

Association of prenatal maternal blood lead levels with birth outcomes in the Japan Environment and Children's Study (JECS): a nationwide birth cohort study

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Abstract

Background

Despite dramatic declines in prenatal maternal blood lead levels (BLLs) in most developed countries, little is known about the effects of extremely low-level ($<1.0 \mu\text{g/dL}$) lead exposure on fetal growth.

Methods

We measured maternal BLL during the second or third trimester of pregnancy and assessed birth outcomes, including birthweight, preterm birth (<37 gestational weeks) risk, small for gestational age births (SGA; birthweight $<$ tenth percentile), and low birthweight (LBW; $<2500\text{g}$). The association between birthweight and maternal BLL was estimated using linear and quadratic spline models. Multivariable logistic models were used to examine the risk of binary responses.

Results

Of 103,099 pregnant women, 20,000 blood samples were randomly selected for analysis.

The maternal BLL range was $0.16\text{--}7.4 \mu\text{g/dL}$, and the median was $0.63 \mu\text{g/dL}$. After adjusting for covariates, the linear model showed that each $0.1 \mu\text{g/dL}$ increase in maternal BLL was associated with a 5.4 g decrease in mean birthweight (95% confidence interval

[CI], 3.4 to 7.5 g). The risk of SGA (adjusted odds ratio [aOR], 1.03; 95% CI, 1.02 to 1.05) and LBW (aOR, 1.03; 95% CI, 1.02 to 1.05) increased, while the risk of preterm delivery did not (aOR, 0.99; 95% CI, 0.97 to 1.02).

Conclusions

Even at a maternal BLL below 1.0 µg/dL, prenatal lead exposure was associated with decreased birthweight and increased risk of SGA and LBW, but not preterm delivery. The adverse effect estimates of prenatal lead exposure on birth outcomes were quantitatively small and clinically limited at this low level.

Key words:

Maternal blood lead levels, low-level lead developmental effects, birthweight, fetal growth, Japan, nationwide birth cohort

Key Messages

- Prenatal lead exposure was associated with lower birthweight even at maternal blood lead levels below 1.0 µg/dL.
- The risk of small for gestational age at birth and low birthweight increased, but that of preterm delivery did not.
- The adverse developmental effects may be due to growth retardation, rather than shortened gestational duration.
- This study found evidence to support the hypothesis that fetal growth is restricted by lead exposure during the prenatal period. However, adverse effect estimates were quantitatively small and clinically limited at this low level.

Introduction

Lead is well-known as a ubiquitous neurotoxic environmental pollutant.^{1,2} The central nervous system is the main target of lead toxicity, and the developing brain of children is more susceptible to poisoning than the fully developed adult brain.³ Recent studies have evaluated the effects of chronic, low-level, prenatal lead exposure by focusing on reproductive adverse effects other than neurodevelopmental defects, such as fertility,⁴ spontaneous abortion,⁵ preterm birth,⁶ and anthropometric measures at birth.^{14-17,21-33}

At the beginning of the second trimester, lead in maternal blood can readily cross the placenta and enter the fetal blood circulation.^{7,8} All organ systems are therefore susceptible to lead exposure. Due to the similarities between lead (Pb^{2+}) and calcium (Ca^{2+}), lead-calcium interactions occur at the cellular level. By competing with calcium, lead inhibits all subtypes of calcium channels and disrupts second messenger functions.⁹ These interactions induce oxidative stress,¹⁰ which could cause placental dysfunction and impair nutrient transport to the fetus.¹¹ Additionally, lead is mainly stored in bone,¹² and may therefore impair fetal bone growth by altering bone cell function.¹³ This idea is supported by multiple epidemiological studies that have shown an association between prenatal lead exposure and lower birthweight.¹⁴⁻¹⁷

Banning lead additives and mixtures in gasoline and paint has dramatically reduced lead exposure in most developed countries.¹⁸ Currently, the most likely sources of lead exposure for pregnant women are ingestion of food that has been contaminated from contact with improperly glazed pottery or ceramic dishes and drinking water from leaded pipes.⁹ Although no safe and allowable fetal exposure level has been identified, the CDC recently reduced the level of concern for blood lead level (BLL) from 10 µg/dL to 5 µg/dL.¹⁹ According to the latest report, only 1% of childbearing-aged women in the US general population have a BLL greater than or equal to 5 µg/dL.²⁰

The great majority of people in developed countries are no longer exposed to the reference level (5 µg/dL) of environmental lead. Few epidemiological studies have estimated the relationship between birth outcomes and an average prenatal lead exposure of less than 5 µg/dL.²¹⁻³³ The results across studies are inconsistent and dose-response relationships have not been confirmed. The largest retrospective cohort study of 43,288 participants²⁵ showed a negative association between maternal whole blood lead levels and birthweight. In contrast, no associations have been observed in smaller cohort studies²⁸⁻³³ or a longitudinal cohort study.²⁴ Furthermore, little is known about the effects of extremely low levels (for example, less than 1.0 µg/dL),²⁶⁻³³ which are most commonly experienced in developed countries. In this study, we examined the relationship between

maternal BLL during the second or third trimester of pregnancy and 7 core birth outcomes (infant birthweight, head circumference, birth length, pregnancy duration, risk of SGA, LBW, and preterm delivery), with a focus on birthweight, using data from the Japan Environment and Children's Study (JECS).

Methods

Study cohort

The JECS is an ongoing, nationwide prospective birth cohort study organized by the Japanese Ministry of the Environment which aims to reveal environmental factors that affect children's health and development.³⁴ Details of the JECS protocols including study locations and schedules as well as participant profiles have been described elsewhere.³⁵ Briefly, the JECS collected prenatal data and information about exposure to chemical substances or metabolites (e.g., toxic metals, inorganic substances, and pesticides) during pregnancy. The eligibility criteria for participants were all pregnant women who resided in the study area. Residents who had difficulty understanding the Japanese language were not recruited. A total of 103,099 pregnant mothers were recruited during their first prenatal examination at cooperating health care providers from January 2011 to March

2014. The children born to these mothers will be followed until age 13. Follow-up mainly comprises a self-administered questionnaire every 6 months. Blood and urine collection are being considered for selected children at age 2 and 4 years from a sub-cohort and all participating children at age 6 and 12 years. The cohort represents the full range of socioeconomic status in Japan and is primarily Asian by race, similar to the demographics of the Japanese Vital Statistics.³⁶ The JECS protocol was approved by the Institutional Review Board on Epidemiological Studies of the Ministry of the Environment and the Ethics Committees of all participating institutions. Written informed consent was obtained from all participants.

Study participants and data sources

A total of 20,000 maternal blood samples were randomly selected from 97,979 participants. We used data from all participants whose clinical data were extracted from hospital records by medical staff using questionnaires developed specifically for the purpose of the JECS. First, we excluded data from participants who withdrew from the study or did not meet the lead measurement quality control criteria (n=2,002). Second, we excluded data from mothers who were lost to follow up; had severe maternal conditions prior to pregnancy such as chronic hypertension, pre-gestational diabetes, or

cardiac disease during pregnancy; or had pregnancies ending in abortions or stillbirths (n=1,209). Third, we excluded data from infants with chromosomal or major congenital anomalies (n=263) or multiple births (n=283). Application of these exclusion criteria in this study left a total of 16,243 newborn records for analysis (Figure 1).

Measurement of prenatal maternal BLL

Maternal venous blood samples (33 ml) were collected at prenatal care visits during the second and third trimesters of pregnancy. Whole blood samples were collected into 3-ml tubes with sodium-EDTA, transferred to a central laboratory within 48 hours, divided into cryo-biobanking tubes, and stored at -80°C until analysis. Measurement of lead and other metallic elements was performed using Agilent 7700 Inductively Coupled Plasma-Mass Spectrometers (ICP-MS) with auto-samplers (Agilent Technologies, Tokyo, Japan). All measured BLLs were above the detection limit (0.14 µg/dL). BLLs were measured in nanograms per gram, and converted to micrograms per deciliter by multiplying by 1.0506 (the typical specific gravity of whole blood).³⁷ Details of the JECS measurement method for maternal BLL and other toxic metals are described elsewhere.³⁸

Birth outcomes and covariates

Birthweight was the primary outcome in this study. Anthropometric data such as birthweight, head circumference, and birth length were measured by trained delivery room staff. Gestational dating was performed from the first accurate ultrasound examination during the first trimester. Preterm birth was defined as a gestational age of less than 37 completed weeks. Small for gestational age (SGA) was defined as a birthweight below the tenth percentile of the national birthweights reported in the Japanese standard growth chart,³⁹ which also considers gestational age, infant sex, and maternal parity. Low birthweight (LBW) was defined as a birthweight below 2,500 g, regardless of gestational age.

Statistical analysis

The sample size of this study was 16,243 participants. Demographic information was described using summary statistics and distribution plots were generated for all variables. Participants with extreme outliers (n=18, 0.1%), which represent apparently unusual values in biomedical studies (e.g., maternal weight gain during pregnancy >30 kg or weight loss <13 kg), or missing covariate data (n=703, 4.4%) were excluded from all analyses.

First, in our primary analysis we used multivariable linear regression models to

examine the associations between maternal BLL and birthweight, head circumference, birth length, and pregnancy duration (days). We used maternal BLL units of 0.1 $\mu\text{g}/\text{dL}$ when performing regression analysis. In addition to determining the coefficient corresponding to a 0.1 $\mu\text{g}/\text{dL}$ difference in maternal BLL, we also estimated the difference in maternal BLL exposure spanning the 25th to 75th percentile range and the log2 transformed range. Regression diagnostics confirmed that residuals from each model had approximately normal distributions, and their Q-Q plots revealed no extreme outliers. Plots of residuals against fitted values did not indicate any assumption violations and there were no substantial influential observations. Second, we estimated the odds ratio (OR) for SGA, LBW and preterm birth using multivariable logistic regression models.

All models were adjusted for potential confounders. Confounders were determined *a priori* based on published reports²¹⁻³³: maternal age at birth (years), body mass index before pregnancy (kg/m^2), weight gain during pregnancy (kg), maternal educational background (categorized into 4 levels: <10, 10-12, 13-16, ≥ 17 years), a history of preterm birth (yes or no), alcohol consumption during pregnancy (categorized into 3 levels: never drank, ex-drinker who quit before early pregnancy, drinker during pregnancy), smoking habit during pregnancy (categorized into 3 levels: never smoked, ex-smoker who quit before early pregnancy, smoker during pregnancy), and parity (categorized into null, first,

or second or higher). Unadjusted and adjusted results are presented. A complete case analysis was conducted, and 95% confidence intervals (CI) were calculated.

Sensitivity analyses

For birthweight, nonlinear dose responses and trends were examined using restricted quadratic spline regression analysis.⁴⁰ Five knots were set based on quintiles of lead distribution in SGA cases. Adding to the original statistical analysis plan, we assessed the effect modification by infant sex for all birth outcomes using stratification and modeling of interaction terms. In additional analyses, we included mothers who had severe maternal conditions prior to pregnancy and excluded preterm birth infants from all analyses. We tested whether the associations between maternal BLL and birthweight were confounded by infant' gestational age by adjusting for pregnancy duration and using age- and sex-standardized birthweight Z-scores. Analyses were conducted using JMP® 13 (SAS Institute Inc., Cary, NC, USA) and SAS version 9.4 (SAS Institute).

Results

Maternal characteristics, blood lead levels and birth outcomes

Of the 16,243 mother-infant pairs selected for this study, 703 had incomplete data and were excluded, leaving 15,540 cases for the main analysis. Maternal sociodemographic and clinical characteristics and infant birth outcomes are summarized in Tables 1 and 2.

The mean (standard deviation; SD) age of women in this cohort was 31 (5.0) years, and 8% were under 18 years of age. The average (SD) body mass index (BMI) before pregnancy was 21.1 (3.2) kg/m², with 10% of women classified as overweight or obese. Approximately 64% graduated from university, and the majority of the study cohort was married. More than 60% of women quit drinking, and approximately 40% quit smoking before early pregnancy (Table 2).

Maternal BLLs ranged from 0.16 to 7.4 µg/dL, with a median (interquartile range; IQR) of 0.63 (0.50, 0.78) µg/dL (Supplementary Figure 1 and Supplementary Table 1, available as Supplementary data at *IJE* online). The distribution of maternal BLLs was right-skewed, and 14,755 participants (90.8%) had BLLs below 1.0 µg/dL. No participants had a maternal BLL above the historic international level of concern (10 µg/dL), and only 4 participants (0.026%) had BLLs above the current reference value (5 µg/dL).¹⁹

Mean (SD) birthweight was 3,034 (398) g. Mean gestational age was 38.9 (1.4) weeks. The percentage of infants born SGA, with LBW, and preterm were 7.8% (n=1,251),

7.2% (n=1,176), and 4.0% (n=656), respectively.

Main analysis

Adjusting for all potential confounders, a 0.1 µg/dL increase in maternal BLL was associated with a 5.4 g decrease (95% CI, 3.4 to 7.5 g) in mean birthweight. Linear regression and restricted quadratic spline regression models showed consistent patterns of the adverse effects of lead on birthweight across the entire study population (Figure 2). Thus, we present the more easily interpreted estimates from linear regression models (Table 3 and Supplementary Table 2, available as Supplementary data at *IJE* online). Each 0.1 µg/dL increase in maternal BLL was associated with an increased risk of SGA (adjusted OR [aOR], 1.03; 95% CI, 1.02 to 1.05) and LBW (aOR, 1.03; 95% CI, 1.02 to 1.05) (Table 3, Supplementary Table 3 and Supplementary Table 4, available as Supplementary data at *IJE* online).

Analysis of the duration of pregnancy revealed that after adjusting for all potential confounders, each 0.1 µg/dL increase in maternal BLL was not associated with a shortening in decrements of 0.02 days (95% CI, -0.03 to 0.08). Further, each 0.1 µg/dL increase in maternal BLL was not associated with an increased risk of preterm delivery (OR, 1.00; 95% CI, 0.97 to 1.03). The results remained unchanged after adjusting for all

potential confounders (Table 3, Supplementary Table 7 and Supplementary Table 8, available as Supplementary data at *IJE* online).

An increase of 0.1 µg/dL in maternal BLL was also associated with a 0.01 cm decrease in head circumference (95% CI, -0.02 to -0.003) and a 0.02 cm decrease in birth length (95% CI, -0.03 to -0.01) (Table 3, Supplementary Table 5 and Supplementary Table 6, available as Supplementary data at *IJE* online).

Estimates for determining the associations between maternal BLL and birth outcomes showed a similar pattern with infant sex (Supplementary Table 2-8, available as Supplementary data at *IJE* online). Sensitivity analyses suggested that including mothers who were susceptible to lead exposure did not substantially change the overall estimates (Supplementary Table 9, available as Supplementary data at *IJE* online). Other sensitivity analyses showed essentially the same results as those in the main analyses. (Supplementary Table 10-13, available as Supplementary data at *IJE* online).

Discussion

Main findings

There were three main findings in this study. First, maternal BLL was associated with a decrease in birthweight. This association remained significant even when the maternal

BLL was below 1.0 µg/dL. In addition, maternal BLL was associated with an increased risk of SGA and LBW. Second, low maternal BLL was not associated with pregnancy duration, indicating that there is no increased risk of preterm delivery. Third, the effect on other anthropometric measurements (head circumference and birth length) was small. Therefore, decreases in anthropometric measurements may be directly caused by mechanisms that suppress growth, rather than premature birth.

Comparison with previous studies

Results of our population-based birth cohort study were consistent with those of previous studies that examined the effects maternal BLLs of less than 5.0 µg/dL.²¹⁻³³ Given the distribution of our sample, we thought it was appropriate to examine the effects of lead using a 0.1 µg/dL scale, as opposed to the more typical 1.0 µg/dL scale used in studies that reported greater maternal BLLs. Our estimated birthweight decrease of 5.4 g (95% CI, 3.4 to 7.5) per 0.1 µg/dL increase in maternal BLL is higher than that reported in other studies, which estimated a birthweight decrease ranging from 13 g to 27 g per 1.0 µg/dL increase in lead.²¹⁻³³ It is possible that the adverse effects of lead on birthweight are relatively larger at low levels than at high levels, which could account for this difference. In support of this theory, a retrospective study of 43,288 participants from the New York

State Heavy Metals Registry found a supralinear dose-response relationship. In that study, mean maternal BLL was 2.1 µg/dL, and an increase in maternal BLL from 0 to 1 µg/dL resulted in a 27 g decrease (95%CI, 17 to 38 g) in birthweight, while an increase from 9 to 10 µg/dL resulted in a 4.4 g decrease (95%CI, 2.8 to 6.1 g).²⁵ Our results for head circumference and birth length were also consistent with findings from other studies, which found quantitatively small adverse effects.²³ Studies on the effect of maternal BLLs below 5.0 µg/dL on pregnancy duration or preterm delivery have yielded inconsistent findings. Some birth cohort studies^{6,23} that collected samples during the first trimester showed an increased risk of preterm birth, while other studies^{25,29-32} showed no relationship between maternal BLL and pregnancy duration. We found no association between the duration of pregnancy and the risk of preterm delivery. These inconsistencies may be due to differences in the timing of blood sample collection during pregnancy or the presence of other key risk factors for preterm birth, such as a history of preterm birth, the ethnicity of participants, and current pregnancy complications.³⁴

Strengths and limitations

This study has several strengths. First, we analyzed samples from a large, population-based birth cohort exposed to low levels of lead, which provided the statistical power to

estimate small effects. Second, our data were obtained from direct analysis of maternal blood samples during the second or third trimester of pregnancy. In contrast, the largest cohort study²⁵ used proxy measures such as occupational history and registry records. Third, we assessed and reported all core birth outcomes, avoiding selective reporting.

However, there are some limitations to this study. First, because over 90% of participants in our study sample had a maternal BLL below 1.0 µg/dL, it may be difficult to extrapolate our estimated results beyond this range. Second, our study did not control for dietary calcium intake or potential deficiencies in essential metals such as iron (Fe), zinc (Zn), and copper (Cu). Calcium supplementation may reduce the release of lead from maternal bone into the blood stream and supplementation of essential metals and multi-vitamin use may reduce lead toxicity.⁴¹ However, the proportion of SGA infants in our study was low compared to previous studies.²¹⁻³³ This suggests that our study participants were unlikely to be nutritionally deficient during pregnancy, and that accordingly our estimated adverse effects in this sample were not distorted by differences in dietary intake, given the low likelihood that participants were severely deficient in only calcium, essential metals or multi-vitamins.

Despite these limitations, our study findings may have implications for public health. Our findings indicate that prenatal exposure to maternal BLLs below 1.0 µg/dL may be

linked to decreased anthropometric measurements, especially birthweight. Further study within the JECS cohort is needed to investigate the long-term effects on the physical and neurological development of children, particularly how childhood anthropometric changes observed at birth persist into later development. Additionally, future studies should assess the associations of lead with fetal growth using mixture analysis, because exposure may involve a simultaneous mixture of chemicals. By considering the effect of the complexity of chemical mixtures to which mothers are exposed on fetal growth, future studies can investigate chemicals that are highly correlated with lead and their potential interactions to confirm the findings of the present study.

Conclusions

Even at a maternal BLL below 1.0 $\mu\text{g/dL}$, prenatal lead exposure was associated with decreased birthweight and increased risk of SGA and LBW, but not preterm delivery. The adverse effect estimates of prenatal lead exposure on birth outcomes were quantitatively small and clinically limited at this low level.

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Table 1. Participants' quantitative characteristics in JECS between 2011 and 2014 (n=16,243)^a.

Characteristic	Mean (SD)	Minimum	25th	Median	75th	Maximum
Blood lead ($\mu\text{g/dL}$)	0.69 (0.3)	0.16	0.50	0.63	0.78	7.4
Maternal age at delivery (years)	31 (5.0)	14	28	31	35	46
Weight gain during pregnancy (kg)	10.3 (3.9)	-8.8	8	10.3	12.7	29.8
Gestational age at birth (weeks)	38.9 (1.4)	24	38	39	40	42
Birthweight (g)	3,034 (398)	746	2,790	3,032	3,288	4,810
Head circumference (cm)	33.2 (1.4)	20	32.5	33	34	53
Birth length (cm)	49.0 (2.1)	30	48	49	50.2	58

Abbreviations: JECS, The Japan Environment and Children's Study. ^a Data were missing for birthweight (n=8), head circumference (n=82), and birth length (n=53).

Table 2. Participants' qualitative characteristics in JECS between 2011 and 2014 (n=16,243)^a.

Characteristic	n	Percentage
Education background, years		
<10	786	4.8
10-12	5,032	31.0
13-16	10,176	62.7
≥17	228	1.4
Smoking habit		
Never smoked	9,273	56.8
Ex-smoker who quit before early pregnancy	6,262	38.3
Smoker during pregnancy	795	4.9
Alcohol consumption		
Never drank	5,443	33.2
Ex-drinker who quit before early pregnancy	10,420	63.6
Drinker during pregnancy	518	3.2
Parity		
0	6,651	40.4
1	6,383	38.8
≥2	3,417	20.8
Body mass index before pregnancy, kg/m ²		
<18.5	2,710	16.4
18.5-24.9	12,150	73.6
≥25	1,645	10.0
Infant sex		
Male	8,369	51.5
Gestational age at birth		
Preterm birth (<37 weeks) ^b	656	4.0
Term birth (37-41 weeks)	15,548	95.7
Small for gestational age (<10th percentile) ^c	1251	7.8
Low birth weight (<2500 g) ^d	1176	7.2

Abbreviations: JECS, The Japan Environment and Children's Study. All percentages are based on the total of current study samples.

^a Data were missing for education background (n=304, 1.8%), smoking habit (n=196, 1.2%), alcohol consumption (n=145,

0.9%), parity (n=75, 0.5%), body mass index before pregnancy (n=21, 0.1%), SGA (n=119, 0.7%), and low birth weight (n=119, 0.7%).

^b Preterm birth was defined as a gestational age of less than 37 completed weeks.

^c Small for gestational age was defined as a birthweight below the tenth percentile of the national birthweights reported in the Japanese standard growth chart, which also considers gestational age, infant sex, and maternal parity.

^d Low birth weight was defined as a birthweight below 2,500 g, regardless of gestational age.

Table 3. Associations between maternal prenatal blood lead levels and infant birth outcomes.

Associations estimated from linear regression models				
	Difference (95%CI)			
	Unadjusted	Adjusted Estimates ^a		
Outcome	Per 0.1µg/dL increment in maternal BLL	Per 0.1µg/dL increment in maternal BLL	Per 25 th to 75 th percentile increment in maternal BLL	Per doubling increment in maternal BLL
Birthweight (g) ^a	-5.2 (-7.3 to -3.0)	-5.4 (-7.5 to -3.4)	-15.2 (-20.9 to -9.6)	-39.8 (-51.5 to -28.0)
Head circumference (cm) ^a	-0.01 (-0.02 to -0.0002)	-0.01 (-0.02 to -0.003)	-0.03 (-0.05 to -0.008)	-0.07 (-0.11 to -0.02)
Birth length (cm) ^a	-0.02 (-0.03 to -0.01)	-0.02 (-0.03 to -0.01)	-0.06 (-0.09 to -0.03)	-0.15 (-0.21 to -0.08)
Pregnancy duration (days) ^b	0.01 (-0.04 to 0.07)	0.02 (-0.03 to 0.08)	0.07 (-0.08 to 0.21)	0.04 (-0.26 to 0.34)
Associations estimated from logistic regression models				
	Odds Ratio (95%CI)			
	Unadjusted	Adjusted Estimates ^a		
Outcome	Per 0.1µg/dL increment in maternal BLL	Per 0.1µg/dL increment in maternal BLL	Per 25 th to 75 th percentile increment in maternal BLL	Per doubling increment in maternal BLL
Small for gestational age ^a	1.04 (1.02 to 1.05)	1.03 (1.02 to 1.05)	1.10 (1.05 to 1.15)	1.36 (1.22 to 1.53)
Low birth weight ^a	1.03 (1.02 to 1.05)	1.03 (1.02 to 1.05)	1.09 (1.04 to 1.15)	1.31 (1.17 to 1.48)
Preterm delivery ^b	1.00 (0.97 to 1.03)	0.99 (0.97 to 1.02)	0.98 (0.91 to 1.06)	0.99 (0.84 to 1.16)

Abbreviations: 95% CI, 95% confidence interval; OR, odds ratio; BLL, blood lead level. Parameter estimate is based on each 1 unit (0.1 µg/dL) increase in BLL and the outcome difference for a value spanning the interquartile range (25th to 75th percentile). A doubling of the change in BLL represents log2 transformed BLL on the original scale.

^a Estimates from linear regression analyses were adjusted for maternal age at birth, body mass index before pregnancy, weight gain during pregnancy, maternal educational background,

alcohol consumption during pregnancy, smoking habit during pregnancy, and parity. Adjusted odds ratios were estimated from logistic regression controlling for the same covariates.

^b Pregnancy duration and preterm delivery were additionally adjusted for a history of preterm birth.

Figure Legends

Figure 1. JECS (The Japan Environment and Children's Study) study profile.

Data used in this study were collected from all participants using the same data collection instruments and methods.

^b Chromosomal anomalies and congenital malformations were diagnosed at birth or at 1 month by clinical assessment.

Figure 2. Association of maternal blood lead levels with birthweight.

(A and B) Scatter and regression plots of predicted mean birthweight in each range of maternal blood lead level. Individual points are maternal blood lead level and birthweight.

(A) Scatterplot of birthweight versus maternal blood lead level of all participants. The line represents the unadjusted linear relationship between maternal blood lead level and birthweight. Shaded areas around the line indicate the 95% confidence interval for the mean and for the individual predicted value.

(B) Scatterplot of birthweight versus maternal blood lead levels of less than 2.0 µg/dL. A quadratic spline regression model of the full range of maternal lead values, with five knots set based on the quintiles of lead distribution in SGA cases, was fitted to the plot.

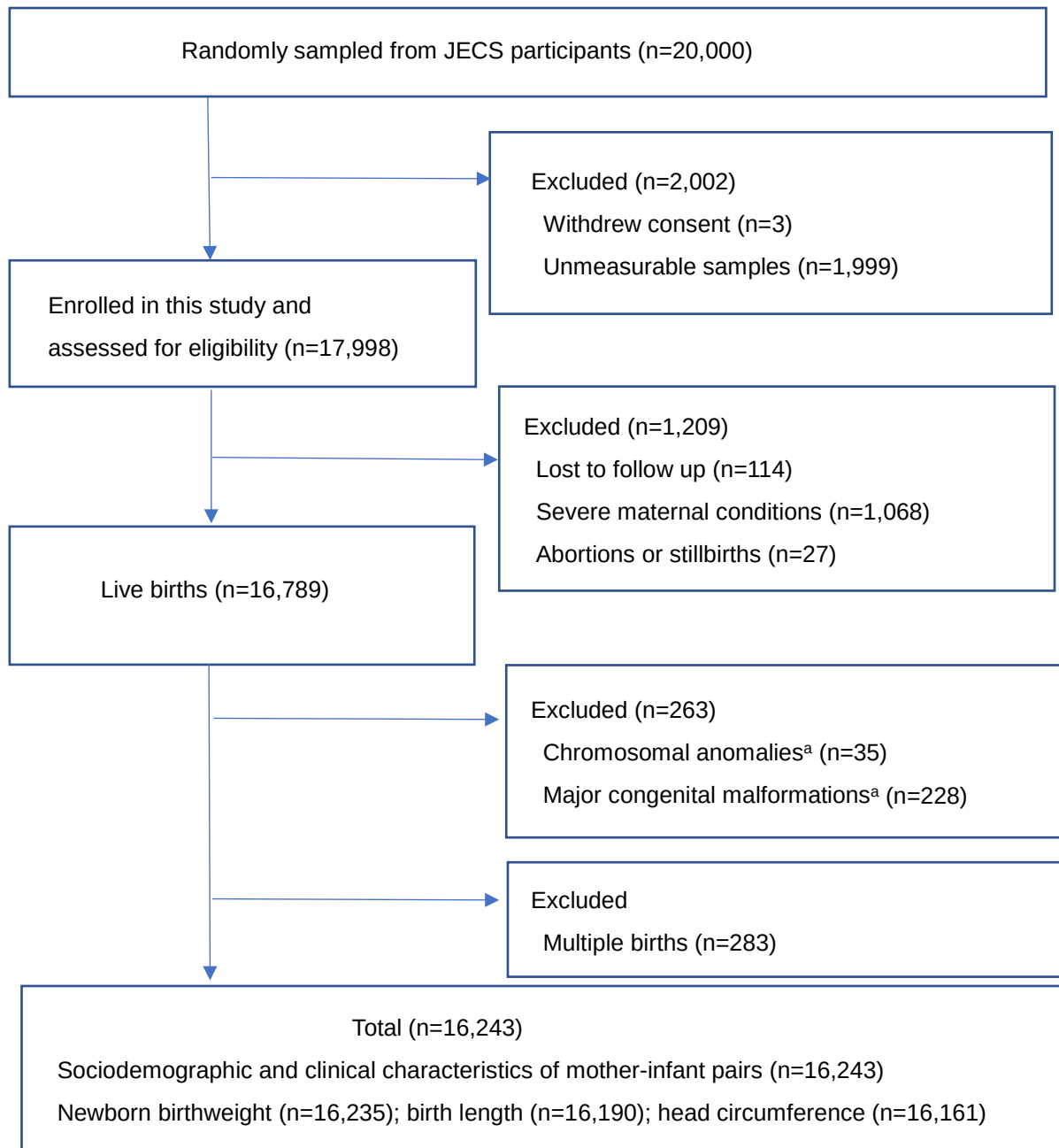
Figure 1.

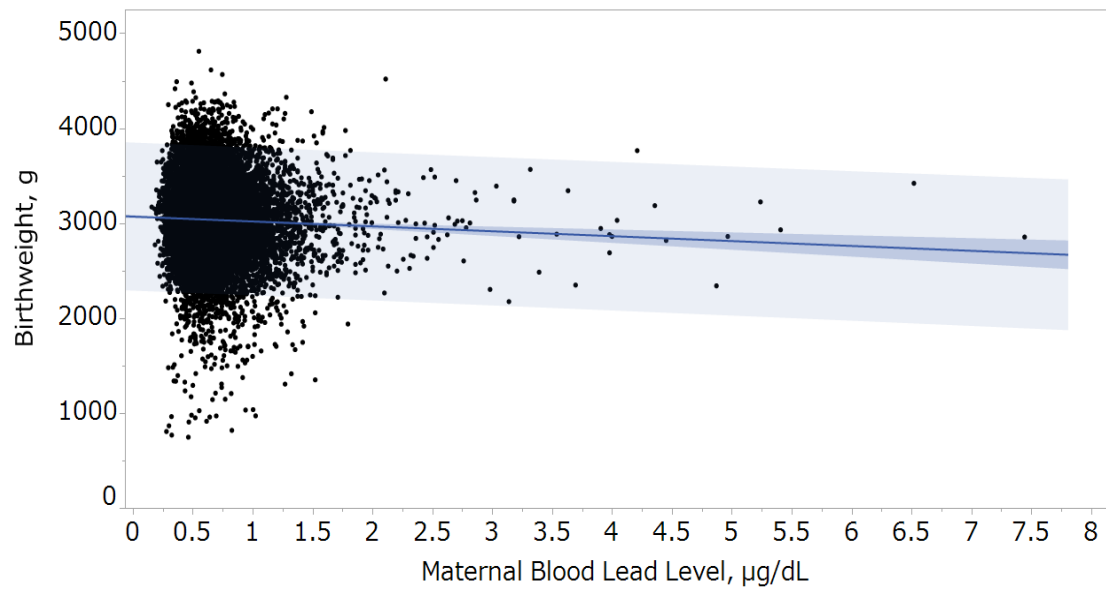
Figure 2 A.

Figure 2 B.