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Association of blood mercury levels during pregnancy with infant birth size by blood selenium levels in the Japan Environment and Children's Study: A prospective birth cohort

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ABSTRACT

Background: It is necessary to determine whether there are adverse health effects of prenatal exposure to long-term, low levels of mercury and selenium. However, there are limited that reports on the association between mercury levels by selenium levels and birth size. Therefore, we examined whether maternal mercury levels during pregnancy had any effect on infant birth size, and size, and whether selenium levels influenced this relationship.

Objectives: To examine the association between mercury and selenium levels during pregnancy with infant birth size.

Methods: The Japan Environment and Children's Study is a prospective birth cohort conducted between 2011 and 2014. Total mercury levels and total selenium levels in maternal blood during the second and third trimesters were measured using Inductively Coupled Plasma-Mass Spectrometry. Birth weight and small-for-gestational-age were confirmed by medical records. Small-for-gestational-age was defined as birth weight below the 10th percentile according to standard percentile for gender, parity, and gestational age. Multiple linear and logistic regression analyses were used to examine the association between maternal mercury exposure and birth weight or small-for-gestational-age adjusted for confounders (including maternal age and body mass index pregnancy).

Results: Overall, 15,444 pregnant women were included in this study. Median (inter-quartile range) of blood mercury and selenium levels were 3.66 (2.59–5.18) ng/g and 170.0 (158.0–183.0) ng/g, respectively. Compared to infants of mothers with the highest blood selenium level, those of mothers with the lowest blood selenium level had neither a significant birth weight increase (9 g, 95% confidence interval: −6, 25) nor a significant odds ratio for small-for-gestational-age (0.903, 95% confidence interval: 0.748, 1.089). Compared to infants of mothers with the lowest blood mercury level, those of mothers with the highest blood mercury level had neither a significant birth weight reduction (−12 g, 95% confidence interval: −27, 4) nor a significant odds ratio for small-for-gestational-age (0.951, 95% confidence interval: 0.786, 1.150). Compared to infants of mothers with the lowest quartile of maternal blood mercury level, all infants of mothers with the highest quartile of maternal

Abbreviations: BMI, body mass index; CI, confidence interval; DHA, docosahexanoic acid; DOHaD, Developmental Origins of Health and Diseases; HUFA, highly unsaturated fatty acid; JECS, The Japan Environment and Children's Study; JPY, Japanese yen; MBML, maternal blood mercury level; MBSL, maternal blood selenium level; MeHg, methylmercury; NMDA, *N*-methyl-D-aspartate; NO, nitric oxide; NOS, nitric oxide synthase; OR, odds ratio; SD, standard deviation

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blood mercury level had a reduced birth head circumference of 0.073 cm (95% confidence interval: −0.134, −0.011).

Conclusions: There was no association between maternal blood mercury levels and small-for-gestational-age and birth weight among 15,444 pregnant women. In a Japanese population, which has a relatively higher blood mercury level than reported in Western population, reduced birth size was not found to be associated with blood mercury levels, with the exception of birth head circumference.

1. Introduction

The hypothesis of "Developmental Origins of Health and Diseases (DOHaD)", which has been suggested to clarify the mechanisms of childhood growth and development, describes the association between a slow fetal growth and the development of chronic diseases such as coronary disease and diabetes mellitus in adulthood (Barker et al., 2005; Bhargava et al., 2004; Eriksson et al., 2003; Phillips, 1996; Swanson et al., 2009). Slow fetal growth is an overall term that includes small-for-gestational-age, birth weight, birth length, birth head circumference, birth chest circumference, and birth Ponderal index. It is necessary to elucidate the maternal-child and environmental health risk factor of slow fetal growth, one of which may be fetal mercury exposure.

In Japan, approximately 80%–90% of human mercury exposure is derived from fish consumption (Ministry of Agriculture, Forestry and Fisheries, Japan, 2008). Inorganic mercury which is converted to methylmercury (MeHg) by bacterial methylation, is well-absorbed in the alimentary tract (Ikingura and Akagi, 1999; Ward et al., 2010). Fish and other seafood are the main source of MeHg exposure (Clémens et al., 2011). One of the risk factors for adverse outcomes in children's growth is MeHg intake during pregnancy (Foldspang and Hansen, 1990), and even relatively low mercury levels in maternal blood can possibly lead to adverse effects for fetuses. In a recent study, Murcia et al. (2016) reported that a 2-fold increase of total mercury in cord blood (geometric mean 8.2 μg/L) was associated with 0.052-cm reduction of birth head circumference, which is an important indicator of brain development. Birth weight is another indicator of fetal bodily functions. Recently, Murcia et al. (2016) reported that a 2-fold increase of total mercury in cord blood (geometric mean 8.2 μg/L) was associated with 35.8-g reduction of birth weight in Valencia, Spain. Tatsuta et al. (2017) reported that total mercury in cord blood (median 10.1 ng/g) was not associated with birth weight among all infants. Miyashita et al. (2015) reported that an increase of mercury in hair (median 1.41 μg/g) was associated with reduced risk of small-for-gestational-age in adjustment for n − 3 unsaturated fatty acids. However, there are also reports that low mercury levels did not affect birth weight, as well as reports of a negative association between low mercury levels and birth weight. Therefore, no firm conclusion has been drawn.

An association between mercury and selenium has also been reported. Selenium is known co-exist with MeHg in fish (Kaneko and Ralston, 2007), and mercury and selenium levels show a positive association in seafood in Japan (Yamashita et al., 2013). Both mercury and selenium have a high degree of maternal-fetal transfer (Chen et al., 2014). Selenium is a component of antioxidative enzymes that play a role in protecting the organism from oxidative stress (Tapiero et al., 2003). Previously, the selenium intake of the Japanese population was estimated as approximately 100 μg/day (Yoshida, 1992). The main sources of dietary selenium in Japan are fish, shellfish, rice, vegetable, and egg (Miyazaki et al., 2004). Selenium is an essential nutrient, but intake levels remain deficient areas in some areas of the world. In China, the association between selenium levels during pregnancy and infant birth weight was found to be not significant (maternal blood median 140.8 ng/g) (Hu et al., 2015). In contract, a positive association was found between selenium levels at 12 weeks of pregnancy and increased risk of preterm birth (maternal blood serum mean 1.01 μmol/L [79.8 μg/L calculated for atomic weight as 78.971]) (Rayman et al., 2011; Chemical Society of Japan, 2015).

Regarding biological mechanism of mercury and selenium, MeHg has been shown to increase glutamate release and inhibits glutamate transport into the spinal cord and cerebral cortical astrocytes in mouse and rats (Albrecht et al., 1993; Aschner et al., 1993; Aschner et al., 2000; Brookes and Kristt, 1989). Stimulation of the ionotropic *N*-methyl-D-aspartate (NMDA) receptors via glutamate by MeHg has been proposed as one possible neurotoxic mechanism of mercury (Yamashita et al., 1997). Overestimation of NMDA receptors induced by MeHg could produce an activation nitric oxide synthase (NOS) and the production of nitric oxide (NO), which could lead to neuronal death (Himi et al., 1996). In chickens, selenium supplementation during the ingestion of dietary cadmium reduced the production of NO, activity of NOS, and apoptosis in the immune organs (Liu et al., 2014). We predict the biological mechanism that the MeHg induces NO-mediated and NOS-mediated apoptosis of neuronal cells, while selenium provides protective effects against MeHg-mediated cell apoptosis. However, although an imbalance between mercury and selenium may affect birth size, this has not yet been validated in a prospective cohort study of the large sample size.

There are a few epidemiological studies reporting an association between both mercury and selenium and adverse health outcomes (He et al., 2013; Park et al., 2013; Wells et al., 2016; Xun et al., 2011). Among these, one study in the United States reported that the association of MeHg with birth weight and Ponderal index was affected by omega-3 highly unsaturated fatty acids, selenium, and inorganic mercury (Wells et al., 2016). However, there is no report on the association between both mercury and selenium levels with infant birth size in Japan. The study by Wells et al. (2016) was performed using a cross-sectional study design, which is susceptible to both drop-out and selection bias and has an unclear causal-relationship between exposure and outcome. Moreover, Japanese pregnant women form a unique study population, due to Japan's culture, fish-based cuisine, and relatively low levels of mercury during pregnancy. Prospective cohort studies are less susceptible to drop-out and selection bias. Therefore, a prospective birth cohort study to determine the association between mercury and selenium levels during pregnancy and birth outcomes in Japanese women is needed.

The Japan Environment and Children's Study (JECS) is an ongoing prospective birth cohort study in Japan that recruited approximately 100,000 pregnant women between January 2011 and March 2014 (Kawamoto et al., 2014). The primary objective of JECS is to investigate relationships between exposure to chemical and children's health and development of infants and children. Using JECS data, the aims of present study are (i) to estimate the association between maternal blood mercury levels during the second and third trimester and infant birth size (primary outcomes: birth weight and small-for-gestational-age; secondary outcomes: birth length, birth head circumference, birth chest circumference, and birth Ponderal index), and (ii) to determine whether selenium levels in the maternal blood modify the association between maternal blood mercury levels and infant birth size.

2. Material and methods

2.1. Participants

The JECS protocol has been published elsewhere as described by

Kawamoto et al. (2014). In brief, fifteen regional centers were selected for their wide geographical distribution in Japan. The women were recruited in early pregnancy at the obstetric facilities and/or at local government offices issuing pregnancy journals (mother-child health handbooks in Japan). Recruitment duration was between January 2011 and March 2014. The present study is based on the datasets of both jecs-ag-20160424 (released in April 2016; dataset of basic information on characteristics and outcome until birth) and jecs-mtl-ai-20170403 (released in April 2017; dataset of mercury and selenium levels in maternal blood from the second and third trimester of pregnancy). Blood mercury and selenium levels were measured in samples from 20,000 mothers randomly selected from 96,095 mothers who provided blood during the second or third trimester. Of 20,000 measurements, 17,998 samples met quality control criteria. After excluding mothers with stillbirth, miscarriage, twins or more, and one or more missing data on the followings (live-birth/miscarriage/stillbirth, singleton/twins or more, age, body mass index before pregnancy, parity, smoking during pregnancy, drinking during pregnancy, education level, annual household income, birth weight, birth length, birth head circumference, birth head circumference, birth chest circumference, small-for-gestational-age, and vaginal delivery/cesarean section), a total of 15,444 mothers were finally included (Fig. 1). The JECS protocol was approved by the Ministry of the Environment's Institutional Review Board on Epidemiological Studies and by the Ethics Committees of all participating institutions (Appendix 1). Written informed consent was obtained from all participating women in accordance with the Declaration of Helsinki. The Ethical Guidelines for Epidemiological Research were followed.

2.2. Measurement of heavy metals

A 33-mL blood sample was taken from peripheral veins during the second and third trimesters (mean [± standard deviation (SD)] gestational age of blood sampling: 27.0 [± 3.1] weeks of gestation). All samples were stored at −80 °C until analysis. Human blood samples (0.2 mL) were mixed with 3.8 mL mixed solution of 2% v/v butan-1-ol, 0.1% tetramethylammonium hydroxide, 0.05% w/v polyoxyethylene-octylphenylether, and 0.05% w/v ethylenediaminetetraacetate. We measured the total mercury (Hg) and selenium (Se) levels using Agilent

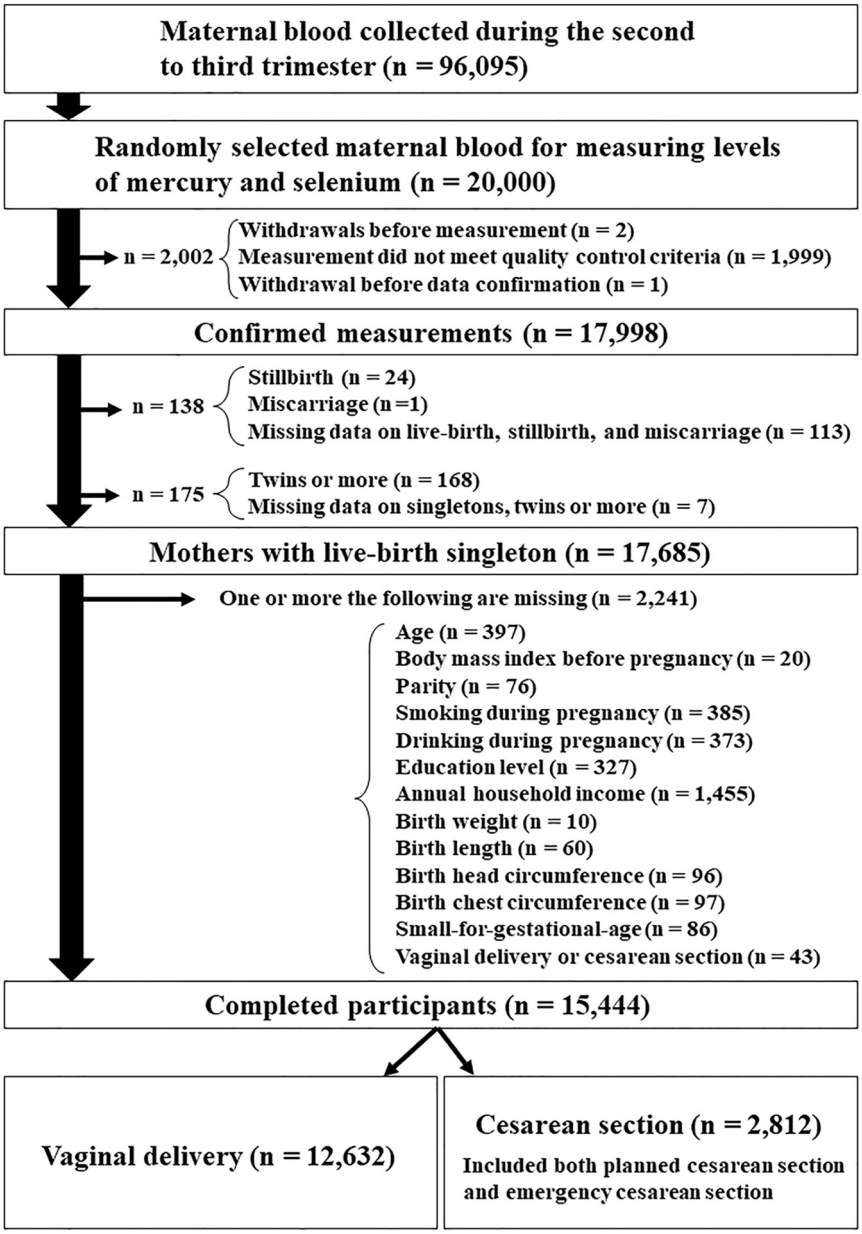

Fig. 1. Flow chart of study participants.

7700 Inductively Coupled Plasma-Mass Spectrometry (ICP-MS) with auto-sampler (Agilent Technologies, Tokyo, Japan) in random sampled 20,000 participants. In the quality control, we chose 1000 random samples to be equal to 5% of 20,000 samples. The mercury and selenium levels in these 1000 random samples were re-measured in another analysis laboratory. When a difference in the blood mercury or selenium level between the first measured blood level and the second measured blood level was < 30%, we used the first measured blood mercury or selenium level. However, if we confirmed a difference in the blood mercury or selenium level between first and second measurement that was > 30%, we did not use the all data on the measured batch including the sample of > 30% difference in the level between them. Method detection limits of mercury and selenium were 0.049 ng/g and 0.84 ng/g, respectively. Method quantitation limits of mercury and selenium were 0.13 ng/g and 2.2 ng/g, respectively. As the density of the mixture with a solution of 2% v/v butan-1-ol, 0.1% tetramethylammonium hydroxide, 0.05% w/v polyoxyethylene-octylphenylether, 0.05% w/v ethylenediaminetetraacetate, and a human blood sample is 0.999 g/mL, the unit of ng/g is almost equal to the unit of μg/L.

2.3. Questionnaires and medical record transcription

Participants completed the self-administered questionnaires during the second and third trimesters (M-T2 questionnaire). Details of the M-T2 questionnaire were described previously (Michikawa et al., 2015). In brief, the M-T2 questionnaire included information related to smoking and drinking status during pregnancy, education levels, and annual household incomes. Transcriptions of medical records of physicians, midwives, and nurses were made twice (Dr-T1 questionnaire obtained from medical record at recruitment and Dr-0m questionnaire obtained from medical record at birth). Details of Dr-T1 and Dr-0m questionnaires were described previously (Michikawa et al., 2015). In brief, the Dr-T1 questionnaire included information related to maternal age, pre-pregnancy height and weight; while the Dr-0m questionnaire included information related to infant weight at birth, length at birth, head circumference at birth, chest circumference at birth, parity, infant gender, gestational age, type of delivery. Maternal pre-pregnancy body mass index (BMI) was calculated as weight (kg)/pre-pregnancy height squared (m^2).

2.4. Definitions of birth weight, birth length, birth head circumference, birth chest circumference, small-for-gestational-age and birth Ponderal index

Birth weight (unit: g), birth length (unit: cm), birth head circumference (unit: cm), and birth chest circumference (unit: cm) were defined as infant weight at birth, infant length at birth, infant birth head circumference at birth, and infant chest circumference at birth, respectively, and were obtained from the Dr-0m questionnaire. Birth Ponderal index was defined as birth weight (g) divided by the cube of birth length (cm), and multiplied by 100 (unit: $g/cm^3 \times 100$). Small-for-gestational-age was defined as a birth weight below the 10th percentile according to standard percentile for gender, parity, and gestational age (Itabashi et al., 2010). Small-for-gestational-age measures were evaluated using Microsoft Excel-based clinical tools for growth evaluation of children among vaginal delivery according to the Japan Pediatric Society definition; these were created by The Japanese Society for Pediatric Endocrinology (2011). In the Japan Pediatric Society, a standard value of birth weight by gestational age was created by physical measurements excluding the factors affected by intrauterine growth. Therefore, the values were created for the factors, excluding those related to caesarean section, that have a strong influence on birth weight distribution by gestational age (Itabashi et al., 2010). For the above-mentioned reason, we evaluated the infants born by vaginal delivery according to the outcome of small-for-gestational-age, and we evaluated the participants of all and vaginal delivery according to the outcomes of birth weight, birth length, birth head circumference, birth chest circumference, and birth Ponderal index.

2.5. Statistical analysis

First, we summarized the background characteristics of all births, vaginal delivery births, and cesarean section births. Mean (± SD) was used for continuous variables and number with percentage was used for categorical variables. We also examined the distribution of maternal blood mercury levels (MBML) and maternal blood selenium levels (MBSL). All mothers (n = 15,444) were divided into MBML and MBSL quartiles. MBML and MBSL concentrations were divided into quartiles to allow us to clearly understand the results of the interaction between MBML, MBSL, and birth outcome. Additionally, due to a non-normal distribution of MBML, we prepared $\log_{10}$-transformed MBML. Second, the associations of the exposure levels on infant birth outcomes were examined using multiple logistic regression (for small-for-gestational-age) and multiple linear regression models (for birth weight, birth length, birth head circumference, birth chest circumference, and birth Ponderal index) among all delivery (vaginal delivery and cesarean section) and vaginal delivery only. The primary exposure variable was MBML. The secondary exposure variable was MBSL. When we examined the association between the primary exposure and outcomes, we considered the secondary exposure variable as a confounding factor. When we examined the association between the secondary exposure and outcomes, we consider the primary exposure variable as a confounding factor. The outcome variables of interest were primary and secondary outcomes. For the adjusted model, confounding factors adjusted for maternal age (< 25, 25 to 29, 30 to 34, and ≥ 35 years), pre-pregnancy BMI (< 18.5, 18.5 to 24.9, and ≤ 25.0 kg/m^2), parity (0, 1, and ≥ 2), smoking status during pregnancy (never smoked, ex-smokers who quit before pregnancy, and smoked during pregnancy), alcohol drinking status during pregnancy (never drank, ex-drinkers who quit before pregnancy, and drank during pregnancy), maternal education level (< 10, 10 to 12, 13 to 16, and ≥ 17 years of education), annual household income (< 2, 2 to < 4, 4 to < 6, 6 to < 8, 8 to < 10, and ≥ 10 million Japanese yen [JPY]), gestational age (continuous), infant gender (male/female), pregnancy-induced hypertension (yes/no), gestational diabetes mellitus (yes/no), and types of delivery (vaginal delivery/caesarean section). Spearman's rho between the smoking habit variable (assigned as never smoked = 1, ex-smokers who quit before pregnancy = 2, and smoked during pregnancy = 3) and the alcohol consumption variable (assigned as never drank = 1, ex-drinkers who quit before pregnancy = 2, and drank during pregnancy = 3) was 0.164. Spearman's rho between the parity variable (assigned as 0 = 0, 1 = 1, and ≥ 2 = 2) and the maternal age variable (assigned as < 25 years = 1, 25 to < 30 years = 2, 30 to < 35 years = 3, and ≥ 35 years = 4) was 0.201. Spearman's rho between the annual household income variable (assigned as < 2 million JPY = 1, 2 to < 4 million JPY = 2, 4 to < 6 million JPY = 3, 6 to < 8 million JPY = 4, 8 to < 10 million JPY = 5, and ≥ 10 million JPY = 6) and the education level (assigned as < 10 years = 1, 10 to < 13 years = 2, 13 to < 17 years = 3, and ≥ 17 years = 4) was 0.288. As the Spearman's rho varied between 0.164 and 0.288, the relationship between each variable was low. Therefore, smoking habit, alcohol consumption, parity, maternal age, annual household income, and education level remained the covariates. Since small-for-gestational-age was calculated separately by gender, parity, and gestational age, the four confounding factors were removed from the model. In addition, to evaluate whether MBSL modified the association between MBML and birth outcomes, we examined these associations according to the subgroup of each selenium level quartile. Interaction term was defined as blood mercury level (assigned as quartile 1 = 0, quartile 2 = 1, quartile 3 = 2, and quartile 4 = 3 or $\log_{10}$-transformed continuous level) × blood selenium level (assigned as quartile 4 = 0, quartile 3 = 1, quartile 2 = 2, and quartile 1 = 3). All analyses were conducted using SPSS version 23 for

Table 1
Maternal and infant characteristics.

Characteristics	All	Vaginal delivery	Cesarean section
	(n = 15,444)	(n = 12,632)	(n = 2812)
Infants			
Gender			
Male	7990 (51.7)	6552 (51.9)	1438 (51.1)
Female	7454 (48.3)	6080 (48.1)	1374 (48.9)
Birth weight (g)	3025.9 ± 405.3	3057.3 ± 379.6	2884.9 ± 480.4
Small-for-gestational-age	(−)	1009 (8.0)	(−)
Birth length (cm)	48.9 ± 2.2	49.1 ± 2.0	48.0 ± 2.7
Birth head circumference (cm)	33.2 ± 1.5	33.1 ± 1.4	33.4 ± 1.7
Birth chest circumference (cm)	31.8 ± 1.8	31.9 ± 1.6	31.4 ± 2.2
Ponderal index ($g/cm^3 \times 100$)	2.579 ± 0.259	2.575 ± 0.256	2.596 ± 0.271
Gestational age (weeks)	38.9 ± 1.5	39.1 ± 1.3	37.9 ± 1.8
Preterm birth (22 to < 37 weeks)	663 (4.4)	390 (3.1)	273 (9.7)
Full-term birth (37 to < 42 weeks)	14,743 (95.5)	12,221 (96.7)	2522 (89.7)
Post-term birth (≥42 weeks)	38 (0.2)	21 (0.2)	17 (0.6)
Mothers			
Age (years)	30.9 ± 4.9	30.6 ± 4.8	32.2 ± 5.0
< 25	1561 (10.1)	1368 (10.8)	193 (6.9)
25 to < 30	4646 (30.1)	3975 (31.5)	671 (23.9)
30 to < 35	5460 (35.4)	4516 (35.8)	944 (33.6)
≥35	3777 (24.5)	2773 (22.0)	1004 (35.7)
Body mass index before pregnancy (kg/m^2)	21.2 ± 3.3	21.1 ± 3.1	22.1 ± 3.9
< 18.5	2476 (16.0)	2142 (17.0)	334 (11.9)
18.5 to < 25.0	11,332 (73.4)	9323 (73.8)	2009 (71.4)
≥25.0	1636 (10.6)	1167 (9.2)	469 (16.7)
Parity			
0	6293 (40.7)	5131 (40.6)	1162 (41.3)
1	5939 (38.5)	4852 (38.4)	1087 (38.7)
≥2	3212 (20.8)	2649 (21.0)	563 (20.0)
Smoking habits			
Never smoked	8784 (56.9)	7259 (57.5)	1525 (54.2)
Ex-smokers who quit before pregnancy	3858 (25.0)	3121 (24.7)	737 (26.2)
Smoked during pregnancy	2802 (18.1)	2252 (17.8)	550 (19.6)
Alcohol consumption			
Never drank	5077 (32.9)	4184 (33.1)	893 (31.8)
Ex-drinkers who quit before pregnancy	2643 (17.1)	2133 (16.9)	510 (18.1)
Drank during pregnancy	7724 (50.0)	6315 (50.0)	1409 (50.1)
History of obstetrical/gynecological diseases			
Pregnancy-induced hypertension	519 (3.4)	296 (2.3)	223 (7.9)
Gestational diabetes mellitus	492 (3.2)	349 (2.8)	143 (5.1)
Education level (years)			
< 10	707 (4.6)	583 (4.6)	124 (4.4)
10 to < 13	4648 (30.1)	3796 (30.1)	852 (30.3)
13 to < 17	9864 (63.9)	8074 (63.9)	1790 (63.7)
≥17	252 (1.5)	179 (1.4)	46 (1.6)
Annual household income (million Japanese yen)			
< 2	854 (5.5)	696 (5.5)	158 (5.6)
2 to < 4	5485 (35.5)	4525 (35.8)	960 (34.1)
4 to < 6	5029 (32.6)	4108 (32.5)	921 (32.8)
6 to < 8	2396 (15.5)	1938 (15.3)	458 (16.3)
8 to < 10	1009 (6.5)	830 (6.6)	179 (6.4)
≥10	671 (4.3)	535 (4.2)	136 (4.8)
Type of vaginal delivery			
Natural delivery	(−)	8952 (70.9)	(−)
Induced labor	(−)	2837 (22.5)	(−)
Vacuum extraction	(−)	817 (6.5)	(−)
Forceps	(−)	26 (0.2)	(−)
Reason for both planned cesarean section and emergency cesarean section (multiple choice allowed)			
Repeat cesarean section	(−)	(−)	1213 (43.1)
Previous uterine surgery	(−)	(−)	69 (2.5)
Pregnancy-induced hypertension	(−)	(−)	139 (4.9)
Placenta previa	(−)	(−)	60 (2.1)
Non-reassuring fetal status	(−)	(−)	266 (9.5)
Malpresentation	(−)	(−)	372 (13.2)
Delayed delivery and arrested labor	(−)	(−)	227 (8.1)
Multiple conception	(−)	(−)	1 (0.0)
Premature rupture	(−)	(−)	158 (5.6)
Intrauterine infection	(−)	(−)	36 (1.3)
Cephalo-pelvic disproportion (CPD)	(−)	(−)	188 (6.7)
Over excepted date of delivery	(−)	(−)	43 (1.5)
Complications and others	(−)	(−)	471 (16.7)
Missing data	(−)	(−)	117 (4.2)

n (%) or mean ± standard deviation.

Windows (IBM Corp., Armonk, NY, US).

3. Results

Table 1 shows maternal and infant characteristics. Of 12,632 infants of mothers with vaginal delivery, 1009 (8.0%) were small-for-gestational-age infants. Infants of mothers with vaginal delivery had a larger birth weight than those of mothers with cesarean section (3057.3 ± 379.6 g and 2884.9 ± 480.4 g). Mothers with vaginal delivery had a lower mean age than those with cesarean section (30.6 ± 4.8 years and 32.2 ± 5.0 years). Among the vaginal delivery group, natural delivery was the highest type of delivery (70.9%). Repeat cesarean section was the most frequent reason for cesarean section (43.1%).

Table 2 presents the levels of MBML and MBSL. Median (interquartile range) of mercury and selenium were 3.66 (2.59–5.18) ng/g and 170.0 (158.0–183.0) ng/g, respectively.

Table 3 shows the association between MBML, MBSL, birth weight, and small-for-gestational-age. Among vaginal delivery, compared to the lowest quartile 1 (0.334 to < 2.59 ng/g) in MBML, the birth weight of infants of mothers with the highest quartile 4 (5.18 to 30.1 ng/g) was reduced by 10 g (95% confidence interval [CI]: −26, 7), with an odds ratio (OR) of 0.966 for small-for-gestational-age (95% CI: 0.798, 1.169). Compared to the highest quartile 4 (183.0 to 371.0 ng/g) in MBSL, infants of mothers with the lowest quartile 1 (99.9 to < 158.0 ng/g) had increased 11 g for birth weight (95% CI: −6, 28) and OR 0.904 for small-for-gestational-age (95% CI: 0.749, 1.092). Among vaginal delivery, one unit increase of $\log_{10}$-transformed MBML corresponded to a reduced −19 g of birth weight (95% CI: −44, 7) and OR 1.008 for small-for-gestational-age (95% CI: 0.750, 1.354) (Table A.1).

Table 4 presents the association between MBML and birth weight and small-for-gestational-age according to the subgroup analysis for quartiles of MBSL. Among infants of all mothers with the lowest quartile 1 (99.9 to < 158.0 ng/g) in MBSL, compared to the lowest quartile 1 (0.334 to < 2.59 ng/g) in MBML, infants of mothers with the highest quartile 4 (5.18 to 30.1 ng/g) had reduced 41 g for birth weight (95% CI: −75, −5). However, each *P* value for interaction between MBML and MBSL for birth weight and small-for-gestational-age was ≥0.05. Among infants of all mothers with the lowest quartile 1 (99.9 to < 158.0 ng/g) in MBSL, one unit increase of $\log_{10}$-transformed MBML corresponded to a reduced −67 g of birth weight (95% CI: −119, −16) (Table A.2).

Additionally, Table 5 shows the associations between MBML or MBSL and birth length, birth head circumference, birth chest circumference, and birth Ponderal index. Among all infants, compared to the lowest quartile 1 (0.334 to < 2.59 ng/g) in MBML, infants of mothers with the quartile 3 (3.66 to < 5.18 ng/g) had reduced 0.063 cm for birth head circumference (95% CI: −0.122, −0.003) and those of mothers with the highest quartile 4 (5.18 to 30.1 ng/g) had reduced 0.076 cm for birth head circumference (95% CI: −0.137, −0.014). One unit increase of $\log_{10}$-transformed MBML corresponded to a reduced −0.144 cm of birth head circumference (95% CI: −0.239, −0.048) (Table A.3). Among vaginal delivery, compared to the lowest quartile 1 (0.334 to < 2.59 ng/g) in MBML, infants of mothers with the quartile 3 (3.66 to < 5.18 ng/g) had reduced 0.067 cm for birth head circumference (95% CI: −0.132, −0.003) and those of mothers with the highest quartile 4 (5.18 to 30.1 ng/g) had reduced 0.076 cm for birth head circumference (95% CI: −0.147, −0.014). One unit increase of $\log_{10}$-transformed MBML corresponded to a reduced −0.141 cm of birth head circumference (95% CI: −0.244, −0.038) (Table A.3).

Table 6 shows the associations between MBML and birth length, birth head circumference, birth chest circumference, and birth Ponderal index according to the subgroup analysis for quartiles of MBSL. Among infants of all mothers with the lowest quartile 1 (99.9 to < 158.0 ng/g) in MBSL, compared to the lowest quartile 1 (0.334 to < 2.59 ng/g) in MBML, infants of mothers with the highest quartile 4 (5.18 to 30.1 ng/g) had reduced 0.156 cm for birth head circumference (95% CI: −0.294, −0.017). One unit increase of $\log_{10}$-transformed MBML corresponded to a reduced −0.317 cm of birth head circumference (95% CI: −0.520, −0.113) (Table A.4). Among infants born to mothers of vaginal delivery with the lowest quartile 1 (99.9 to < 158.0 ng/g) in MBSL, compared to the lowest quartile 1 (0.334 to < 2.59 ng/g) in MBML, infants of mothers with the quartile 3 (3.66 to < 5.18 ng/g) had reduced 0.140 cm for birth head circumference (95% CI: −0.262, −0.017). One unit increase of $\log_{10}$-transformed MBML had reduced −0.098 cm for birth head circumference (95% CI: −0.324, 0.129) (Table A.4). Each *P* value for interaction between MBML and MBSL for birth length, birth head circumference, birth chest circumference, and birth Ponderal index was ≥0.05.

4. Discussion

We found no association between MBML and birth weight and small-for-gestational-age among 15,444 pregnant Japanese women. In secondary outcomes, we determined an association between MBML and birth head circumference. Hence, the results of the present study suggest that the low levels of MBML in Japan's current environment might have no impact on not only infant birth weight and small-for-gestational-age but also birth length, birth chest circumference, and birth Ponderal index. However, there may be a slight impact on birth head circumference. A difference in birth head circumference of infants of mothers with both the highest MBML and the lowest MBSL levels compared to infants of mothers with both the lowest MBML and the lowest MBSL levels was about 16 mm. The clinical implication of this value is that it is possible that a fetus who was supposed to be born at −1.16 SD (12.3 percentiles) may be born as infants of less than 10th percentile at 37 weeks of gestation, according to the data on standard normal distribution of birth head circumference for gestational age in Japanese infants (Itabashi et al., 2010).

Previous studies found differences in not only exposure levels during pregnancy but also indicators such as total mercury, inorganic mercury, and methylmercury (Miyashita et al., 2015; Murcia et al., 2016; Obi et al., 2015; Ramón et al., 2009; Tatsuta et al., 2017; van Wijngaarden et al., 2014; Wells et al., 2016). As the exposure indicators of the previous papers were different, it was not possible to compare the association with the exposure levels in the present study.

When we assumed a blood specific gravity 1.05, MBML in this study were higher than those of pregnant women in Western countries (Golding et al., 2013; Mahaffey et al., 2004). In a report on total mercury and MeHg levels of maternal and/or cord blood among pregnant Japanese women, Tsuchiya et al. (1984) showed that the mean total mercury in maternal blood, mean MeHg in maternal blood, mean total

Table 2
Levels of mercury and selenium in maternal blood.

	Mean	Minimum	10 percentiles	25 percentiles	Median	75 percentiles	90 percentiles	Maximum
Mercury (ng/g)	4.21	0.334	1.87	2.59	3.66	5.18	7.17	30.1
Selenium (ng/g)	171.4	99.9	148.0	158.0	170.0	183.0	197.0	371.0

As the density of the mixture with a solution of 2% v/v butan-1-ol, 0.1% tetramethylammonium hydroxide, 0.05% w/v polyoxyethylene-octylphenylether, 0.05% w/v ethylenediaminetetraacetate, and a human blood sample is 0.999 g/mL, the unit of ng/g is almost equal to the unit of μg/L.

Table 3
Regression coefficient and odds ratio (95% confidence interval) between blood mercury levels, blood selenium levels, birth weight, and small-for-gestational-age.

Participants	Blood levels	Birth weight (g)[a]		Small-for-gestational-age[b]	
		n_{all}	β (95% CI)	n_{SGA}	β (95% CI)
All (n = 15,444)	Blood mercury levels (ng/g)				
	Quartile 1 (0.334 to < 2.59)	3848	Reference		
	Quartile 2 (2.59 to < 3.66)	3840	-6 (−21, 9)		
	Quartile 3 (3.66 to < 5.18)	3888	-11 (−26, 4)		
	Quartile 4 (5.18 to 30.1)	3868	−13 (−28, 3)		
	Blood selenium levels (ng/g)				
	Quartile 4 (183.0 to 371.0)	3928	Reference		
	Quartile 3 (170.0 to < 183.0)	3795	−3 (−18, 12)		
	Quartile 2 (158.0 to < 170.0)	3903	14 (−1, 29)		
	Quartile 1 (99.9 to < 158.0)	3818	9 (−6, 25)		
Vaginal delivery (n = 12,632)	Blood mercury levels (ng/g)				
	Quartile 1 (0.334 to < 2.59)	3190	Reference	264	Reference
	Quartile 2 (2.59 to < 3.66)	3174	−1 (−17, 15)	236	0.904 (0.751, 1.088)
	Quartile 3 (3.66 to < 5.18)	3144	−6 (−22, 10)	261	1.018 (0.847, 1.222)
	Quartile 4 (5.18 to 30.1)	3124	−10 (−26, 7)	248	0.966 (0.798, 1.169)
	Blood selenium levels (ng/g)				
	Quartile 4 (183.0 to 371.0)	3216	Reference	271	Reference
	Quartile 3 (170.0 to < 183.0)	3180	3 (−13, 19)	242	0.927 (0.772, 1.113)
	Quartile 2 (158.0 to < 170.0)	3079	12 (−4, 28)	250	0.930 (0.774, 1.117)
	Quartile 1 (99.9 to < 158.0)	3216	11 (−6, 28)	246	0.904 (0.749, 1.092)

β (95% CI) represents the change (95% confidence interval) in birth weight (g), in comparison with the reference group.
OR (95% CI) represents the odds ratio (95% confidence interval) for small-for-gestational-age, in comparison with the reference group.
As the density of the mixture with a solution of 2% v/v butan-1-ol, 0.1% tetramethylammonium hydroxide, 0.05% w/v polyoxyethylene-octylphenylether, 0.05% w/v ethylenediaminetetraacetate, and a human blood sample is 0.999 g/mL, the unit of ng/g is almost equal to the unit of μg/L.

[a] Multiple linear regression models are adjusted for maternal age, body mass index before pregnancy, parity, smoking during pregnancy, drinking during pregnancy, education level, annual household income, pregnancy-induced hypertension, gestational diabetes mellitus, vaginal delivery/cesarean section, infant gender, gestational age, mercury levels, and selenium levels.

[b] Logistic regression models are adjusted for maternal age, body mass index before pregnancy, smoking during pregnancy, drinking during pregnancy, education level, annual household income, pregnancy-induced hypertension, gestational diabetes mellitus, vaginal delivery/cesarean section, mercury levels, and selenium levels.

mercury in cord blood, and mean MeHg in cord blood were 19 ppb, 9 ppb, 30 ppb, and 14 ppb, respectively. Moreover, Sakamoto et al. (2007) showed that the mean total mercury in maternal blood, mean MeHg in maternal blood, mean total mercury in cord blood, mean MeHg in maternal blood, and mean total mercury in hair were 5.18 ng/g, 4.77 ng/g, 9.81 ng/g, 9.32 ng/g, and 1.624 μg/g, respectively. The cord blood levels of both total mercury and MeHg was 1.6 to 2.0 times higher than in that in the maternal blood of pregnant Japanese women. The mean MeHg percentages out of mean total mercury (MeHg/total mercury × 100) in cord blood and maternal blood were 92%–95% in the current study of pregnant Japanese women. From this fact, we consider that we can explain the association between MeHg and birth size from the results of the association between MBML and birth size in the present study.

In the previous studies, Tatsuta et al. (2017) examined the association between total mercury levels in whole cord blood (median: 10.1 ng/g) and birth weight in Tohoku region of Japan. They found that total mercury levels were not associated with a reduced birth weight among all infants (Tatsuta et al., 2017). In our previous study out of the JECS, Miyashita et al. (2015) examined the association between mercury levels in maternal hair (median: 1.41 μg/g) and small-for-gestational-age by birth weight in the Hokkaido region of Japan in that study, an increased mercury level was not associated with a reduced small-for-gestational-age. The MBML found in the present study is lower than the total mercury level reported by Sakamoto et al. (2007), Murcia et al. (2016), Tatsuta et al. (2017), and Miyashita et al. (2015). In Japan, mean intake of methylmercury remained roughly unchanged from 1994 to 2003 (8.4 μg/person/day) (Food Safety Communication Japan, 2004). Hence, both the results of these previous studies and the unchanged intake of methylmercury in Japan support the findings of the present study of a non-association between maternal mercury levels and a reduced birth weight and small-for-gestational-age.

Regarding association between both mercury and selenium and adverse health outcomes, Wells et al. (2016) used a cross-sectional study design to examine the association between MeHg levels in cord blood, selenium, omega-3 highly unsaturated fatty acids (n − 3 HUFAs), and to analyze their effects on birth size. They observed an interaction between MeHg and n − 3 HUFAs, and found that infants with high MeHg and n − 3 HUFAs had lower birth length and birth head circumference, and that selenium slight modified the association between MeHg levels and birth outcomes (Wells et al., 2016). And, methylmercury during pregnancy and HUFA were associated with birth weight (van Wijngaarden et al., 2014). The results of the present study on the association between mercury and birth head circumference were also observed in the participants that were adjusted for fish intake, monovalent saturated fatty acid, polyhydric saturated fatty acid, n − 3 HUFAs, and n-6 HUFAs (data not shown). A previous study reported that n − 3 HUFA docosahexanoic acid (DHA) strongly inhibited NO production and NOS expression in mice macrophages (Komatsu et al., 2003). Based on the biological mechanisms suggested in animal and cell experiments, it is possible that the same mechanism may apply to human fetal mercury, selenium, and DHA exposure in terms of their interactions and alleviation of neurocytotoxicity in Japanese fetuses. The results of the present study might suggest that, in pregnant Japanese women, the NO-mediated and NOS-mediated apoptosis of neuronal cells induced by MeHg may be greater than the protective effects of selenium and HUFA against MeHg-mediated cell apoptosis. We consider that a nutritionally balanced diet, including fish and shellfish, is necessary to prevent the adverse health effects of an association between prenatal mercury levels and birth size.

The strengths of this study were that: (1) the design was a prospective birth cohort study; (2) the cohort size of 15,444 pregnant women were larger than participants in previous study (Wells et al., 2016); and (3) the use of MBML during second and third trimesters of pregnancy provides important results because fourth to eighth months (second and third trimesters) of pregnancy is the critical window of

Table 4
Regression coefficient and odds ratio (95% confidence interval) between blood mercury levels and birth weight and small-for-gestational-age: subgroup analysis for quartiles of blood selenium levels.

Participants	Blood selenium levels (ng/g)	Blood mercury level (ng/g)	Birth weight (g)[a]		Small-for-gestational-age[b]	
			n_{all}	β (95% CI)	n_{SGA}	OR (95% CI)
All (n = 15,444)	Quartile 4 (183.0 to 371.0)	Quartile 1 (0.334 to < 2.59)	630	Reference		
		Quartile 2 (2.59 to < 3.66)	735	17 (−18, 52)		
		Quartile 3 (3.66 to < 5.18)	1017	8 (−25, 40)		
		Quartile 4 (5.18 to 30.1)	1546	11 (−20, 42)		
	Quartile 3 (170.0 to < 183.0)	Quartile 1 (0.334 to < 2.59)	800	Reference		
		Quartile 2 (2.59 to < 3.66)	938	−16 (−47, 15)		
		Quartile 3 (3.66 to < 5.18)	1009	−22 (−53, 8)		
		Quartile 4 (5.18 to 30.1)	1048	−26 (−57, 5)		
	Quartile 2 (158.0 to < 170.0)	Quartile 1 (0.334 to < 2.59)	995	Reference		
		Quartile 2 (2.59 to < 3.66)	1071	−6 (−35, 22)		
		Quartile 3 (3.66 to < 5.18)	1037	−11 (−40, 18)		
		Quartile 4 (5.18 to 30.1)	800	−3 (−34, 28)		
	Quartile 1 (99.9 to < 158.0)	Quartile 1 (0.334 to < 2.59)	1423	Reference		
		Quartile 2 (2.59 to < 3.66)	1096	−10 (−36, 16)		
		Quartile 3 (3.66 to < 5.18)	825	−12 (−41, 17)		
		Quartile 4 (5.18 to 30.1)	474	−41 (−75, −5)		
		Interaction term[c]		−1 (−3, 2)		
				P_{int} = 0.541		
Vaginal delivery (n = 12,632)	Quartile 4 (183.0 to 371.0)	Quartile 1 (0.334 to < 2.59)	520	Reference	52	Reference
		Quartile 2 (2.59 to < 3.66)	610	35 (−3, 72)	44	0.706 (0.462, 1.080)
		Quartile 3 (3.66 to < 5.18)	832	25 (−10, 60)	76	0.900 (0.617, 1.312)
		Quartile 4 (5.18 to 30.1)	1254	23 (−10, 56)	99	0.782 (0.546, 1.119)
	Quartile 3 (170.0 to < 183.0)	Quartile 1 (0.334 to < 2.59)	666	Reference	51	Reference
		Quartile 2 (2.59 to < 3.66)	752	−14 (−48, 20)	54	0.994 (0.664, 1.489)
		Quartile 3 (3.66 to < 5.18)	820	−18 (−51, 16)	66	1.161 (0.792, 1.713)
		Quartile 4 (5.18 to 30.1)	841	−30 (−64, 4)	71	1.283 (0.876, 1.892)
	Quartile 2 (158.0 to < 170.0)	Quartile 1 (0.334 to < 2.59)	817	Reference	66	Reference
		Quartile 2 (2.59 to < 3.66)	895	−1 (−33, 30)	73	0.979 (0.687, 1.394)
		Quartile 3 (3.66 to < 5.18)	827	−9 (−41, 23)	59	0.855 (0.588, 1.242)
		Quartile 4 (5.18 to 30.1)	641	−2 (−36, 33)	52	0.951 (0.642, 1.409)
	Quartile 1 (99.9 to < 158.0)	Quartile 1 (0.334 to < 2.59)	1187	Reference	95	Reference
		Quartile 2 (2.59 to < 3.66)	917	−10 (−38, 18)	65	0.904 (0.648, 1.260)
		Quartile 3 (3.66 to < 5.18)	665	−13 (−44, 19)	60	1.180 (0.837, 1.664)
		Quartile 4 (5.18 to 30.1)	388	−31 (−68, 7)	26	0.868 (0.548, 1.373)
		Interaction term[c]		−1 (−3, 2)		0.994 (0.966, 1.022)
				P_{int} = 0.593		P_{int} = 0.667

β (95% CI) represents the change (95% confidence interval) in birth weight (g), in comparison with the reference group.
OR (95% CI) represents the odds ratio (95% confidence interval) for small-for-gestational-age, in comparison with the reference group.
P_{int} represents the *P* value of the interaction term.
As the density of the mixture with a solution of 2% v/v butan-1-ol, 0.1% tetramethylammonium hydroxide, 0.05% w/v polyoxyethylene-octylphenylether, 0.05% w/v ethylenediaminetetraacetate, and a human blood sample is 0.999 g/mL, the unit of ng/g is almost equal to the unit of μg/L.

[a] Multiple linear regression models are adjusted for maternal age, body mass index before pregnancy, parity, smoking during pregnancy, drinking during pregnancy, education level, annual household income, pregnancy-induced hypertension, gestational diabetes mellitus, vaginal delivery/cesarean section, infant gender, and gestational age.

[b] Logistic regression models are adjusted for maternal age, body mass index before pregnancy, smoking during pregnancy, drinking during pregnancy, education level, annual household income, pregnancy-induced hypertension, gestational diabetes mellitus, and vaginal delivery/cesarean section.

[c] Interaction term is defined as blood mercury levels (assigned as quartile 1 = 0, quartile 2 = 1, quartile 3 = 2, and quartile 4 = 3) × blood selenium levels (assigned as quartile 4 = 0, quartile 3 = 1, quartile 2 = 2, and quartile 1 = 3).

maternal exposure to chemicals causing low birth weight (Selevan et al., 2000). However, there were also limitations of this study. First, potential selection bias might have occurred because this study was based on the data of a prospective birth cohort (of approximately 100,000 pregnant women) in 15 regional area in Japan. Second, among 17,998 pregnant women with available maternal mercury and selenium levels, we excluded 2554 pregnant women due to exclusion criteria or missing data on the confounding factors. This exclusion might decrease the statistical power of the present study. Third, we collected birth weight, birth length, birth head circumference, and birth chest circumference from medical records written by gynecologists. As this data was measured by many different Japanese gynecologists, anthropometric measurements might have systematic errors due to birth length, birth head and chest molding.

5. Conclusion

Our findings suggest that there are no associations between blood mercury level during pregnancy and birth size (birth weight and small-for-gestational-age) among Japanese pregnant women, although there was a slight impact on birth head circumference. In implications for practice, this study shows that blood mercury levels are not currently associated with reduced birth weight or increased risk of small-for-gestational-age in Japan.

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Table 5
Regression coefficient and odds ratio (95% confidence interval) between blood mercury levels, blood selenium levels, birth length, birth head circumference, birth chest circumference, and birth Ponderal index.

Participants	Blood levels	n_{all}	Birth length (cm)	Birth head circumference (cm)	Birth chest circumference (cm)	Birth Ponderal index ($g/cm^3 \times 100$)
			β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
All (n = 15,444)	Blood mercury levels (ng/g)					
	Quartile 1 (0.334 to < 2.59)	3848	Reference	Reference	Reference	Reference
	Quartile 2 (2.59 to < 3.66)	3840	−0.022 (−0.104, 0.060)	−0.018 (−0.077, 0.041)	−0.041 (−0.108, 0.027)	0.000 (−0.012, 0.011)
	Quartile 3 (3.66 to < 5.18)	3888	−0.033 (−0.116, 0.050)	−0.063 (−0.122, −0.003)	−0.049 (−0.116, 0.019)	−0.002 (−0.014, 0.010)
	Quartile 4 (5.18 to 30.1)	3868	−0.055 (−0.140, 0.031)	−0.076 (−0.137, −0.014)	−0.053 (−0.123, 0.017)	−0.002 (−0.014, 0.010)
	Blood selenium levels (ng/g)					
	Quartile 4 (183.0 to 371.0)	3928	Reference	Reference	Reference	Reference
	Quartile 3 (170.0 to < 183.0)	3795	−0.042 (−0.124, 0.040)	−0.014 (−0.072, 0.045)	−0.023 (−0.090, 0.044)	0.001 (−0.010, 0.013)
	Quartile 2 (158.0 to < 170.0)	3903	0.042 (−0.041, 0.124)	0.003 (−0.056, 0.063)	0.029 (−0.038, 0.097)	0.005 (−0.007, 0.017)
	Quartile 1 (99.9 to < 158.0)	3818	−0.007 (−0.092, 0.078)	−0.025 (−0.086, 0.036)	0.017 (−0.052, 0.086)	0.009 (−0.003, 0.021)
Vaginal delivery (n = 12,632)	Blood mercury levels (ng/g)					
	Quartile 1 (0.334 to < 2.59)	3190	Reference	Reference	Reference	Reference
	Quartile 2 (2.59 to < 3.66)	3174	−0.006 (−0.094, 0.090)	−0.029 (−0.092, 0.035)	−0.027 (−0.098, 0.045)	0.001 (−0.011, 0.014)
	Quartile 3 (3.66 to < 5.18)	3144	0.002 (−0.088, 0.077)	−0.067 (−0.132, −0.003)	−0.014 (−0.086, 0.059)	−0.002 (−0.015, 0.011)
	Quartile 4 (5.18 to 30.1)	3124	−0.026 (−0.118, 0.046)	−0.080 (−0.147, −0.014)	−0.034 (−0.109, 0.040)	−0.004 (−0.017, 0.009)
	Blood selenium levels (ng/g)					
	Quartile 4 (183.0 to 371.0)	3216	Reference	Reference	Reference	Reference
	Quartile 3 (170.0 to < 183.0)	3180	−0.007 (−0.095, 0.082)	0.041 (−0.023, 0.105)	0.016 (−0.056, 0.087)	0.003 (−0.010, 0.016)
	Quartile 2 (158.0 to < 170.0)	3079	0.030 (−0.059, 0.119)	0.003 (−0.061, 0.067)	0.015 (−0.057, 0.087)	0.004 (−0.008, 0.017)
	Quartile 1 (99.9 to < 158.0)	3216	0.013 (−0.078, 0.104)	0.014 (−0.052, 0.080)	0.029 (−0.045, 0.103)	0.009 (−0.004, 0.022)

Multiple linear regression models are adjusted for maternal age, body mass index before pregnancy, parity, smoking during pregnancy, drinking during pregnancy, education level, annual household income, pregnancy-induced hypertension, gestational diabetes mellitus, vaginal delivery/cesarean section, infant gender, gestational age, mercury levels, and selenium levels.
β (95% CI) represents the change (95% confidence interval) in birth length (cm), birth head circumference (cm), birth chest circumference (cm), and birth Ponderal index ($g/cm^3 \times 100$), in comparison with the reference group.
As the density of the mixture with a solution of 2% v/v butan-1-ol, 0.1% tetramethylammonium hydroxide, 0.05% w/v polyoxyethylene-octylphenylether, 0.05% w/v ethylenediaminetetraacetate, and a human blood sample is 0.999 g/mL, the unit of ng/g is almost equal to the unit of μg/L.

Table 6
Regression coefficient (95% confidence interval) between blood mercury levels and birth length, birth head circumference, birth chest circumference, and birth Ponderal index: subgroup analysis for quartiles of blood selenium level.

Participants	Blood selenium levels (ng/g)	Blood mercury levels (ng/g)	n_{all}	Birth length (cm)	Birth head circumference (cm)	Birth chest circumference (cm)	Birth Ponderal index (g/cm^3 × 100)
				β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
All (n = 15,444)	Quartile 4 (183.0 to 371.0)	Quartile 1 (0.334 to < 2.59)	630	Reference	Reference	Reference	Reference
		Quartile 2 (2.59 to < 3.66)	735	0.131 (−0.062, 0.324)	0.038 (−0.095, 0.172)	−0.025 (−0.184, 0.134)	−0.006 (−0.032, 0.020)
		Quartile 3 (3.66 to < 5.18)	1017	0.123 (−0.058, 0.304)	−0.034 (−0.159, 0.091)	−0.027 (−0.175, 0.122)	−0.015 (−0.040, 0.009)
		Quartile 4 (5.18 to 30.1)	1546	0.082 (−0.087, 0.252)	−0.075 (−0.192, 0.042)	−0.060 (−0.200, 0.079)	−0.006 (−0.029, 0.017)
	Quartile 3 (170.0 to < 183.0)	Quartile 1 (0.334 to < 2.59)	800	Reference	Reference	Reference	Reference
		Quartile 2 (2.59 to < 3.66)	938	−0.035 (−0.210, 0.140)	−0.015 (−0.139, 0.109)	−0.103 (−0.246, 0.040)	−0.006 (−0.030, 0.017)
		Quartile 3 (3.66 to < 5.18)	1009	−0.051 (−0.224, 0.122)	−0.005 (−0.127, 0.118)	−0.056 (−0.197, 0.085)	−0.011 (−0.034, 0.012)
		Quartile 4 (5.18 to 30.1)	1048	−0.090 (−0.263, 0.083)	−0.065 (−0.188, 0.058)	−0.080 (−0.222, 0.061)	−0.007 (−0.030, 0.017)
	Quartile 2 (158.0 to < 170.0)	Quartile 1 (0.334 to < 2.59)	995	Reference	Reference	Reference	Reference
		Quartile 2 (2.59 to < 3.66)	1071	−0.090 (−0.248, 0.067)	0.028 (−0.091, 0.147)	0.033 (−0.096, 0.163)	0.010 (−0.011, 0.031)
		Quartile 3 (3.66 to < 5.18)	1037	−0.061 (−0.221, 0.099)	−0.084 (−0.205, 0.036)	−0.039 (−0.170, 0.093)	−0.001 (−0.022, 0.020)
		Quartile 4 (5.18 to 30.1)	800	−0.033 (−0.205, 0.140)	0.015 (−0.116, 0.145)	0.010 (−0.132, 0.151)	0.004 (−0.019, 0.027)
	Quartile 1 (99.9 to < 158.0)	Quartile 1 (0.334 to < 2.59)	1423	Reference	Reference	Reference	Reference
		Quartile 2 (2.59 to < 3.66)	1096	−0.012 (−0.158, 0.135)	−0.080 (−0.184, 0.024)	−0.068 (−0.185, 0.049)	−0.006 (−0.029, 0.017)
		Quartile 3 (3.66 to < 5.18)	825	−0.101 (−0.261, 0.059)	−0.112 (−0.225, 0.002)	−0.081 (−0.209, 0.047)	0.017 (−0.008, 0.042)
		Quartile 4 (5.18 to 30.1)	474	−0.157 (−0.352, 0.038)	−0.156 (−0.294, −0.017)	−0.058 (−0.215, 0.098)	−0.012 (−0.042, 0.019)
		Interaction term[a]		−0.008 (−0.020, 0.005)	−0.009 (−0.018, 0.000)	−0.002 (−0.012, 0.008)	0.001 (−0.001, 0.003)
				P_{int} = 0.217	P_{int} = 0.055	P_{int} = 0.742	P_{int} = 0.311
Vaginal delivery (n = 12,632)	Quartile 4 (183.0 to 371.0)	Quartile 1 (0.334 to < 2.59)	520	Reference	Reference	Reference	Reference
		Quartile 2 (2.59 to < 3.66)	610	0.217 (0.010, 0.424)	0.076 (−0.067, 0.219)	0.070 (−0.098, 0.239)	−0.002 (−0.030, 0.025)
		Quartile 3 (3.66 to < 5.18)	832	0.261 (0.067, 0.456)	0.005 (−0.129, 0.140)	0.084 (−0.074, 0.243)	−0.020 (−0.046, 0.006)
		Quartile 4 (5.18 to 30.1)	1254	0.200 (0.018, 0.382)	−0.045 (−0.171, 0.081)	−0.007 (−0.156, 0.141)	−0.014 (−0.038, 0.011)
	Quartile 3 (170.0 to < 183.0)	Quartile 1 (0.334 to < 2.59)	666	Reference	Reference	Reference	Reference
		Quartile 2 (2.59 to < 3.66)	752	−0.009 (−0.195, 0.178)	−0.027 (−0.162, 0.107)	−0.141 (−0.293, 0.011)	−0.010 (−0.036, 0.015)
		Quartile 3 (3.66 to < 5.18)	820	−0.048 (−0.232, 0.135)	−0.014 (−0.146, 0.119)	−0.038 (−0.188, 0.112)	−0.007 (−0.032, 0.018)
		Quartile 4 (5.18 to 30.1)	841	−0.134 (−0.319, 0.050)	−0.068 (−0.201, 0.066)	−0.098 (−0.249, 0.053)	−0.006 (−0.031, 0.019)
	Quartile 2 (158.0 to < 170.0)	Quartile 1 (0.334 to < 2.59)	817	Reference	Reference	Reference	Reference
		Quartile 2 (2.59 to < 3.66)	895	−0.102 (−0.272, 0.068)	−0.011 (−0.140, 0.118)	0.046 (−0.093, 0.185)	0.015 (−0.007, 0.038)
		Quartile 3 (3.66 to < 5.18)	827	−0.009 (−0.183, 0.166)	−0.090 (−0.223, 0.043)	−0.012 (−0.155, 0.131)	−0.006 (−0.029, 0.017)
		Quartile 4 (5.18 to 30.1)	641	0.013 (−0.175, 0.202)	−0.023 (−0.166, 0.120)	−0.033 (−0.121, 0.187)	−0.004 (−0.029, 0.021)
	Quartile 1 (99.9 to < 158.0)	Quartile 1 (0.334 to < 2.59)	1187	Reference	Reference	Reference	Reference
		Quartile 2 (2.59 to < 3.66)	917	−0.023 (−0.180, 0.133)	−0.095 (−0.206, 0.016)	−0.067 (−0.191, 0.057)	−0.005 (−0.030, 0.021)
		Quartile 3 (3.66 to < 5.18)	665	−0.132 (−0.305, 0.041)	−0.140 (−0.262, −0.017)	−0.084 (−0.221, 0.053)	0.023 (−0.005, 0.052)
		Quartile 4 (5.18 to 30.1)	388	−0.148 (−0.359, 0.062)	−0.148 (−0.297, 0.001)	0.011 (−0.156, 0.178)	0.001 (−0.033, 0.036)
		Interaction term[a]		−0.007 (−0.021, 0.006)	−0.008 (−0.018, 0.001)	0.000 (−0.011, 0.011)	0.001 (−0.001, 0.003)
				P_{int} = 0.292	P_{int} = 0.097	P_{int} = 0.992	P_{int} = 0.290

Multiple linear regression models are adjusted for maternal age, body mass index before pregnancy, parity, smoking during pregnancy, drinking during pregnancy, education level, annual household income, pregnancy-induced hypertension, gestational diabetes mellitus, vaginal delivery/cesarean section, infant gender, and gestational age.
β (95% CI) represents the change (95% confidence interval) in birth length (cm), birth head circumference (cm), birth chest circumference (cm), and birth Ponderal index (g/cm^3 × 100), in comparison with the reference group.
P_{int} represents the *P* value of the interaction term.
As the density of the mixture with a solution of 2% v/v butan-1-ol, 0.1% tetramethylammonium hydroxide, 0.05% w/v polyoxyethylene-octylphenylether, 0.05% w/v ethylenediaminetetraacetate, and a human blood sample is 0.999 g/mL, the unit of ng/g is almost equal to the unit of μg/L.
[a] Interaction term is defined as blood mercury levels (assigned as quartile 1 = 0, quartile 2 = 1, quartile 3 = 2, and quartile 4 = 3) × blood selenium levels (assigned as quartile 4 = 0, quartile 3 = 1, quartile 2 = 2, and quartile 1 = 3).

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Declaration of competing financial interests (CFI)

The authors declare they have no actual or potential competing financial interest.

Appendix 1. Members of the Japan Environment and Children's Study (JECS) Group 2017

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Appendix 2. Supplementary data

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