Coefficients * | 95% CI |
| Total effect       | 13.43        | 7.99–18.86 |
| Direct effect      | 5.59         | 0.15–11.02 |
| Indirect effect    | 7.84         | 5.92–9.76 |
| Proportion mediated by GWG | 58.4% | |
| **Moderate**       |               |        |
| Total effect       | 23.76        | 18.20–29.32 |
| Direct effect      | 7.50         | 1.92–12.38 |
| Indirect effect    | 16.27        | 14.31–18.23 |
| Proportion mediated by GWG | 68.5% | |
| **High**           |               |        |
| Total effect       | 23.76        | 18.20–29.32 |
| Direct effect      | 7.50         | 1.92–12.38 |
| Indirect effect    | 16.27        | 14.31–18.23 |

CI: confidence interval

Mediation analysis was performed by employing the Karlson–Holm–Breen method using a linear regression model. The model was adjusted for maternal age, parity, pre-pregnancy body mass index, educational level, type of occupation during pregnancy, physical activity level during pregnancy, alcohol consumption and smoking during pregnancy, nausea and vomiting during pregnancy, presence of chronic disease, receipt of health guidance, female sex, and gestational age (weeks)

* Regression coefficients can be interpreted as, for example, mean birth weight was increased by 13.43 g when moving from low to moderate energy intake

**Table 3** Relative risk ratios (RRR) and risk differences (RD) for abnormal birth sizes according to the level of energy intake during pregnancy

| Cases, n (%) | RRR 95% CI | RRR 95% CI | 95% CI | RD 95% CI | 95% CI |
|--------------|------------|------------|--------|-----------|--------|
| **Small-for-gestational age** | | | | | |
| Energy intake level | | | | | |
| Low | 2428 (8.1) | 1.11 | 1.04–1.18 | 1.12 | 1.04–1.19 | 0.007 | 0.003–0.012 |
| Moderate | 2272 (7.4) | Ref. | Ref. | Ref. | Ref. | Ref. | |
| High | 2064 (7.2) | 0.98 | 0.92–1.04 | 1.00 | 0.93–1.07 | −0.001 | −0.005–0.004 |
| **Large-for-gestational age** | | | | | |
| Energy intake level | | | | | |
| Low | 2908 (9.7) | 0.99 | 0.94–1.05 | 0.97 | 0.91–1.02 | −0.004 | −0.009–0.001 |
| Moderate | 3041 (9.8) | Ref. | Ref. | Ref. | Ref. | Ref. | |
| High | 3061 (10.6) | 1.09 | 1.03–1.14 | 1.09 | 1.03–1.16 | 0.008 | 0.003–0.013 |

CI: confidence interval

Multinomial logistic regression models were used to estimate the relative risk ratios and risk differences

* Adjusted for maternal age, parity, pre-pregnancy body mass index, educational level, type of occupation during pregnancy, physical activity level during pregnancy, alcohol consumption and smoking during pregnancy, nausea and vomiting during pregnancy, presence of chronic disease, and receipt of health guidance

* Risk difference can be interpreted as, for example, when compared to moderate energy intake, low energy intake had 7 more women per 1000 women with an SGA birth
Table 4  Participants’ characteristics according to inclusion status in the current study

|                              | Eligible | Included | Excluded |
|------------------------------|----------|----------|----------|
| **Total, Number (%)**        | 97,182   | 89,817(92.4) | 7365(7.6) |
| **Maternal age, year**       |          |          |          |
| Up to 25 years               | 13,146(13.8) | 11,952(13.3) | 1464(19.9) |
| 26–35 years                  | 63,497(65.3) | 58,970(65.7) | 4527(61.5) |
| 36 or more years             | 20,264(20.9) | 18,892(21.0) | 1071(13.6) |
| **Pre-pregnancy BMI, kg/m²** |          |          |          |
| Underweight, < 18.5          | 15,680(16.2) | 14,451(16.1) | 1229(16.9) |
| Normal weight, 18.5–24.9     | 70,990(73.1) | 65,772(73.3) | 5218(71.7) |
| Overweight and obese, ≥25    | 10,387(10.7) | 9551(10.6) | 8366(11.5) |
| **GWG**                      |          |          |          |
| Low                          | 17,246(18.2) | 15,917(18.1) | 1329(19.1) |
| Appropriate                  | 44,904(47.3) | 41,932(47.6) | 2972(42.8) |
| High                         | 32,887(34.6) | 30,238(34.3) | 2649(38.1) |
| **Educational level**        |          |          |          |
| High school or less          | 34,503(36.4) | 32,419(36.2) | 2084(30.6) |
| Vocational school/College    | 39,886(42.0) | 37,680(42.1) | 2206(40.8) |
| University or higher         | 20,509(21.6) | 19,395(21.7) | 1114(20.6) |
| **Occupation during pregnancy** |        |          |          |
| Non-employed                 | 31,192(34.1) | 29,422(34.4) | 1770(29.4) |
| Low physical job             | 36,271(39.6) | 33,884(39.6) | 2387(39.6) |
| Moderate physical job        | 19,862(21.7) | 18,254(21.3) | 1608(26.7) |
| High physical job            | 4232(4.6) | 3971(4.6) | 261(4.3) |
| **Smoking during pregnancy** |          |          |          |
| Yes                          | 4302(4.6) | 4052(4.6) | 310(5.6) |
| No                           | 90,285(95.4) | 85,049(95.5) | 5236(94.4) |
| **Drinking alcohol during pregnancy** |    |          |          |
| Yes                          | 2672(2.8) | 2521(2.8) | 151(2.8) |
| No                           | 91,982(97.2) | 86,679(97.2) | 5303(97.2) |
| **Chronic diseases**         |          |          |          |
| Yes                          | 2678(2.8) | 2453(2.8) | 225(3.2) |
| No                           | 92,702(97.2) | 85,858(97.2) | 6845(96.8) |
| **Newborn weight for age**   |          |          |          |
| SGA                          | 7471(7.7) | 6767(7.5) | 704(9.6) |
| AGA                          | 79,958(82.3) | 74,040(82.4) | 5918(80.5) |
| LGA                          | 9744(10.0) | 9010(10.0) | 734(10.0) |

AGA appropriate-for-gestational-age, BMI body mass index, GWG gestational weight gain, LGA large-for-gestational-age, SD standard deviation, SGA small-for-gestational-age

* Note that the numbers in the columns do not add up to total numbers

GWG was stratified by applying the appropriate GWG ranges of 9 to 12 kg, 7 to 12 kg, and 5 to 7 kg for underweight, normal-weight, and overweight pregnant women, respectively

Categorised as ‘unemployed’ including students and women not classifiable by occupation, ‘low physical job’ (e.g. managers, engineers, and clerks), ‘moderate physical job’ (e.g. manufacturing process workers, farmers, construction workers, carrying workers, and cleaners) and ‘high physical job’ (e.g. sales, services, and security workers), and ‘high physical job’ (e.g. manufacturing process workers, farmers, construction workers, carrying workers, and cleaners).
We suggest that sufficient antenatal education and nutritional guidance be offered to all pregnant women. This promotes an individualised approach to ensuring optimal nutrition and an appropriate GWG, thus better pregnancy and birth outcomes.

Our findings are likely limited to Japanese women, and they may not be directly transferable to other populations around the world, which have much higher rates of pre-pregnancy overweight, obesity, and excessive weight gain. The association between energy intake and birth weight may actually be higher in other populations.

The main strengths of this study include the large sample size, which broadly represents pregnant women in Japan; the prospective design; the comprehensive information about maternal diet; and the wide range of potential confounding factors with small missingness. Since the energy expenditure of pregnant women may influence daily energy intake, fetal growth, and birth weight, we adjusted for physical activity level and occupation during pregnancy (occupational groups stratified by levels of physical activity) in our analysis.

This study also has some limitations. For example, 16% of our cohort was underweight; thus, the findings of this study may not be generalisable to the entire obstetric population. Furthermore, our analysis relied solely on dietary information collected at a single time point during pregnancy. Dietary intake could have changed according to the stage of pregnancy. Considering the various dietary changes, including those caused by the occurrence of nausea and vomiting during pregnancy, evaluating the diet at only one point does not give us a complete dietary assessment across the entire pregnancy. However, a previous study [13] reported no significant changes in dietary intake throughout pregnancy in Japanese women. Also, the energy intake estimated using FFQs may not reflect the actual intake [42, 43]. It is also undeniable that some pregnant women may have under-reported their FFQ responses. Nevertheless, the FFQ is a validated tool for grouping pregnant women according to high and low energy intake at the population level [43], and the present study analysed energy intake as ordinal categories. Moreover, we defined GWG as the last measured weight closest to birth minus the self-reported prepregnancy weight. Generally, self-reported weights are susceptible to underestimation, which may influence the calculated GWG. Furthermore, we defined birth size using the neonatal birth weight chart for the Japanese; thus, finding different percentages using other population charts is possible. Finally, there was a probable exclusion of women with less favourable pregnancy and birth outcomes, resulting in a possible underestimation of the risks.

Conclusions
There is a discrepancy between studies investigating the effects of maternal energy intake on fetal growth and birth weight. The reasons could be the heterogeneity in the study cohorts and analytical methods employed. We found a positive association between energy intake during pregnancy and birth weight in a Japanese cohort of non-anomalous singleton pregnancies, where GWG mediated a significant portion of the association. Because both extremes in energy intake during pregnancy increase the risk of abnormal birth size, we suggest that nutritional guidance be offered to all pregnant women to ensure appropriate nutrition for optimal GWG and fetal growth.

Abbreviations
AGA: Appropriate-for-gestational-age; BMI: Body mass index; FFQ: Food frequency questionnaires; GWG: Gestational weight gain; LGA: Large-for-gestational-age; OR: Odds ratio; SGA: Small-for-gestational-age.

Acknowledgments
The authors are grateful to all the participants in the study. We thank all staff members of the JECS. 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. Members of the JECS Group as of 2021: Michihiro Kamijima (principal investigator; Nagoya City University, Nagoya, Japan), Shin Yamasaki (National Institute for Environmental Studies, Tsukuba, Japan), Yukihiro Ohya (National Center for Child Health and Development, Tokyo, Japan), Reko Kishi (Pikikkado 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 Is (Osaka University, Suita, Japan), Masayuki Shima (Hyogo College of Medicine, Nishinomiya, Japan), Youchi 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). We also acknowledge all members of the Environmental Medicine Department of Kochi University for their support.

Authors’ contributions
MM, NAJ-P, and NS designed the study; MM, ME, N Mitsuda, KK, KYL, N Maeda, MF, NS and the Japan Environment and Children’s Study collected the data; MM, SN, NAJ-P, ME, SJMJ, and NS analyzed the data; MM, NAJ-P, and NS contributed to the writing of the manuscript. All authors have read and approved the final manuscript.

Funding
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.

Availability of data and materials
Data are unsuitable for public deposition because of ethical considerations and restrictions as per legal framework of Japan. It is prohibited by the Act on the Protection of Personal Information (Act No. 57 of 30 May 2003, amended on 9 September 2015) to publicly deposit data containing personal information. Ethical Guidelines for Medical and Health Research Involving Human Subjects, enforced by the Japan Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare, also restricts the open sharing of epidemiologic data. All inquiries about access to data should be addressed Dr. Shoji F. Nakayama, JECS Programme Office, National Institute for Environmental Studies, at jeecs-en@nies.go.jp.
Declarations

Ethics approval and consent to participate
The JECs protocol was approved by the Institutional Review Board on Epidemiological Studies of the Ministry of the Environment and by the ethics committees of all the participating institutions, i.e., the National Institute for Environmental Studies, the National Center for Child Health and Development, Hokkaido University, Sapporo Medical University, Ashikawa Medical College University, Japanese Red Cross Hokkaido College of Nursing, Tohoku University, Fukushima Medical University, Chiba University, Yokohama City University, University of Yamanashi, Shinshu University, University of Toyama, Nagoya City University, Kyoto University, Doshisha University, Osaka University, Osaka Medical Center and Research Institute for Maternal and Child Health, Hyogo College of Medicine, Tottori University, Kochi University, University of Occupational and Environmental University, Kyushu University, Kumamoto University, University of Miyazaki, and University of the Ryukyus. The JECs was conducted in accordance with the Declaration of Helsinki and other nationally valid regulations. Written informed consent was obtained from all participating mothers.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Author details
1. Department of Environmental Medicine, Kochi Medical School, Kochi University, Nankoku, Kochi, Japan.
2. Department of Obstetrics and Gynecology, Kochi Medical School, Kochi University, Nankoku, Kochi, Japan.
3. Department of Pediatrics, Kochi Medical School, Kochi University, Nankoku, Kochi, Japan.
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