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Citation	Reproductive Toxicology, 107, 112-122 https://doi.org/10.1016/j.reprotox.2021.12.004
Issue Date	2022-01
Doc URL	http://hdl.handle.net/2115/87636
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Type	article (author version)
File Information	3_Reprod Toxicol_2022.pdf

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Relationships between maternal perfluoroalkyl substance levels, polymorphisms of receptor genes, and adverse birth outcomes in the Hokkaido birth cohort study, Japan

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Highlights

- Maternal perfluorooctanesulfonate levels were associated with birth weight.
- Gene-perfluorooctanesulfonate interaction were related to birth outcomes.
- Only female infants show gene-perfluorooctanesulfonate interaction.
- *LXRB* (rs1405655) affects birth weight, chest circumference, and ponderal index.

Abstract

We assessed the associations between perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA) levels in third trimester maternal serum, the maternal genotypes of genes encoding nuclear receptors, and birth outcomes. We studied a prospective birth cohort of healthy pregnant Japanese women (n = 372) recruited in Sapporo between July 2002 and October 2005. We analyzed PFOS and PFOA levels using liquid chromatography-tandem mass spectrometry and analyzed 13 single nucleotide polymorphisms (SNPs) of *proliferator-activated receptor alpha*, *gamma*, *gamma coactivator 1A*, *delta*, *constitutive androstane receptor*, *liver X receptor alpha*, and *beta* (*LXRB*) using real-time polymerase reaction (PCR). We employed multiple linear regression models to establish the influences of log_{10}-transformed PFOS and PFOA levels and maternal genotypes on birth size. In female infants, we identified interactions between PFOS levels, the maternal genotype of *LXRB* (rs1405655), and birth weight. The estimated mean changes in birth weight in response to PFOS levels, the maternal genotype *LXRB* (rs1405655)-TC/CC (compared to TT), and their interactions were -502.9 g (95% confidence interval [CI] = -247.3, -758.5 g), -526.3 g (95% CI = -200.7, -852.0 g), and 662.1 g (95% CI = 221.0, 1,103.2 g; p_{int} = 0.003), respectively. Interactions between PFOS levels and the maternal genotype of *LXRB* (rs1405655) also significantly affected birth chest circumference and the Ponderal index (p_{int} = 0.037 and 0.005, respectively). Thus, interactions between PFOS levels and the maternal genotype of *LXRB* (rs1405655) affects birth sizes in female infants. We found that certain SNPs modify the effects of PFOS levels on birth size.

Keywords

Perfluoroalkyl substance; Pregnancy; Polymorphism; Liver X receptor; Birth size; Ponderal index

Abbreviations

BCC, birth chest circumference

BHC, birth head circumference

BL, birth length

BMI, body mass index

BPI, birth Ponderal index

BW, birth weight

CAR, constitutive androstane receptor

CI, confidence interval

LOD, limit of detection

LXR, liver X receptor

LXRA, liver X receptor alpha

LXRB, liver X receptor beta

PFAS, perfluoroalkyl substance

PFOA, perfluorooctanoate

PFOS, perfluorooctanesulfonate

PPAR, peroxisome proliferator-activated receptor

PPARA, peroxisome proliferator-activated receptor alpha

PPARD, peroxisome proliferator-activated receptor delta

PPARG, peroxisome proliferator-activated receptor gamma

PPARGC1A, peroxisome proliferator-activated receptor gamma coactivator 1 alpha

SNP, single nucleotide polymorphism

1. Introduction

Perfluoroalkyl substances (PFASs) have been manufactured for more than 60 years, and have been used in a wide range of industrial and consumer products; specifically, they are used as processing aids in impregnation agents during the production of paper and carpets. Humans are commonly exposed to PFASs through food. The trans-placental transfer rates of perfluorooctanoate (PFOA) and perfluorooctanesulfonate (PFOS), which are representative PFASs, have been determined to be 0.73 and 0.42 %, respectively [1]. It has therefore been suggested that PFOS and PFOA undergo maternal-to-fetal transfer. PFOS and PFOA have recently been found to lead to a reduction in birth size [2-19]. Currently, however, the biological mechanism underlying the association between PFOS and PFOA levels and fetal growth restriction are not clearly understood.

Genetic factors may be key to elucidating the underlying biological mechanisms between these relationships. The heritability of birth weight (BW) is moderate, with estimates of 38% from studies on twins. This suggests that both genetic and environmental factors affect the etiology of birth weight [20]. The "Developmental origins of health and disease (DOHaD)" theory suggests that fetal conditions not only affect birth characteristics such as BW, birth length (BL), birth chest circumference (BCC), birth head circumference (BHC), and birth Ponderal index (BPI), but also have lifelong health implications [21,22]. Despite widespread interest in this hypothesis, only limited advances have been made regarding fetal gene-environment interactions with respect to chemical exposure during pregnancy and maternal genetic factors. Therefore, the gene-environment interaction studies are necessary to improve the current understanding of fetal conditions.

Future adverse health effects have recently been partially revealed by five investigations into interactions between the genotypes of specific biologically relevant genes and PFOS and PFOA levels [23-27]. Of these five studies, four investigated the interactions between specific genetic susceptibility-conferring genes and prenatal PFOS and PFOA levels in relation to changes in maternal lipid levels [23], cord sex hormone levels [24], reductions in BW [25], and the risk of atopic dermatitis at 2 years of age [27]. Maternal genotypes of the receptor genes *peroxisome proliferator-activated receptor (PPAR) gamma coactivator 1 alpha* (*PPARGC1A*) and *PPAR delta* (*PPARD*) have been revealed to crosstalk with PFOS levels during pregnancy. Specifically, they were found to reduce maternal lipid levels [23]. Furthermore, the fetal genotypes of *cytochrome P450 17A1* (*CYP17A1*) have been shown to crosstalk with PFOS levels during pregnancy by changing cord sex hormone levels [24]. In addition, the maternal genotypes of the xenobiotic metabolizing genes *cytochrome P450 1A1* (*CYP1A1*) and *glutathione S-transferase mu 1* (*GSTM1*) have been revealed to interact with PFOS and PFOA during pregnancy, augmenting the reduction in BW [25] and the risk of dermatitis at 2 years of age [27]. Previous studies have also suggested that PFOS and PFOA during pregnancy act on the developing fetus, thus affecting fetal growth and child diseases after birth, and that differences in maternal genetic susceptibility can affect fetal their growth and child diseases.

PFOS and PFOA are known to change the induction levels of *PPAR alpha* (*PPARA*), *PPAR gamma* (*PPARG*), *PPAR delta* (*PPARD*), *constitutive androstane receptor* (*CAR*), *liver X receptor* (*LXR*) *alpha* (*LXRA*), and *LXR beta* (*LXRB*) [28-30]. However, to date no interactions between maternal PFOS and PFOA and the genetic polymorphisms of their receptors have been reported with respect to birth size. As PFOS and PFOA bind to receptors and elicit biological responses, we hypothesize that the maternal genotypes of receptor genes may modify the associations between PFOS and PFOA levels during pregnancy and decreased birth size. Sex-specific associations between PFOS and PFOA levels during pregnancy and reductions in birth size have been reported [17], as have the associations between PFOS levels during pregnancy and the maternal genotypes of *PPARGC1A* and *PPARD* with respect to maternal lipid levels [23]. The present study aimed to expand these studies to examine the associations between PFOS and PFOA levels during pregnancy and the maternal genotypes of the receptor genes of *PPARA*, *PPARG*, *PPARGC1A*, *PPARD*, *CAR*, *LXRA*, and *LXRB* regarding their effects on birth outcomes (BW, BL, BCC, BHC, and BPI). This study also aimed to investigate the sex differences with respect to the effects of associations on birth outcomes.

2. Methods

2.1. Study participants

This prospective birth cohort study was based on the Hokkaido Study on Environment and Children's Health (Sapporo cohort). The study protocol has been described previously [31,32]. Briefly, from July 2002 to October 2005, pregnant Japanese women (n = 514) were recruited from a local obstetrics and gynecology hospital in Sapporo City. Of these, ten participants withdrew from the study. Of the remaining 504, after excluding mothers with pregnancy-induced hypertension and gestational diabetes mellitus as exclusion criteria, 372 participants were included in the current investigation; complete data on the levels of PFOS, PFOA, and fatty acids, maternal genotypes, and birth size were available for each participant.

2.2. Data collection

Each participant completed a self-administered questionnaire upon enrollment regarding their maternal age, height before pregnancy, weight before pregnancy, annual household income, maternal educational level, maternal smoking in the third trimester, and maternal alcohol consumption during pregnancy. Maternal records were also obtained to collect information on parity, gestational age, infant sex, BW, BL, BCC, and BHC. The pre-pregnancy body mass index (BMI) was defined as maternal weight before pregnancy over the square of maternal height before pregnancy (kg/m^2). BPI was defined as BW divided by the cube of BL (kg/m^3).

2.3. Measurement of PFOS and PFOA in maternal serum

For each participant, a 40 mL blood sample was taken from the maternal peripheral vein in the 3rd trimester. All samples were stored at -80 °C until analysis. In 447 maternal blood samples, PFOS and PFOA levels were measured using liquid chromatography-tandem mass spectrometry (LC/MS/MS). The measurement protocol has been described previously [23,24,33]. Samples from other participants were not analyzed, either because they were not available or because the sample volume was insufficient. Of the 447 blood samples, 228 were collected during pregnancy and 159 were obtained after delivery (owing to anemia during pregnancy). For all the samples, the limit of detection (LOD; 0.50 ng/mL) for PFOS was excessed. However, 16 (5.9%) samples had PFOA levels below the LOD (0.50 ng/mL); these were assigned a value of 0.25 ng/mL (50% of LOD).

2.4. Maternal genotype analysis

We analyzed the genotypes of the 494 maternal blood samples. The remaining samples were not analyzed because they were not available or because there was insufficient blood volume for measurement. Maternal blood samples were collected when participants gave birth; 400 μL of each sample was used to isolate and purify genomic DNA using a QIAamp DNA Blood Mini Kit (Qiagen GmbH, Hilden, Germany) or a Maxwell 16 DNA Purification Kit (Promega, Madison, WI, USA), according to the manufacturer's instructions [34]. We evaluated 13 genetic polymorphisms, namely those in *PPARA* (rs1800234 and rs135561), *PPARG* (rs3856806), *PPARGC1A* (rs2970847 and rs8192678), *PPARD* (rs1053049 and rs2267668), *CAR* (rs2307424 and rs2501873), *LXRA* (rs2279238), and *LXRB* (rs1405655, rs2303044, and rs4802703).

When selecting genetic polymorphisms, we examined three genes, i.e., *PPARs*, *CAR*, and *LXRs*, from the orphan receptors that were expected to be activated by PFASs and affected by fatty acid levels. Next, using the single nucleotide polymorphism (SNP) database (dbSNP), we selected the following 13 genetic polymorphisms, which have been reported to be located in potentially functional regions (mainly promotor and coding regions), and to be associated with disease susceptibilities to cancer, non-alcohol fatty acid disease, type 2 diabetes mellitus, obesity, and other diseases: *PPARA* (T>C, Val227Ala; dbSNP ID: rs1800234; G>A, dbSNP ID: rs135561), *PPARD* (T>C, dbSNP ID: rs1053049; A>G, dbSNP ID: rs2267668), *PPARG* (C>T, His449His; dbSNP ID: rs3856806), *PPARGC1A* (C>T, Thr394Thr; dbSNP ID: rs2970847; G>A, dbSNP ID: rs8192678), *CAR* (T>C, Pro180Pro; dbSNP ID: rs2307424; A>G, dbSNP ID: rs2501873), *LXRA* (C>T, Ser99Ser; dbSNP ID: rs2279238), and *LXRB* (T>C, dbSNP ID: rs1405655; G>A, dbSNP ID: rs2303044; G>A; dbSNP ID: rs4802703) [35-45]. Approximately 5 % or more of the minor alleles among pregnant Japanese women are necessary to secure statistical power when examining adverse health outcomes. All 13 genetic polymorphisms satisfied a minor allele frequency of ≥ 5 %. These polymorphisms were analyzed using high-throughput gene expression of pre-amplification, real-time polymerase chain reaction (PCR) with dynamic chips, and TaqMan gene expression measurements. The assessment protocol has been described previously [23].

2.5. Fatty acid measurement in maternal serum

For each participant, a 40 mL blood sample was taken from the maternal peripheral vein in the third trimester. All samples were stored at -80 ℃ until analysis. In 491 maternal blood samples, fatty acid levels were measured using gas chromatography-mass spectrometry (GC/MS) as described previously [23,46]. Samples for other participants were not analyzed either because they were not available or because the sample volume was insufficient. Of the 491 blood samples analyzed, 307 were collected during pregnancy and 184 were obtained after delivery (owing to anemia during pregnancy). The nine fatty acids targeted for measurement were palmitic acid, palmitoleic acid, stearic acid, oleic acid, linoleic acid, α-linolenic acid, arachidonic acid, eicosapentaenoic acid, and docosahexaenoic acid. The detection limits were 2.4 μg/mL for palmitic acid, 0.069 μg/mL for palmitoleic acid, 1.3 μg/mL for stearic acid, 3.6 μg/mL for oleic acid, and 2.0 μg/mL for the other fatty acids. The detection rates for all fatty acids were more than 99.0 % except for eicosapentaenoic acid (97.8 %). Non-fasting blood triglyceride levels were measured using triglyceride E-Test Wako Kits (Wako, Osaka, Japan) after lipid extraction, according to the methods described by Folch et al. [47].

2.6. Statistical analyses

Of the 372 participants, one (0.3%), three (0.8%), and six (1.6%) had missing data on parity, educational level, and annual household income, respectively. Using simple imputation, these participants were assigned to the multiparous parity group, to an educational level group with more than high school graduation, and to an annual household income group of more than 5 million Japanese yen (the most frequent group). First, we examined the characteristics of the participants. A chi-squared test, independent *t*-test, and a Mann-Whitney's U-test were employed to test whether there were differences between the male and female groups. Then, a chi-squared test was used to determine whether the frequency of genotype distribution conformed to the Hardy-Weinberg equilibrium (HWE). Third, PFOS, PFOA and fatty acid levels were $\log_{10}$-transformed before the following analyses, because of their non-normal distribution. Birth outcomes were defined using BW, BL, BCC, BHC, and BPI. Multiple linear regression analyses were used to evaluate the associations between PFAS levels and birth outcomes in both the crude and adjusted models. Infant sex was also subjected to stratified analysis. Maternal age (continuous), pre-pregnancy BMI (continuous), maternal smoking in the third trimester (yes/no), maternal alcohol consumption during pregnancy (yes/no), parity (primiparous/multiparous), educational level (less than or equal to high school graduation/more than high school graduation), annual household income (less than 5 million Japanese yen/more than or equal to 5 million Japanese yen), cesarean section (yes/no), maternal blood sampling periods (during pregnancy or after delivery), gestational age (continuous), and infant sex (male/female; total infants only) were adjusted in the multiple linear regression models (except for in the crude model). Multiple linear regression analyses were then performed to evaluate the interactions between infant sex and PFAS levels regarding birth outcomes, for both the crude and adjusted models. The covariates were the same as those used in the fourth analysis, except for the infant sex. Multiple linear regression analyses were then conducted again to evaluate the association between PFOS or PFOA levels and maternal genotypes, and the associations between birth outcomes and maternal genotypes (for both the crude and adjusted models); infant sex was also subjected to a stratified analysis. The covariates were the same as those used in the fourth analysis. Multiple linear regression analyses were also used to evaluate the interactions between PFOS or PFOA levels and maternal genotypes on birth outcomes, in both the crude and adjusted models; infant sex was subjected to a stratified analysis and the covariates were the same as those used in the fourth analysis. Multiple linear regression analyses were then used to evaluate the association between PFAS levels and birth outcomes in both the crude and adjusted models after stratification, based on the maternal genotypes of *LXRB* (rs1405655). This was done because only the effects of the interactions between PFOS levels and the maternal genotype of *LXRB* (rs1405655) on BW, BCC, and BPI in female infants were statistically significant. Infant sex was also subjected to a stratified analysis. The covariates were the same as those used in the fourth analysis. Multiple linear regression models were then used to evaluate the interactions between PFOS levels and the maternal genotype of *LXRB* (rs1405655) regarding fatty acid levels. Infant sex was also subjected to a stratified analysis. The covariates, except for cesarean section, gestational age, and infant sex, were the same as those used in the fourth analysis. In addition, PFOS levels were divided into quartile levels before the following analyses, because of their non-normal distribution. Multiple linear regression analyses were used to evaluate the dose-dependent associations between PFOS levels and BW, BCC, and BPI, in both the crude and adjusted models. This was done after stratification based on the maternal genotype of *LXRB* (rs1405655) because only the effects of the interactions between PFOS levels and the maternal genotype of *LXRB* (rs1405655) on BW, BCC, and BPI were statistically significant. Infant sex was also subjected to a stratified analysis; the covariates were the same as those used in the fourth analysis.

The PFAS-sex interaction term was defined as "$\log_{10}$-transformed PFOS or PFOA levels (continuous) × sex (0 = males and 1 = females)." The PFOS-gene or PFOA-gene interaction term was defined as "$\log_{10}$-transformed PFOS or PFOA levels (continuous) × genotype (0 = referent genotype and 1 = genotype to be compared)." The interaction term was included in the multiple linear regression models except in stratified analysis. Furthermore, we refuted or confirmed the validity of the results for all participants using sensitivity analyses. We achieved this by restricting participants to those whose maternal blood samples were collected during pregnancy (i.e., before delivery). In the sensitivity analyses, multiple linear regressions were performed using the same covariates for all participants.

Data were considered statistically significant at $p < 0.05$. All statistical analyses were performed using SPSS software version 26 (IBM Corp., Armonk, NY, USA).

2.7. Ethics

Written informed consent was obtained from all participants. All procedures were conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the Institutional Ethical Board for Human Gene and Genome Studies and the Epidemiological Studies Programs of the Hokkaido University Center for Environmental and Health Sciences (approval number: 21-137; approval date: September 3rd, 2021).

3. Results

The characteristics of this study are summarized in Table 1. The mean maternal age (30.8 vs. 29.7 years; $p = 0.020$), median PFOA levels in maternal blood (1.4 vs. 1.2 ng/mL; $p = 0.041$), mean BW (3,098.3 vs 2,997.8 g; $p = 0.012$), mean BL (48.3 vs. 47.7 cm; $p = 0.004$), and BHC (33.6 vs. 32.8 cm; $p < 0.001$) were all significantly lower in females than in males, respectively.

The maternal genotype frequencies are summarized in Table 2. All genotypes conformed to Hardy-Weinberg equilibrium ($p > 0.05$, for all).

The associations between PFOS and PFOA levels in maternal blood and birth outcomes are shown in Table 3. Multiple linear regression analysis showed that maternal PFOS levels during pregnancy were associated with lower BW (mean reduction = 182.3 g [95% confidence interval (CI) = 28.2, 336.5]) for all infants, and lower BW (mean reduction = 292.1 g [95% CI = 79.8, 504.3]) and lower BL (mean reduction = 1.384 cm [95% CI = 0.297, 2.472]) in female infants. Furthermore, maternal PFOA levels during pregnancy were associated with lower BW (mean reduction = 183.0 g [95% CI = 4.1, 361.9]) in female infants, after adjusting for the covariates. These results were almost the same as the results of the sensitivity analysis (Supplementary Table 1). However, no interactions were detected between PFOS levels in maternal blood and fetal sex on birth outcomes, and between PFOA levels in maternal blood and fetal sex on birth outcomes (Supplementary Table 2).

The interactions between PFOS and PFOA levels in maternal blood and the maternal genotype of *LXRB* (rs1405655) on birth size in female infants are summarized in Table 4 (also see Fig. 1.). Regarding the interaction between PFOS levels in maternal blood and the maternal genotype of *LXRB* (rs1405655) on BW (after adjusting for the covariates), the mean estimated decrease (95% CI) in BW for a one-unit increase in PFOS levels in maternal blood was 502.9 g (95 % confidence interval [CI] = 247.3, 758.5 g). The corresponding mean estimated decrease in BW for the *LXRB* (rs1405655)-TC/CC genotype was 526.3 g (95 % CI = 200.7, 852.0 g), compared with the *LXRB*-TT genotype. The estimated increase in BW related to interactions between PFOS levels in maternal blood and the *LXRB* (rs1405655) genotype was 662.1 g (95 % CI = 221.0, 1,103.2 g; *p* for interaction [p_{int}] = 0.003). Moreover, after adjusting for the covariates, the effects of the interactions between PFOS levels in maternal blood and the maternal genotype of *LXRB* (rs1405655) on the BCC (p_{int} = 0.037) and BPI (p_{int} = 0.005) were also significant. These results were almost the same as those obtained from the sensitivity analysis (Supplementary Table 3). However, no interactions were observed between PFOS and fatty acid levels in maternal blood (Supplementary Table 4). In male infants, there were no interactions between PFOS levels in maternal blood and the maternal genotype of *LXRB* (rs1405655) regarding BW, BL, BCC, BHC, or BPI (data not shown). Across all infants, there were also no interactions between PFOS levels in maternal blood and the SNPs of *PPARA*, *PPARG*, *PPARGC1A*, *PPARD*, *CAR*, or *LXRA* regarding BW, BL, BCC, BHC, or BPI (data not shown). Moreover, there were no interactions between PFOA levels in maternal blood and all the SNPs of *PPARA*, *PPARG*, *PPARGC1A*, *PPARD*, *CAR*, *LXRA*, or *LXRB* regarding BW, BL, BCC, BHC, or BPI (data not shown).

The associations between PFOS and PFOA levels in maternal blood and birth outcomes, stratified by the maternal genotype of *LXRB* (rs1405655) in female infants, are shown in Table 5. After adjusting for the covariates, for the *LXRB*-TT genotype the estimated decreases in BW, BCC, and BPI for a one-unit increase in PFOS levels in maternal blood were 538.5 g (95 % CI = 278.1, 799.0 g), 1.368 cm (95 % CI = 0.159, 2.576 cm), and 0.242 kg/m^3 (95 % CI = 0.056, 0.429 kg/m^3), respectively. For the *LXRB*-TC/CC genotype, the estimated increase in BPI for a one-unit increase in PFOS levels in maternal blood was 0.321 kg/m^3 (95 % CI = 0.038, 0.605 kg/m^3). However, the associations between PFOS levels in maternal blood and BW and BCC were not significant. These results were almost the same as those obtained in the sensitivity analysis (Supplementary Table 5).

The dose-dependent associations between PFOS quartile levels in maternal blood and BW, BCC, and BPI, stratified by the maternal genotype of *LXRB* (rs1405655) in female infants, are illustrated in Fig. 2 (also see Supplementary Table 6). PFOS dose-dependent associations with BP (p for trend [p_{trend}] = 0.001), BCC (p_{trend} = 0.004), and BPI (p_{trend} = 0.018) were observed among female infants born to mothers with the *LXRB* (rs1405655) TT genotype, after adjusting for the covariates. Female infants born to mothers with the rs1405655 TT genotype had the highest quartiles of PFOS levels (≥7.2 ng/mL) weighed 306.1 g less (95% CI = 136.2, 475.9 g) in BW, were 1.242 cm shorter (95% CI = 0.431, 1.271 cm) in BCC, and were 0.144 kg/m^3 smaller (95% CI = 0.023, 0.265 kg/m^3) in BPI, compared with female infants born to mothers with levels in the lowest quartile of PFOS (<3.7 ng/mL) and who had the rs1405655 TT genotype (after adjusting for the covariates).

4. Discussion

Here, we found that female infants born to mothers with *LXRB* (rs1405655) major homozygotes (TT genotype) appeared to be susceptible to the adverse health effects of maternal PFOS levels. This was manifested in increased risks of reductions in BW, BCC, and BPI. In contrast, female infants born to mothers with the *LXRB* (rs1405655) heterozygote and minor homozygotes (TC/CC genotype) appeared to be resistant to the adverse health effects of maternal PFOS levels. This suggests that there was a gene-environment interaction between a specific *LXRB* TT genotype of receptor genes and PFOS exposure during pregnancy, with relation to decreasing birth size.

We found that increased PFOS levels in maternal blood were associated with lighter BW and shorter BL, but only in female infants. Furthermore, we discovered that increased PFOA levels in maternal blood were associated with lighter BW, but again only in female infants. Sex differences in fetal growth related to PFOS and PFOA levels have also been reported in previous 18 studies [2-19]. Four of these studies reported that PFOS levels were only associated with reduced birth outcomes in male infants [8,12,14,16]. These studies reported median PFOS levels in maternal blood of 13.8 [12], 25.7 [14], and 27.2 ng/mL [16]. A previous study also reported a median PFOS level in cord blood of 3.0 ng/mL [8], which is equal to approximately 7.1 ng/mL in maternal blood, when converted using data from Cai et al. [1]. Conversely, three studies have reported PFOS levels to be associated only with reduced birth outcomes in female infants

[10,13,19]. These studies reported the following median PFOS levels in maternal blood: 5.4 [19], 19.6 [10], and 30.1 ng/mL [13]. The PFOS levels obtained in our study (median = 5.2 ng/mL) were comparable to these values.

Of the 18 abovementioned studies, one reported that PFOA levels were only associated with reduced birth outcomes in male infants [7]; it reported a median PFOA level in maternal blood of 2.3 ng/mL [7]. Conversely, six of these studies reported that PFOA levels were only associated with reduced birth outcomes in female infants [5,8,10,13,18,19]; they reported the following median PFOA levels in maternal blood: 1.6 [19], 3.7 [10], and 4.6 ng/mL [13]. These studies also reported the following median PFOA levels in cord blood: 1.3 [8] and 2.0 ng/mL [18]; these are equal to approximately 1.7 and 2.8 ng/mL ng/mL in maternal blood, when converted using data from Cai et al. [1]. The PFOA levels in our study (median = 1.3 ng/mL) were lower than these values.

Regarding the sex-specific influence on the associations between PFOS and PFOA levels during pregnancy and fetal growth, one possible mechanism may explain the observed associations between PFOS and hepatic nuclear factor 4 alpha (HNF4α) via LXRB. Cell studies have revealed that the exposure of primary human hepatocytes to PFOS results in decreased HNF4α protein expression [48]. Furthermore, the overexpression of HNF4α has been shown to increase the promoter expression of *LXRA* [49]. *LXRA* shares 78 % of its amino acid sequence with *LXRB* and binds to similar ligands with similar affinities [50]. Therefore, the decreased activation of *LXRB* could be affected by PFOS exposure via the decreased activation of HNF4α. Studies in rabbits and mice have shown that HNF4α synergistically enhances the signal transducer and activator of transcription 5b (STAT5b) [51] to regulate the sex-dependent expression of liver *cytochrome P450* (*CYP*) genes [52,53]. Hence, we speculate that the sex differences observed here in the associations between PFOS levels in maternal blood and birth outcomes might have been modified by the maternal genotype of *LXRB* (rs1405655). This may have resulted in the obtained reductions in BW, BCC, and BPI, only in female infants.

The LXR agonist has been shown to selectively increase interleukin-1beta (IL-1β) messenger ribonucleic acid (mRNA) levels in human macrophages *in vitro* [54]; increased levels of IL-1β have also been associated with a risk of preterm birth [55]. As a possible biological mechanism, the activation of LXRB may increase IL-1β levels, leading to reductions in BW, BCC, and BPI. Compared with the *LXRB* (rs1405655) minor homozygous (CC) genotype, the *LXRB* (rs1405655) TT genotype of major homozygotes has been associated with higher risks of tuberculosis [36], decreased insulin secretion in type 2 diabetes mellitus [56], and Alzheimer's disease [57]. It has previously been shown that the linkage disequilibrium over the genomic region containing *LXRB* underlies the intronic associations among rs1405655, rs2303044, and rs4802703 [23]. Thus, we consider that the *LXRB* (rs1405655) TT genotype was associated with higher activation of LXR and IL-1β than the TC/CC genotype, and with subsequent decreases in BW, BCC, and BPI. Compared with the *LXRB* (rs1405655) TT genotype without minor C allele, there may have been a protective effect regarding the increased risk of birth size reduction in the minor allele heterozygote (TC genotype) and homozygotes (CC genotype) for the increasing PFOS levels during pregnancy. Future investigations into the adverse birth health effects of various alleles at these positions are needed, in relation to the *LXRB* promotor and transcription factor binding.

The maternal genotype *LXRA* (rs2279238) is located at an exon-splicing-enhancer region, but the nucleotide variation is synonymous, thus resulting in a protein sequence of the mutant genotype that is identical to that of the wild genotype [58]. Therefore, we observed no interactions between PFOS and PFOA levels during pregnancy and the maternal genotype *LXRA* (rs2279238) regarding birth outcomes.

One of the direct LXR target genes is *fatty acid transporter protein* [59]. In addition, *LXR* regulates the *long chain acyl-CoA synthase 3* (*ACSL3*) and *sterol regulatory element binding protein* (*SREBP*) genes during lipogenesis [60-62]. However, no changes in fatty acid levels were observed regarding interactions between PFOS levels during pregnancy and the maternal genotype *LXRB* (rs1405655, rs2303044, and rs4802703) in a previous study [23]. Here, no changes in fatty acid levels were obtained regarding interactions between these factors, when stratified by infant sex. Our data suggest that the decreases BW, BCC, and BPI resulting from the interactions between PFOS levels during pregnancy and the maternal genotype *LXRB* (rs1405655) were not affected by maternal fatty acid levels. Further studies are needed to elucidate the biological mechanism underlying the effects of the interactions between PFOS levels during pregnancy and the maternal genotype *LXRB* (rs1405655) regarding the observed decreases in BW, BCC, and BPI.

A previous study found that the maternal genotypes *PPARGC1A* (rs8192679) and *PPARD* (rs1053049 and rs2267668) modified the association between PFOS and fatty acid levels during pregnancy [23]. However, here we found that the maternal genotypes *PPARA* (rs1800234 and rs135561), *PPARG* (rs3856806), *PPARGC1A* (rs2970847 and rs8192678), *PPARD* (rs1053049 and rs2267668), and *CAR* (rs2307424 and rs2501873) did not modify the association between PFOS and PFOA levels during pregnancy and birth outcomes. Moreover, no associations between PFOS and PFOA levels in maternal blood and birth outcomes, stratified by the maternal genotypes *PPARA* (rs1800234 and rs135561), *PPARG* (rs3856806), *PPARGC1A* (rs2970847 and rs8192678), *PPARD* (rs1053049 and rs2267668), and *CAR* (rs2307424 and rs2501873), were observed (data not shown). Overall, the results of these studies suggest that these genotypes in mothers did not modify the associations between PFOS and PFOA levels during pregnancy and birth outcomes via maternal fatty acid levels.

One advantage of this study is that the risk of maternal exposure misclassification was minimal because the PFOS and PFOA levels were determined based on measured levels in blood samples using LC/MS/MS with a reliable, well-established, and accurate method. However, this study has some limitations. First, no statistical corrections were performed for multiple comparisons. As multiple hypothesis tests were performed in this study, this may have increased the possibility of false positive errors. One limitation of the adopted no multiple correction approach is that it does not consider type I errors. Second, although potential study limitations include the small sample size used, a significant interaction was observed between PFOS levels during pregnancy and the maternal genotype *LXRB* (rs1405655) regarding BW, BCC, and BPI in female infants. Third, fetal genotypes were not considered in this study because we focused on the association between maternal PFOS and PFOA exposure and maternal receptor genotypes on birth size in this study. As the placenta is a fetal origin tissue and is likely a significant target organ for PFOS and PFOA, and a key mediator of sex differences in developmental outcomes, we need to examine the association between maternal PFOS and PFOA exposure and fetal receptor genotypes on birth size in a future study. Finally, as the study population considered mostly of infants with BWs greater than 2,500 g, our findings may not be representative of infants with low birth weights.

Extensive efforts should be made to examine other polymorphisms that affect further child growth trajectory regarding interactions between PFOS and PFOA levels during pregnancy and maternal and child genotypes. Here, we only examined maternal genotypes; the roles that child genotypes play in modifying the adverse effects of PFOS and PFOA levels during pregnancy and maternal-child gene interactions still need to be elucidated.

5. Conclusion

Here, we have demonstrated that PFOS levels during pregnancy were associated with decreased BW, BCC, and BPI, and that those associations were significantly modified by the maternal genotype *LXRB* (rs1405655). This study provides evidence of gene-environment interactions between PFOS levels during pregnancy and the maternal genotype *LXRB* (rs1405655). For the first time, we reported the existence of the *LXRB* (rs1405655) TC/CC genotype, which protects against decreases in birth size regarding increased PFOS levels during pregnancy. This suggests the importance of further assessing the role of genetic susceptibility when evaluating mother-child relationships and environmental health. Further studies with gene-environment interaction approaches may help identify more preventive genetic groups that can guide precision public health in the future [63,64].

Acknowledgements

The authors thank the mothers and the infants who participated in the Hokkaido Study on Environment and Children's Health, and the staff of Sapporo Toho Hospital.

Funding

This work was supported by the Japanese Ministry of Health, Labour, and Welfare, Health and Labour Sciences Research Grants (No. H29 Kagaku-Ippan-002), Scientific Research from the Japan Society for the Promotion of Sciences, the Ministry of Education, Culture, Sports, Science and Technology (Nos. 15K15220, 18H03035, 18K17348, 19H01071, 19K22730, 20K10445, 2589300403, and 26740028), the Environment Research and Technology Development Fund of the Ministry of the Environment, Government of Japan (Nos. 5C-1252 and 5-1554), and the Japan Agency for Medical Research and Development (AMED) (No. 21gk0110039h0003). The funders had no role in the study design, data collection, data analysis, decision to publish, or manuscript preparation.

Conflicts of interest

The authors declare no conflicts of interest.

Data statement

The data and materials used to derive our conclusions are unsuitable for public deposition due to ethical restrictions and the specific legal framework in Japan. It is prohibited by the Act on the Protection of Personal Information (Act No. 57 of May 30, 2003, amended on September 9, 2015) to publicly deposit data containing personal information. The Ethical Guidelines for Epidemiological Research enforced by the Japan Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare also restrict the open sharing of the epidemiologic data. All inquiries about access to data should be sent to rkishi@med.hokudai.ac.jp. The person responsible for handling inquiries sent to this e-mail address is Professor Reiko Kishi, Principal Investigator of the Hokkaido Study on Environment and Children’s Health, Center for Environmental and Health Sciences, Hokkaido University.

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Figure legends

Fig. 1. Interaction plots between PFOS levels and the maternal genotype *LXRB* (rs1405655) on (a) birth weight, (b) birth chest circumference, and (c) birth Ponderal index among female infants born to pregnant Japanese women in the Hokkaido study

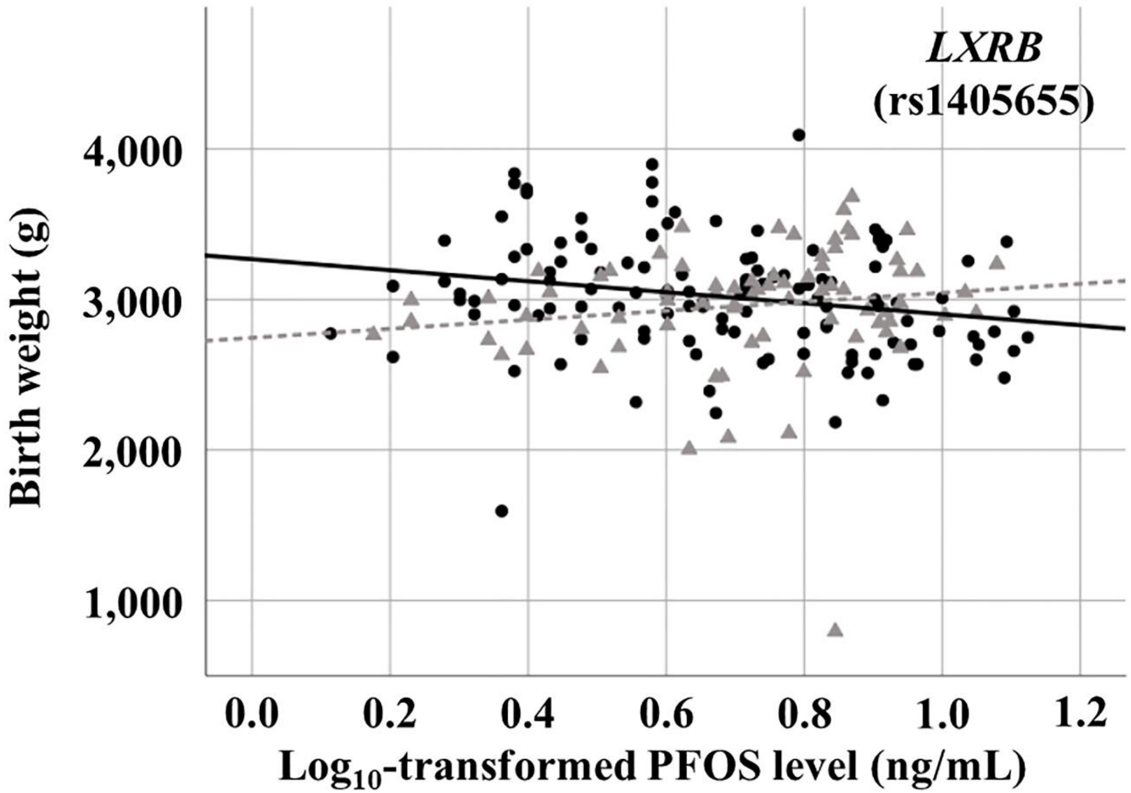
Fig. 2. Associations between PFOS quartile levels and (a) birth weight, (b) birth chest circumference, and (c) birth Ponderal index stratified by the maternal genotype *LXRB* (rs1405655) among female infants born to pregnant Japanese women in the Hokkaido study

Bars represent the changes (95% confidence interval [CI]) in birth weight (g), birth chest circumference (cm), and birth Ponderal index (kg/m^3) compared to the reference group.

p_{trend} represents p-values for trends.

$^{*}p<0.05$, $^{**}p<0.01$.

Fig. 1 (a)



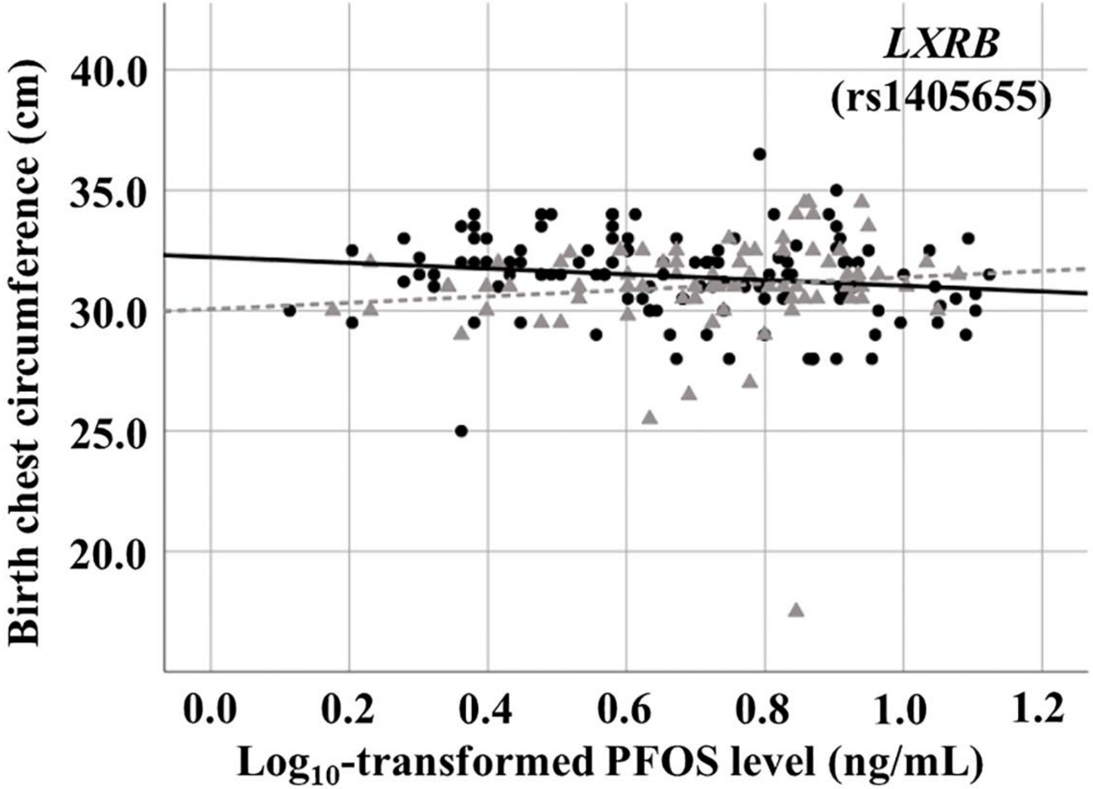
● **TT genotype (Solid line):**

Birth weight (g) = 3,268.1 − 365.4 × Log$_{10}$-transformed PFOS level (ng/mL)

▲ **TC/CC genotype (Dotted line):**

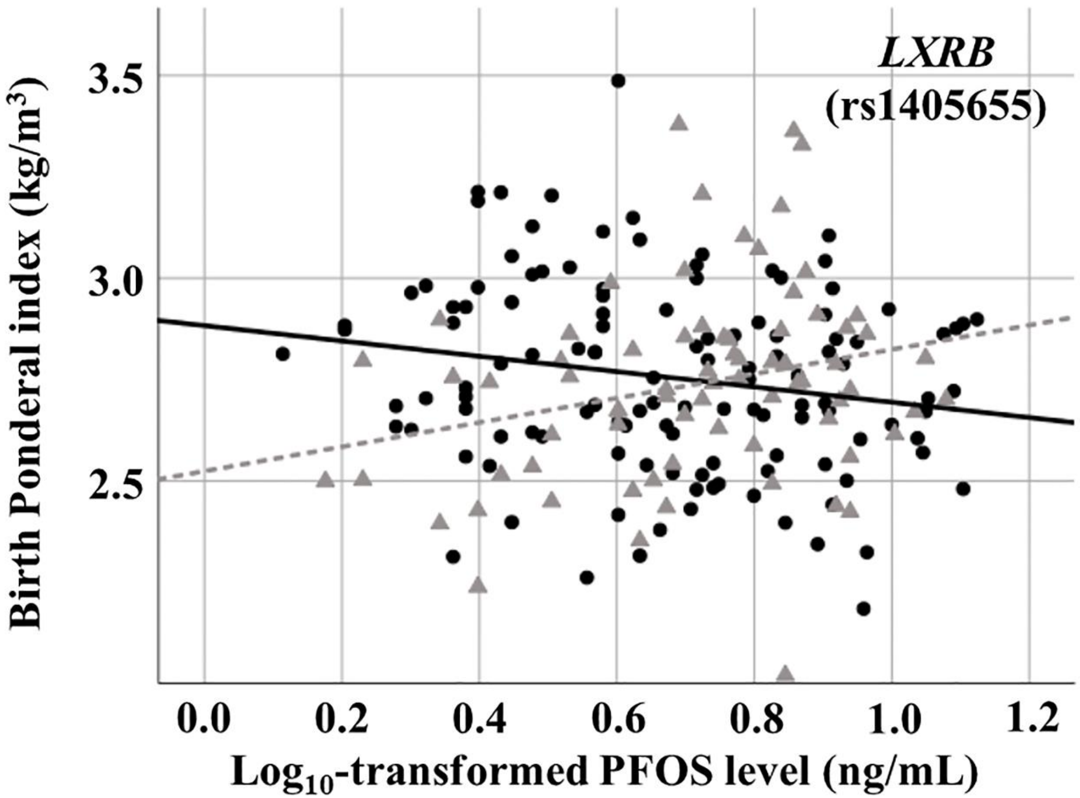
Birth weight (g) = 2,746.0 + 298.7 × Log$_{10}$-transformed PFOS level (ng/mL)

Fig. 1 (b)



● TT genotype (Solid line): Birth chest circumference (cm)
= 32.221 − 1.188 × Log_{10}-transformed PFOS level (ng/mL)
▲ TC/CC genotype (Dotted line): Birth chest circumference (cm)
= 30.064 + 1.319 × Log_{10}-transformed PFOS level (ng/mL)

Fig. 1 (c)



● **TT genotype (Solid line): Birth Ponderal index (kg/m^3)**
= 2.883 − 0.189 × Log_{10}-transformed PFOS level (ng/mL)

▲ **TC/CC genotype (Dotted line): Birth Ponderal index (kg/m^3)**
= 2.524 + 0.300 × Log_{10}-transformed PFOS level (ng/mL)

Fig. 2 (a)

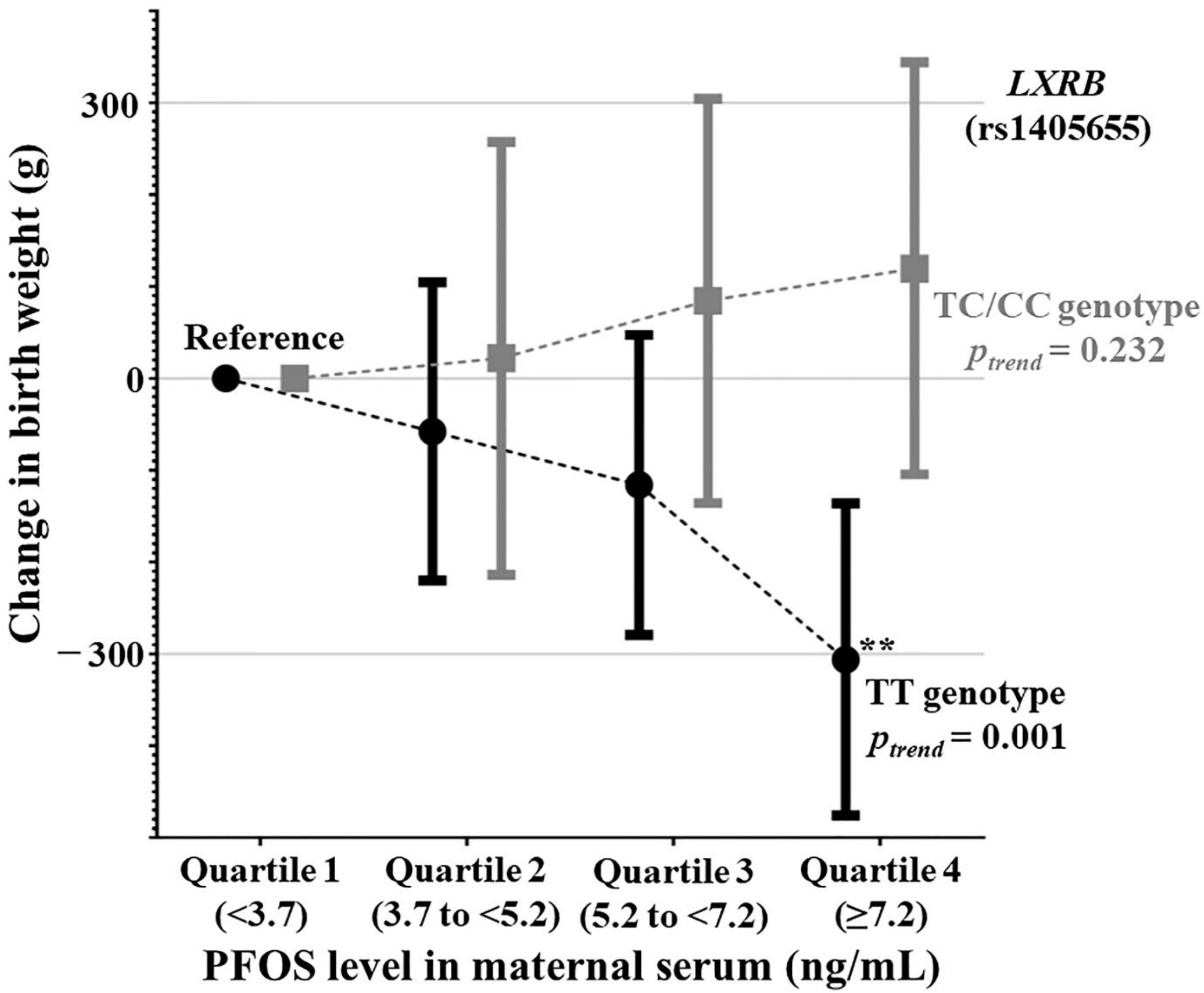

LXRB
(rs1405655)
Change in birth weight (g)
300
0
−300
Reference
TC/CC genotype
p_{trend} = 0.232
**
TT genotype
p_{trend} = 0.001
Quartile 1
(<3.7)
Quartile 2
(3.7 to <5.2)
Quartile 3
(5.2 to <7.2)
Quartile 4
(≥7.2)
PFOS level in maternal serum (ng/mL)

Fig. 2 (b)

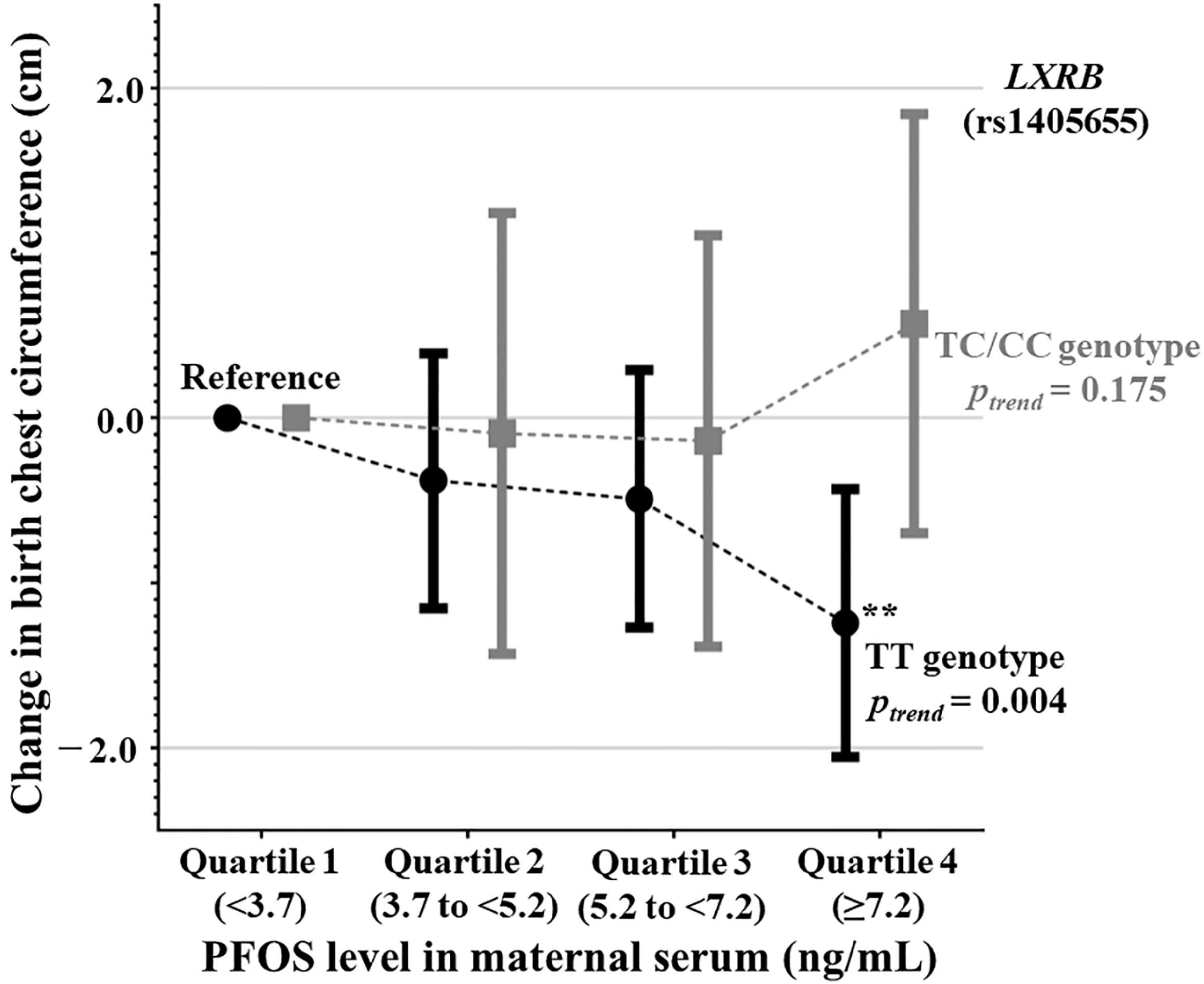

LXRB
(rs1405655)
2.0
0.0
−2.0
Change in birth chest circumference (cm)
Reference
TC/CC genotype
p_{trend} = 0.175
**
TT genotype
p_{trend} = 0.004
Quartile 1
(<3.7)
Quartile 2
(3.7 to <5.2)
Quartile 3
(5.2 to <7.2)
Quartile 4
(≥7.2)
PFOS level in maternal serum (ng/mL)

Fig. 2 (c)

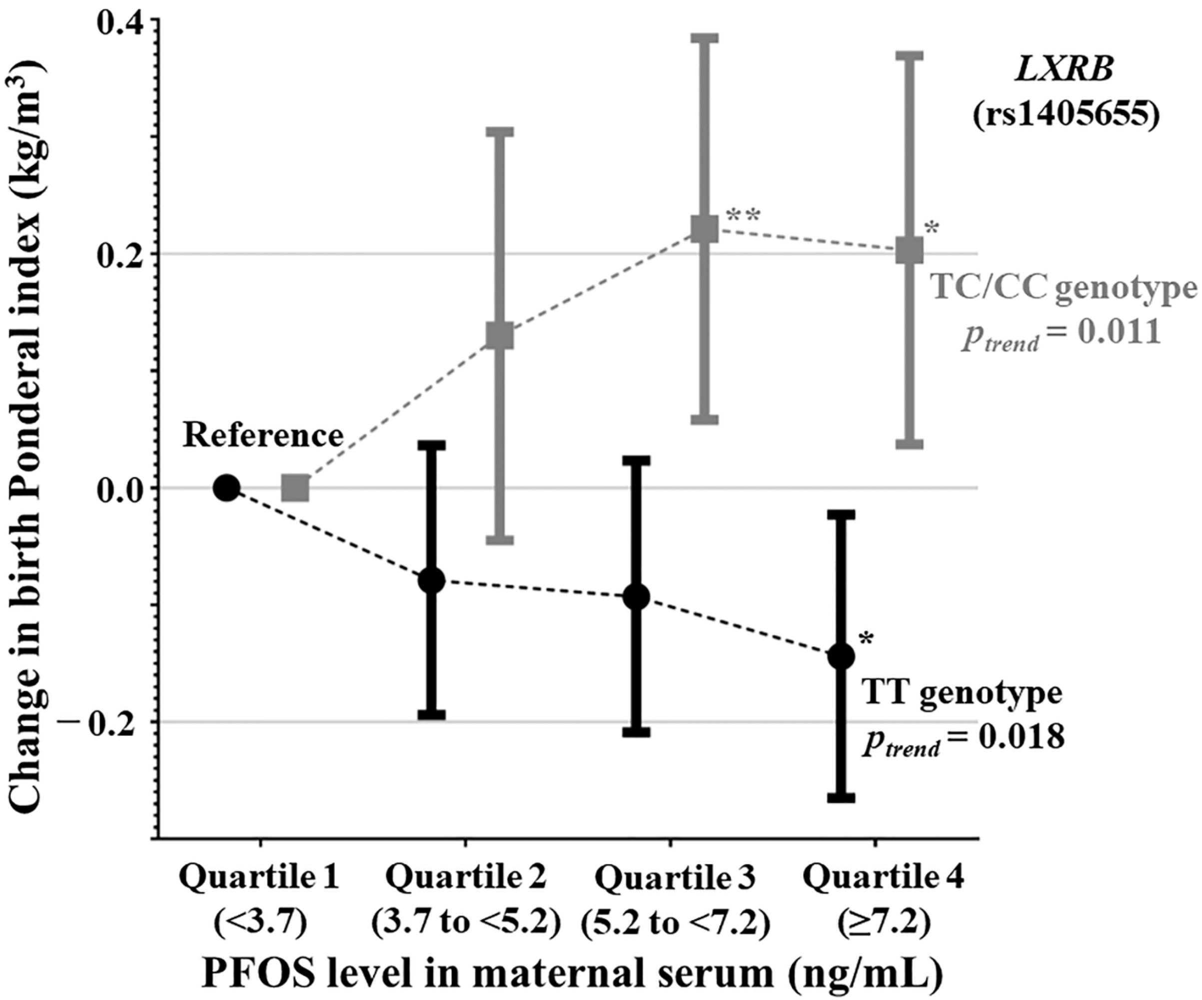

LXRB
(rs1405655)
0.4
0.2
0.0
−0.2
Change in birth Ponderal index (kg/m³)
Reference
**
*
TC/CC genotype
p trend = 0.011
*
TT genotype
p trend = 0.018
Quartile 1
(<3.7)
Quartile 2
(3.7 to <5.2)
Quartile 3
(5.2 to <7.2)
Quartile 4
(≥7.2)
PFOS level in maternal serum (ng/mL)

Table 1. Characteristics of the study participants (*n* = 372)

Characteristics	Total (*n* = 372)	Male (*n* = 174)	Female (*n* = 198)	*p* value[g]
Mothers				
Age (years)[a,d]	30.2 ± 4.8	30.8 ± 4.7	29.7 ± 4.9	0.020
Pre-pregnancy body mass index (BMI) (kg/m^2)[a,d]	21.0 ± 2.9	20.7 ± 2.6	21.2 ± 3.1	0.106
Parity[b,e]				
Primiparous	173 (46.5)	79 (45.4)	94 (47.5)	0.727
Multiparous	198 (53.2)	94 (54.0)	104 (52.5)	
Missing data	1 (0.3)	1 (0.6)	0 (0.0)	
Smoking in the third trimester[b,e]				
No	303 (81.5)	147 (84.5)	156 (78.8)	0.159
Yes	69 (18.5)	27 (15.5)	42 (21.2)	
Alcohol consumption during pregnancy[b,e]				
No	260 (69.9)	121 (69.5)	139 (70.2)	0.890
Yes	112 (30.1)	53 (30.5)	59 (29.8)	
Educational level[b,e]				
Less than or equal to high school graduation	160 (43.0)	79 (45.4)	81 (40.9)	0.401
More than high school graduation	209 (56.2)	94 (54.0)	115 (58.1)	
Missing data	3 (0.8)	1 (0.6)	2 (1.0)	
Annual household income (million Japanese yen)[b,e]				
Less than 5	262 (70.4)	123 (70.7)	139 (70.2)	0.977
More than or equal to 5	104 (28.0)	49 (28.2)	55 (27.8)	
Missing data	6 (1.6)	2 (1.1)	4 (2.0)	
Cesarean section[b,e]				
No	296 (79.6)	138 (79.3)	158 (79.8)	0.907
Yes	76 (20.4)	36 (20.7)	40 (20.2)	
Blood sampling period[b,e]				
During pregnancy	235 (63.2)	106 (62.6)	126 (63.6)	0.843
After delivery	137 (36.8)	65 (37.4)	72 (36.4)	
Blood serum level[c,f]				
PFOS (ng/mL)	5.2 (3.7, 7.2)	5.3 (3.9, 7.0)	5.2 (3.4, 7.3)	0.491
PFOA (ng/mL)	1.3 (0.8, 1.8)	1.4 (0.9, 1.8)	1.2 (0.8, 1.7)	0.041
Triglyceride (mg/100-mL)	84.4 (61.7, 117.0)	82.8 (58.4, 123.3)	85.1 (64.5, 114.7)	0.686
Palmitic acid (μg/mL)	1,876.8 (1,557.3, 2,145.8)	1,785.5 (1,529.9, 2,412.1)	1,948.1 (1,564.8, 2,438.7)	0.203
Palmitoleic acid (μg/mL)	107.5 (77.5, 155.9)	104.4 (76.0, 150.6)	109.4 (80.1, 159.6)	0.380
Stearic acid (μg/mL)	526.4 (429.2, 635.5)	526.3 (425.5, 670.6)	526.7 (432.4, 623.8)	0.938
Oleic acid (μg/mL)	1,122.1 (891.4, 1,430.2)	1,112.1 (838.5, 1,435.8)	1,153.3 (927.0, 1,429.0)	0.372
Linoleic acid (μg/mL)	725.5 (532.1, 949.9)	746.2 (533.3, 951.2)	707.3 (527.3, 943.3)	0.719
Linolenic acid (μg/mL)	10.5 (5.5, 15.1)	10.4 (5.8, 15.4)	10.7 (5.1, 15.1)	0.925
Arachidonic acid (μg/mL)	65.0 (44.4, 93.8)	63.9 (47.2, 96.8)	67.2 (41.1, 92.0)	0.490
Eicosapentaenoic acid (μg/mL)	8.6 (4.8, 14.5)	8.5 (4.8, 14.1)	9.0 (4.8, 14.8)	0.971
Docosahexaenoic acid (μg/mL)	25.5 (13.5, 40.1)	24.1 (13.9, 40.8)	26.4 (13.1, 38.9)	0.690
Infants				

Sex[b,e]				
Male	174 (46.8)	174 (100.0)	0 (0.0)	(-)
Female	198 (53.2)	0 (0.0)	198 (100.0)	
Gestational age (weeks)[a,d]	38.9 ± 1.5	38.8 ± 1.5	39.0 ± 1.5	0.131
Birth weight (BW)(g)[a,d]	3,044.8 ± 386.2	3,098.3 ± 366.5	2,997.8 ± 397.7	0.012
Birth length (BL)(cm)[a,d]	48.0 ± 2.1	48.3 ± 2.1	47.7 ± 2.0	0.004
Birth chest circumference (BCC)(cm)[a,d]	31.4 ± 1.7	31.5 ± 1.5	31.3 ± 1.9	0.188
Birth head circumference (BHC)(cm)[a,d]	33.2 ± 1.4	33.6 ± 1.3	32.8 ± 1.4	<0.001
Birth Ponderal index (BPI)(kg/m^3)[a,d]	2.754 ± 0.387	2.759 ± 0.507	2.749 ± 0.238	0.812

[a] Mean ± Standard deviation (SD).
[b] *n* (%).
[c] Median (inter-quartile range; IQR).
[d] Independent *t*-test.
[e] Chi-squared test.
[f] Mann-Whitney's *U*-test.
[g] Male versus female.
Abbreviations: PFOS, perfluorooctanesulfonate; PFOA, perfluorooctanoic acid.

Table 2. Maternal genotype frequencies (n = 372)

Gene name/genotype	Total (n = 372) n (%)	Male (n = 174) n (%)	Female (n = 198) n (%)	HWE[a]	Gene name/genotype	Total (n = 372) n (%)	Male (n = 174) n (%)	Female (n = 198) n (%)	HWE[a]
PPARA (rs1800234)					*CAR* (rs2307044)				
TT	334 (89.8)	158 (90.8)	176 (88.9)		TT	103 (27.7)	44 (25.3)	59 (29.8)	
TC	35 (9.4)	16 (9.2)	19 (9.6)	$\chi^2 = 3.468$	TC	195 (52.4)	92 (52.9)	103 (52.0)	$\chi^2 = 1.117$
CC	3 (0.8)	0 (0.0)	3 (1.5)	$p = 0.062$	CC	74 (19.9)	38 (21.8)	36 (18.2)	$p = 0.291$
PPARA (rs135561)					*CAR* (rs2501873)				
GG	331 (89.0)	159 (91.4)	172 (86.9)		AA	123 (33.1)	66 (37.9)	57 (28.8)	
GA	41 (11.0)	15 (8.6)	26 (13.1)	$\chi^2 = 1.265$	AG	194 (52.2)	80 (46.0)	114 (57.6)	$\chi^2 = 2.326$
AA	0 (0.0)	0 (0.0)	0 (0.0)	$p = 0.261$	GG	55 (14.8)	28 (16.1)	27 (13.6)	$p = 0.127$
PPARG (rs3856806)					*LXRA* (rs2278238)				
GG	263 (70.3)	129 (74.1)	134 (67.7)		CC	160 (43.0)	66 (37.9)	94 (47.5)	
GA	98 (26.3)	39 (22.4)	59 (29.8)	$\chi^2 = 0.257$	CT	168 (45.2)	92 (52.9)	76 (38.4)	$\chi^2 = 0.000$
AA	11 (3.0)	6 (3.4)	5 (2.5)	$p = 0.612$	TT	44 (11.8)	16 (9.2)	28 (14.1)	$p = 0.992$
PPARGC1A (rs2970847)					*LXRB* (rs1405655)				
CC	235 (63.2)	101 (58.0)	134 (67.7)		TT	242 (65.1)	119 (68.4)	123 (62.1)	
CT	120 (32.3)	62 (35.6)	58 (29.3)	$\chi^2 = 0.112$	TC	111 (29.8)	47 (27.0)	64 (32.3)	$\chi^2 = 1.744$
TT	17 (4.6)	11 (6.3)	6 (3.0)	$p = 0.737$	CC	19 (5.1)	8 (4.6)	11 (5.6)	$p = 0.187$
PPARGC1A (rs8192678)					*LXRB* (rs2303044)				
GG	101 (27.2)	46 (26.4)	55 (27.8)		GG	252 (67.7)	121 (69.5)	131 (66.2)	
GA	182 (48.9)	93 (53.4)	89 (44.9)	$\chi^2 = 0.156$	GA	106 (28.5)	46 (26.4)	60 (30.3)	$\chi^2 = 0.461$
AA	89 (23.9)	35 (20.1)	54 (27.3)	$p = 0.693$	AA	14 (3.8)	7 (4.0)	7 (3.5)	$p = 0.497$
PPARD (rs1053049)					*LXRB* (rs4802703)				
TT	226 (60.8)	108 (62.1)	118 (59.6)		GG	265 (71.2)	132 (75.9)	133 (67.2)	
TC	135 (36.3)	58 (33.3)	77 (38.9)	$\chi^2 = 3.004$	GA	95 (25.5)	36 (20.7)	59 (29.8)	$\chi^2 = 0.918$
CC	11 (3.0)	8 (4.6)	3 (1.5)	$p = 0.083$	AA	12 (3.2)	6 (3.4)	6 (3.0)	$p = 0.338$
PPARD (rs2267668)									
AA	242 (65.1)	118 (67.8)	124 (62.6)						
AG	120 (32.3)	48 (27.6)	72 (36.4)	$\chi^2 = 1.159$					
GG	10 (2.7)	8 (4.6)	2 (1.0)	$p = 0.282$					

[a] Chi-squared test was employed to test whether the frequency of genotype distribution conformed to the Hardy-Weinberg equilibrium (HWE).

Table 3. Association between PFOS and PFOA levels and birth outcomes stratified by infant sex

	Total				Males				Females			
	Crude		Adjusted		Crude		Adjusted		Crude		Adjusted	
Outcome	β (95% CI)	*p* value	β (95% CI)	*p* value	β (95% CI)	*p* value	β (95% CI)	*p* value	β (95% CI)	*p* value	β (95% CI)	*p* value
Exposure: PFOS (ng/mL)												
BW (g)	-77.0 (-256.0, 102.1)	0.398	-182.3 (-336.5, -28.2)	0.021	8.5 (-246.7, 263.6)	0.948	17.7 (-207.0, 242.5)	0.876	-165.3 (-414.4, 83.7)	0.192	-292.1 (-504.3, -79.8)	0.007
BL (cm)	0.023 (-0.945, 0.991)	0.963	-0.552 (-1.433, 0.328)	0.218	0.780 (-0.701, 2.261)	0.300	0.635 (-0.832, 2.102)	0.394	-0.709 (-1.965, 0.548)	0.267	-1.384 (-2.472, -0.297)	0.013
BCC (cm)	-0.158 (-0.960, 0.644)	0.698	-0.625 (-1.343, 0.093)	0.088	0.166 (-0.844, 1.177)	0.746	0.113 (-0.796, 1.022)	0.806	-0.467 (-1.683, 0.749)	0.450	-1.033 (-2.122, 0.056)	0.063
BHC (cm)	-0.225 (-0.869, 0.418)	0.492	-0.339 (-0.957, 0.280)	0.282	-0.226 (-1.120, 0.668)	0.618	-0.034 (-0.931, 0.864)	0.941	-0.335 (-1.228, 0.519)	0.424	-0.612 (-1.483, 0.258)	0.167
BPI (kg/m^3)	-0.054 (-0.234, 0.126)	0.556	-0.079 (-0.270, 0.111)	0.412	-0.077 (-0.430, 0.276)	0.668	-0.070 (-0.480, 0.321)	0.724	-0.037 (-0.187, 0.112)	0.625	-0.057 (-0.211, 0.097)	0.466
Exposure: PFOA (ng/mL)												
BW (g)	-69.0 (-206.9, 68.9)	0.326	-107.1 (-232.5, 18.4)	0.094	-29.9 (-223.9, 164.0)	0.761	-55.8 (-235.4, 123.8)	0.540	-130.3 (-325.1, 64.6)	0.189	-183.0 (-361.9, -4.1)	0.045
BL (cm)	-0.027 (-0.773, 0.719)	0.944	-0.408 (-1.122, 0.307)	0.262	0.047 (-1.083, 1.176)	0.935	-0.077 (-1.253, 1.099)	0.897	-0.254 (-1.239, 0.732)	0.612	-0.618 (-1.538, 0.302)	0.187
BCC (cm)	-0.234 (-0.851, 0.384)	0.458	-0.445 (-1.028, 0.138)	0.134	0.165 (-0.603, 0.933)	0.672	0.015 (-0.712, 0.742)	0.968	-0.644 (-1.593, 0.305)	0.182	-0.844 (-1.754, 0.067)	0.069
BHC (cm)	-0.169 (-0.065, 0.327)	0.502	-0.294 (-0.796, 0.207)	0.249	-0.283 (-0.962, 0.396)	0.412	-0.189 (-0.907, 0.528)	0.603	-0.262 (-0.946, 0.422)	0.450	-0.431 (-1.159, 0.298)	0.245
BPI (kg/m^3)	-0.054 (-0.193, 0.084)	0.442	-0.054 (-0.208, 0.101)	0.495	-0.016 (-0.284, 0.253)	0.908	-0.067 (-0.379, 0.245)	0.673	-0.091 (-0.207, 0.026)	0.126	-0.090 (-0.218, 0.038)	0.168

The associations between PFOS or PFOA levels and birth outcomes were tested using a multiple linear regression model.

Crude: Non-adjusted.

Adjusted for maternal age (continuous), pre-pregnancy BMI (continuous), maternal smoking in the third trimester (yes/no), maternal alcohol consumption during pregnancy (yes/no), parity (primiparous/multiparous), educational level (less than or equal to high school graduation/more than high school graduation), annual household income (less than 5 million Japanese yen/more than or equal to 5 million Japanese yen), cesarean section (yes/no), maternal blood sampling period (during pregnancy/after delivery), gestational age (continuous), and infant sex (male/female; total infants only).

β (95% CI) represents the change in BW (g), BL (cm), BCC (cm), BHC (cm), and BPI (kg/m^3) for each ten-fold increase in PFOS or PFOA levels (ng/mL).

Table 4. Interactions between PFOS and PFOA levels and the maternal genotype *LXRB* (rs1405655) regarding birth outcomes in female infants

Outcome	Exposure/genotype	Crude β (95% CI)	Crude *p* value	Adjusted β (95% CI)	Adjusted *p* value
BW (g)	PFOS (ng/mL)	-365.4 (-664.1, -66.8)	0.017	-502.9 (-758.5, -247.3)	<0.001
	LXRB-TC/CC (vs. TT)	-522.2 (-912.5, -131.8)	0.009	-526.3 (-852.0, -200.7)	0.002
	PFOS × *LXRB*-TC/CC (Interaction term)	664.2 (133.5, 1,194.8)	0.014	662.1 (221.0, 1,103.2)	0.003
BL (cm)	PFOS (ng/mL)	-0.754 (-2.284, 0.776)	0.332	-1.468 (-2.808, -0.129)	0.032
	LXRB-TC/CC (vs. TT)	-0.444 (-2.444, 1.556)	0.662	-0.594 (-2.301, 1.113)	0.493
	PFOS × *LXRB*-TC/CC (Interaction term)	0.287 (-2.433, 3.006)	0.836	0.420 (-1.892, 2.732)	0.720
BCC (cm)	PFOS (ng/mL)	-1.188 (-2.651, 0.276)	0.111	-1.767 (-3.089, -0.445)	0.009
	LXRB-TC/CC (vs. TT)	-2.157 (-4.070, -0.244)	0.027	-2.133 (-3.817, -0.449)	0.013
	PFOS × *LXRB*-TC/CC (Interaction term)	2.507 (-0.094, 5.108)	0.059	2.427 (0.146, 4.708)	0.037
BHC (cm)	PFOS (ng/mL)	-0.532 (-1.560, 0.495)	0.308	-0.786 (-1.819, 0.247)	0.135
	LXRB-TC/CC (vs. TT)	-1.437 (-2.780, -0.094)	0.036	-1.401 (-2.718, -0.084)	0.037
	PFOS × *LXRB*-TC/CC (Interaction term)	0.996 (-0.830, 2.822)	0.283	0.940 (-0.843, 2.723)	0.300
BPI (kg/m^3)	PFOS (ng/mL)	-0.189 (-0.368, -0.011)	0.037	-0.212 (-0.398, -0.025)	0.026
	LXRB-TC/CC (vs. TT)	-0.360 (-0.593, -0.127)	0.003	-0.340 (-0.578, -0.103)	0.005
	PFOS × *LXRB*-TC/CC (Interaction term)	0.490 (0.173, 0.806)	0.003	0.468 (0.146, 0.789)	0.005
BW (g)	PFOA (ng/mL)	-136.6 (-382.3, 109.1)	0.274	-227.6 (-446.3, -8.9)	0.041
	LXRB-TC/CC (vs. TT)	-57.3 (-174.9, 60.3)	0.338	-67.6 (-166.1, 30.9)	0.177
	PFOA × *LXRB*-TC/CC (Interaction term)	38.1 (-369.5, 445.7)	0.854	157.8 (-185.5, 501.1)	0.366
BL (cm)	PFOA (ng/mL)	0.077 (-1.164, 1.318)	0.903	-0.488 (-1.614, 0.638)	0.394
	LXRB-TC/CC (vs. TT)	-0.213 (-0.807, 0.381)	0.480	-0.304 (-0.811, 0.204)	0.239
	PFOA × *LXRB*-TC/CC (Interaction term)	-0.813 (-2.871, 1.246)	0.437	-0.175 (-1.942, 1.593)	0.846
BCC (cm)	PFOA (ng/mL)	-0.207 (-1.397, 0.983)	0.732	-0.591 (-1.702, 0.519)	0.295
	LXRB-TC/CC (vs. TT)	-0.321 (-0.891, 0.248)	0.267	-0.379 (-0.880, 0.121)	0.137
	PFOA × *LXRB*-TC/CC (Interaction term)	-1.061 (-3.035, 0.914)	0.291	-0.457 (-2.201, 1.287)	0.606
BHC (cm)	PFOA (ng/mL)	0.268 (-0.561, 1.097)	0.525	0.002 (-0.857, 0.862)	0.995
	LXRB-TC/CC (vs. TT)	-0.671 (-1.068, -0.275)	0.001	-0.693 (-1.080, -0.306)	0.001
	PFOA × *LXRB*-TC/CC (Interaction term)	-1.182 (-2.558, 0.193)	0.092	-0.761 (-2.110, 0.588)	0.267
BPI (kg/m^3)	PFOA (ng/mL)	-0.136 (-0.283, 0.010)	0.068	-0.145 (-0.303, 0.012)	0.069
	LXRB-TC/CC (vs. TT)	-0.019 (-0.090, 0.051)	0.585	-0.016 (-0.086, 0.055)	0.666
	PFOA × *LXRB*-TC/CC (Interaction term)	0.130 (-0.113, 0.373)	0.293	0.157 (-0.090, 0.404)	0.211

The associations between PFOS or PFOA levels and the maternal genotype *LXRB* (rs1405655) on birth outcomes were tested using a multiple linear regression model.
Crude: Non-adjusted.
Adjusted for maternal age (continuous), pre-pregnancy BMI (continuous), maternal smoking in the third trimester (yes/no), maternal alcohol consumption during pregnancy (yes/no), parity (primiparous/multiparous), educational level (less than or equal to high school graduation/more than high school graduation), annual household income (less than 5 million Japanese yen/more than or equal to 5 million Japanese yen), cesarean section (yes/no), maternal blood sampling period (during pregnancy/after delivery), and gestational age (continuous).
β (95% CI) represents the change in BW (g), BL (cm), BCC (cm), BHC (cm), and BPI (kg/m^3).
PFOS and PFOA levels were log_{10}-transformed scales.
PFOS-*LXRB* or PFOA-*LXRB* interaction term was defined as "log_{10}-transformed PFOS or PFOA levels (continuous) × genotype (0 = TT and 1 = TC/CC)."

Table 5. Associations between PFOS and PFOA levels and birth outcomes stratified by the maternal genotype *LXRB* (rs1405655) in female infants

		Crude		Adjusted	
Outcome	Genotype	β (95% CI)	*p* value	β (95% CI)	*p* value
Exposure: PFOS (ng/mL)					
BW (g)	TT	-365.4 (-657.6, -73.3)	0.015	-538.5 (-799.0, -278.1)	<0.001
	TC/CC	298.7 (-162.6, 760.1)	0.201	135.6 (-240.4, 511.6)	0.474
BL (cm)	TT	-0.754 (-2.037, 0.529)	0.247	-1.368 (-2.576, -0.159)	0.027
	TC/CC	-0.467 (-3.251, 2.317)	0.739	-1.616 (-3.894, 0.661)	0.161
BCC (cm)	TT	-1.188 (-2.487, 0.112)	0.073	-1.928 (-3.188, -0.668)	0.003
	TC/CC	1.319 (-1.215, 3.854)	0.303	0.391 (-1.750, 2.533)	0.716
BHC (cm)	TT	-0.532 (-1.402, 0.338)	0.228	-0.831 (-1.747, 0.086)	0.075
	TC/CC	0.464 (-1.391, 2.318)	0.464	-0.224 (-1.896, 1.448)	0.790
BPI (kg/m^3)	TT	-0.189 (-0.367, -0.012)	0.036	-0.242 (-0.429, -0.056)	0.011
	TC/CC	0.300 (0.032, 0.569)	0.029	0.321 (0.038, 0.605)	0.027
Exposure: PFOA (ng/mL)					
BW (g)	TT	-136.6 (-378.0, 104.8)	0.265	-196.7 (-427.4, 34.0)	0.094
	TC/CC	-98.5 (-438.4, 241.4)	0.565	-108.0 (-420.6, 204.7)	0.493
BL (cm)	TT	0.077 (-0.968, 1.122)	0.884	-0.253 (-1.285, 0.799)	0.628
	TC/CC	-0.736 (-2.763, 1.291)	0.472	-1.044 (-2.949, 0.862)	0.278
BCC (cm)	TT	-0.207 (-1.273, 0.860)	0.702	-0.532 (-1.623, 0.560)	0.337
	TC/CC	-1.268 (-3.108, 0.573)	0.174	-0.870 (-2.639, 0.898)	0.329
BHC (cm)	TT	0.268 (-0.439, 0.975)	0.455	0.108 (-0.669, 0.886)	0.783
	TC/CC	-0.914 (-2.254, 0.425)	0.178	-0.674 (-2.054, 0.706)	0.333
BPI (kg/m^3)	TT	-0.136 (-0.280, 0.008)	0.064	-0.137 (-0.296, 0.021)	0.089
	TC/CC	-0.006 (-0.209, 0.196)	0.951	0.049 (-0.196, 0.294)	0.692

The associations between PFOS or PFOA levels and birth outcomes were tested using a multiple linear regression model.

Crude: Non-adjusted.

Adjusted: Adjusted for maternal age (continuous), pre-pregnancy BMI (continuous), maternal smoking in the third trimester (yes/no), maternal alcohol consumption during pregnancy (yes/no), parity (primiparous/multiparous), educational level (less than or equal to high school graduation/more than high school graduation), annual household income (less than 5 million Japanese yen/more than or equal to 5 million Japanese yen), cesarean section (yes/no), maternal blood sampling period (during pregnancy/after delivery), and gestational age (continuous).

β (95% CI) represents the change in BW (g), BL (cm), BCC (cm), BHC (cm), and BPI (kg/m^3) for each 10-fold increase in PFOS or PFOA levels (ng/mL).

Supplementary Table 1. Sensitivity analysis of the associations between PFOS and PFOA levels and birth outcomes, stratified by infant sex, among participants whose maternal blood samples were collected during pregnancy (before delivery)

	Total				Males				Females			
	Crude		Adjusted		Crude		Adjusted		Crude		Adjusted	
Outcome	β (95% CI)	*p* value	β (95% CI)	*p* value	β (95% CI)	*p* value	β (95% CI)	*p* value	β (95% CI)	*p* value	β (95% CI)	*p* value
Exposure: PFOS (ng/mL)												
BW (g)	-137.2 (-350.7, 76.4)	0.207	-167.6 (-362.4, 27.2)	0.091	140.4 (-214.2, 495.1)	0.434	56.6 (-259.7, 372.8)	0.723	-317.7 (-586.4, -49.0)	0.021	-314.4 (-575.2, -53.6)	0.019
BL (cm)	-0.329 (-1.546, 0.888)	0.595	-0.501 (-1.637, 0.634)	0.385	0.699 (-1.690, 3.089)	0.563	0.319 (-1.939, 2.577)	0.780	-1.117 (-2.337, 0.104)	0.073	-1.176 (-2.331, -0.020)	0.046
BCC (cm)	-0.520 (-1.407, 0.366)	0.249	-0.623 (-1.431, 0.185)	0.130	0.342 (-1.084, 1.767)	0.635	-0.079 (-1.357, 1.199)	0.903	-1.024 (-2.181, 0.132)	0.082	-0.990 (-2.094, 0.115)	0.079
BHC (cm)	-0.067 (-0.822, 0.688)	0.861	-0.125 (-0.871, 0.622)	0.743	0.302 (-0.988, 1.592)	0.644	0.061 (-1.212, 1.334)	0.924	-0.501 (-1.404, 0.402)	0.274	-0.440 (-1.376, 0.496)	0.354
BPI (kg/m^3)	-0.026 (-0.311, 0.258)	0.857	-0.045 (-0.344, 0.253)	0.765	0.098 (-0.536, 0.732)	0.760	0.049 (-0.627, 0.725)	0.885	-0.097 (-0.289, 0.095)	0.321	-0.082 (-0.282, 0.118)	0.417
Exposure: PFOA (ng/mL)												
BW (g)	-61.7 (-212.0, 88.6)	0.420	-50.7 (-197.9, 96.4)	0.497	98.5 (-144.2, 341.2)	0.423	-23.8 (-257.8, 210.2)	0.841	-174.8 (-368.4, 18.7)	0.076	-112.0 (-322.5, 98.5)	0.294
BL (cm)	0.169 (-0.686, 1.024)	0.697	0.153 (-0.701, 1.007)	0.724	0.538 (-1.097, 2.172)	0.516	0.273 (-1.397, 1.943)	0.746	-0.176 (-1.058, 0.706)	0.694	0.082 (-0.849, 1.013)	0.862
BCC (cm)	-0.227 (-0.851, 0.397)	0.474	-0.171 (-0.781, 0.439)	0.581	0.562 (-0.408, 1.533)	0.253	0.025 (-0.920, 0.971)	0.958	-0.735 (-1.560, 0.091)	0.081	-0.367 (-1.251, 0.517)	0.412
BHC (cm)	-0.211 (-0.740, 0.319)	0.434	-0.213 (-0.773, 0.347)	0.454	-0.216 (-1.099, 0.667)	0.629	-0.600 (-1.534, 0.334)	0.205	-0.354 (-0.999, 0.290)	0.279	-0.222 (-0.965, 0.521)	0.555
BPI (kg/m^3)	-0.078 (-0.278, 0.121)	0.440	-0.088 (-0.312, 0.136)	0.439	0.003 (-0.432, 0.437)	0.990	-0.151 (-0.650, 0.348)	0.550	-0.130 (-0.265, 0.006)	0.061	-0.117 (-0.274, 0.040)	0.143

The associations between PFOS or PFOA levels and birth outcomes were tested using a multiple linear regression model.
Crude: Non-adjusted.
Adjusted for maternal age (continuous), pre-pregnancy BMI (continuous), maternal smoking in the third trimester (yes/no), maternal alcohol consumption during pregnancy (yes/no), parity (primiparous/multiparous), educational level (less than or equal to high school graduation/more than high school graduation), annual household income (less than 5 million Japanese yen/more than or equal to 5 million Japanese yen), cesarean section (yes/no), maternal blood sampling periods (during pregnancy/after delivery), gestational age (continuous), and infant sex (male/female; total infants only).
β (95% CI) represents the change in BW (g), BL (cm), BCC (cm), BHC (cm), and BPI (kg/m^3) for each 10-fold increase in PFOS or PFOA levels (ng/mL).

Supplementary Table 2. Interactions between PFOS and PFOA levels and infant sex on birth outcomes

		Crude		Adjusted	
Outcome	Exposure/sex	β (95% CI)	*p* value	β (95% CI)	*p* value
BW (g)	PFOS (ng/mL)	8.5 (-256.8, 273.7)	0.950	-85.7 (-313.2, 141.9)	0.460
	Female (vs. male)	19.9 (-243.2, 283.0)	0.882	-20.9 (-239.7, 197.9)	0.851
	PFOS × Sex (Interaction term)	-173.8 (-531.4, 183.8)	0.340	-171.4 (-468.4, 125.6)	0.257
BL (cm)	PFOS (ng/mL)	0.780 (-0.648, 2.208)	0.283	0.222 (-1.076, 1.520)	0.737
	Female (vs. male)	0.427 (-0.990, 1.843)	0.554	0.169 (-1.079, 1.417)	0.790
	PFOS × Sex (Interaction term)	-1.488 (-3.414, 0.437)	0.129	-1.372 (-3.066, 0.321)	0.112
BCC (cm)	PFOS (ng/mL)	0.166 (-1.030, 1.362)	0.785	-0.262 (-1.323, 0.799)	0.627
	Female (vs. male)	0.204 (-0.982, 1.391)	0.735	0.073 (-0.947, 1.093)	0.888
	PFOS × Sex (Interaction term)	-0.633 (-2.246, 0.980)	0.440	-0.643 (-2.028, 0.742)	0.362
BHC (cm)	PFOS (ng/mL)	-0.226 (-1.156, 0.704)	0.633	-0.205 (-1.119, 0.709)	0.660
	Female (vs. male)	-0.631 (-1.554, 0.291)	0.179	-0.625 (-1.504, 0.254)	0.163
	PFOS × Sex (Interaction term)	-0.128 (-1.382, 1.126)	0.841	-0.237 (-1.430, 0.956)	0.697
BPI (kg/m^3)	PFOS (ng/mL)	-0.077 (-0.346, 0.192)	0.575	-0.094 (-0.375, 0.187)	0.512
	Female (vs. male)	-0.039 (-0.305, 0.228)	0.776	-0.033 (-0.304, 0.237)	0.809
	PFOS × Sex (Interaction term)	0.040 (-0.323, 0.402)	0.830	0.025 (-0.342, 0.393)	0.892
BW (g)	PFOA (ng/mL)	-29.9 (-231.6, 171.7)	0.771	-115.2 (-293.1, 62.6)	0.203
	Female (vs. male)	-97.5 (-178.3, -16.6)	0.018	-143.0 (-211.1, -74.9)	<0.001
	PFOA × Sex (Interaction term)	-100.3 (-375.8, 175.1)	0.474	15.0 (-215.8, 245.8)	0.898
BL (cm)	PFOA (ng/mL)	0.047 (-1.042, 1.135)	0.933	-0.493 (-1.506, 0.520)	0.339
	Female (vs. male)	-0.602 (-1.039, -0.166)	0.007	-0.813 (-1.200, -0.425)	<0.001
	PFOA × Sex (Interaction term)	-0.300 (-1.788, 1.187)	0.692	0.157 (-1.158, 1.471)	0.815
BCC (cm)	PFOA (ng/mL)	0.165 (-0.743, 1.073)	0.721	-0.267 (-1.093, 0.559)	0.525
	Female (vs. male)	-0.194 (-0.558, 0.170)	0.295	-0.361 (-0.677, -0.045)	0.025
	PFOA × Sex (Interaction term)	-0.809 (-2.049, 0.431)	0.200	-0.326 (-1.398, 0.746)	0.551
BHC (cm)	PFOA (ng/mL)	-0.283 (-0.990, 0.424)	0.432	-0.414 (-1.124, 0.297)	0.253
	Female (vs. male)	-0.730 (-1.013, -0.446)	<0.001	-0.813 (-1.085, -0.541)	<0.001
	PFOA × Sex (Interaction term)	0.021 (-0.945, 0.986)	0.967	0.218 (-0.704, 1.140)	0.642
BPI (kg/m^3)	PFOA (ng/mL)	-0.016 (-0.220, 0.189)	0.880	-0.036 (-0.254, 0.183)	0.749
	Female (vs. male)	-0.007 (-0.089, 0.075)	0.866	-0.014 (-0.097, 0.070)	0.750
	PFOA × Sex (Interaction term)	-0.075 (-0.354, 0.204)	0.598	-0.033 (-0.317, 0.251)	0.820

Abbreviations: BCC, birth chest circumference; BHC, birth head circumference; BL, birth length; BMI, body mass index; BPI, birth Ponderal index; BW, birth weight; CI, confidence interval; PFAS, perfluoroalkyl substance; PFOS, perfluorooctanesulfonate; PFOA, perfluorooctanoic acid.

The associations between PFOS or PFOA levels and infant sex on birth outcomes were tested using a multiple linear regression model.

Crude: Non-adjusted.

Adjusted for maternal age (continuous), pre-pregnancy BMI (continuous), maternal smoking in the third trimester (yes/no), maternal alcohol consumption during pregnancy (yes/no), parity (primiparous/multiparous), educational level (less than or equal to high school graduation/more than high school graduation), annual household income (less than 5 million Japanese yen/more than or equal to 5 million Japanese yen), cesarean section (yes/no), maternal blood sampling periods (during pregnancy/after delivery), and gestational age (continuous).

β (95% CI) represents the change in BW (g), BL (cm), BCC (cm), BHC (cm), and BPI (kg/m^3).

PFOS or PFOA levels were log_{10}-transformed scales.

The PFOS-sex or PFOA-sex interaction term was defined as "log_{10}-transformed PFOS or PFOA levels (continuous) × sex (0 = male and 1 = female)."

Supplementary Table 3. Sensitivity analysis of interactions between PFOS and PFOA levels and the maternal genotype *LXRB* (rs1405655) on birth outcomes in female infants, among participants whose maternal blood samples were collected during pregnancy (before delivery)

Outcome	Exposure/genotype	Crude β (95% CI)	*p* value	Adjusted β (95% CI)	*p* value
BW (g)	PFOS (ng/mL)	-601.6 (-921.0, -282.1)	<0.001	-592.1 (-906.1, -278.0)	<0.001
	LXRB-TC/CC (vs. TT)	-655.5 (-1,077.7, -233.4)	0.003	-623.8 (-1,040.1, -207.5)	0.004
	PFOS × *LXRB*-TC/CC (Interaction term)	881.2 (322.3, 1,440.2)	0.002	836.0 (287.1, 1,384.9)	0.003
BL (cm)	PFOS (ng/mL)	-1.634 (-3.132, -0.135)	0.033	-1.694 (-3.131, -0.257)	0.021
	LXRB-TC/CC (vs. TT)	-0.910 (-2.890, 1.070)	0.365	-0.941 (-2.846, 0.964)	0.330
	PFOS × *LXRB*-TC/CC (Interaction term)	1.472 (-1.151, 4.094)	0.269	1.462 (-1.050, 3.974)	0.251
BCC (cm)	PFOS (ng/mL)	-2.166 (-3.540, -0.792)	0.002	-1.998 (-3.335, -0.661)	0.004
	LXRB-TC/CC (vs. TT)	-2.907 (-4.722, -1.092)	0.002	-2.522 (-4.294, -0.750)	0.006
	PFOS × *LXRB*-TC/CC (Interaction term)	3.671 (1.268, 6.075)	0.003	3.148 (0.812, 5.485)	0.009
BHC (cm)	PFOS (ng/mL)	-0.732 (-1.812, 0.347)	0.182	-0.564 (-1.697, 0.570)	0.327
	LXRB-TC/CC (vs. TT)	-1.324 (-2.751, 0.102)	0.069	-1.091 (-2.593, 0.411)	0.153
	PFOS × *LXRB*-TC/CC (Interaction term)	1.089 (-0.800, 2.979)	0.256	0.729 (-1.251, 2.710)	0.467
BPI (kg/m^3)	PFOS (ng/mL)	-0.264 (-0.494, -0.034)	0.025	-0.241 (-0.485, 0.003)	0.053
	LXRB-TC/CC (vs. TT)	-0.424 (-0.729, -0.120)	0.007	-0.383 (-0.707, -0.059)	0.021
	PFOS × *LXRB*-TC/CC (Interaction term)	0.537 (0.135, 0.940)	0.009	0.490 (0.064, 0.917)	0.025
BW (g)	PFOA (ng/mL)	-219.1 (-467.7, 29.5)	0.084	-177.7 (-444.1, 88.7)	0.189
	LXRB-TC/CC (vs. TT)	-31.5 (-162.8, 99.8)	0.636	-35.9 (-163.6, 91.8)	0.579
	PFOA × *LXRB*-TC/CC (Interaction term)	127.0 (-277.9, 532.0)	0.536	177.3 (-218.6, 573.1)	0.377
BL (cm)	PFOA (ng/mL)	-0.076 (-1.210, 1.058)	0.895	0.006 (-1.176, 1.188)	0.992
	LXRB-TC/CC (vs. TT)	0.148 (-0.451, 0.747)	0.625	0.053 (-0.514, 0.619)	0.854
	PFOA × *LXRB*-TC/CC (Interaction term)	-0.325 (-2.172, 1.522)	0.728	0.142 (-1.614, 1.899)	0.873
BCC (cm)	PFOA (ng/mL)	-0.418 (-1.474, 0.638)	0.435	-0.118 (-1.235, 0.999)	0.835
	LXRB-TC/CC (vs. TT)	-0.169 (-0.726, 0.389)	0.551	-0.193 (-0.728, 0.343)	0.478
	PFOA × *LXRB*-TC/CC (Interaction term)	-0.718 (-2.439, 1.002)	0.410	-0.453 (-2.112, 1.207)	0.590
BHC (cm)	PFOA (ng/mL)	0.015 (-0.789, 0.818)	0.971	0.131 (-0.781, 1.043)	0.776
	LXRB-TC/CC (vs. TT)	-0.463 (-0.888, -0.039)	0.033	-0.518 (-0.955, -0.081)	0.021
	PFOA × *LXRB*-TC/CC (Interaction term)	-0.707 (-2.016, 0.602)	0.287	-0.477 (-1.832, 0.879)	0.488
BPI (kg/m^3)	PFOA (ng/mL)	-0.195 (-0.368, -0.022)	0.027	-0.173 (-0.372, 0.025)	0.087
	LXRB-TC/CC (vs. TT)	-0.048 (-0.140, 0.043)	0.297	-0.034 (-0.129, 0.061)	0.476
	PFOA × *LXRB*-TC/CC (Interaction term)	0.189 (-0.093, 0.471)	0.188	0.154 (-0.141, 0.449)	0.303

The associations between PFOS or PFOA levels and the maternal genotype *LXRB* (rs1405655) on birth outcomes were tested using a multiple linear regression model.
Crude: Non-adjusted.
Adjusted for maternal age (continuous), pre-pregnancy BMI (continuous), maternal smoking in the third trimester (yes/no), maternal alcohol consumption during pregnancy (yes/no), parity (primiparous/multiparous), educational level (less than or equal to high school graduation/more than high school graduation), annual household income (less than 5 million Japanese yen/more than or equal to 5 million Japanese yen), cesarean section (yes/no), maternal blood sampling periods (during pregnancy/after delivery), and gestational age (continuous).
β (95% CI) represents the change in BW (g), BL (cm), BCC (cm), BHC (cm), and BPI (kg/m^3).
PFOS or PFOA levels were $\log_{10}$-transformed scales.
The PFOS-*LXRB* or PFOA-*LXRB* interaction term was defined as "$\log_{10}$-transformed PFOS or PFOA levels (continuous) × genotype (0 = TT and 1 = TC/CC)."

Supplementary Table 4. Interactions between PFOS levels and the maternal genotype *LXRB* (rs1405655) regarding fatty acid levels in female infants

		Crude		Adjusted	
Outcome	Exposure/genotype	β (95% CI)	*p* value	β (95% CI)	*p* value
Triglyceride (mg/100-mL)	PFOS (ng/mL)	-0.187 (-0.327, -0.048)	0.009	-0.181 (-0.328, -0.033)	0.016
	LXRB-TC/CC (vs. TT)	0.140 (-0.042, 0.323)	0.131	0.120 (-0.068, 0.307)	0.210
	PFOS × *LXRB*-TC/CC (Interaction term)	-0.102 (-0.350, 0.146)	0.417	-0.085 (-0.339, 0.169)	0.512
Palmitic acid (μg/mL)	PFOS (ng/mL)	-0.114 (-0.230, 0.002)	0.053	-0.104 (-0.228, 0.020)	0.099
	LXRB-TC/CC (vs. TT)	0.054 (-0.097, 0.206)	0.478	0.058 (-0.100, 0.216)	0.472
	PFOS × *LXRB*-TC/CC (Interaction term)	-0.048 (-0.254, 0.157)	0.645	-0.053 (-0.267, 0.161)	0.625
Palmitoleic acid (μg/mL)	PFOS (ng/mL)	-0.192 (-0.361, -0.023)	0.026	-0.160 (-0.340, 0.019)	0.080
	LXRB-TC/CC (vs. TT)	0.049 (-0.171, 0.270)	0.659	0.058 (-0.170, 0.287)	0.616
	PFOS × *LXRB*-TC/CC (Interaction term)	0.005 (-0.295, 0.306)	0.971	-0.010 (-0.319, 0.300)	0.951
Stearic acid (μg/mL)	PFOS (ng/mL)	0.063 (-0.049, 0.175)	0.268	0.080 (-0.040, 0.199)	0.192
	LXRB-TC/CC (vs. TT)	0.028 (-0.119, 0.175)	0.705	0.030 (-0.123, 0.182)	0.703
	PFOS × *LXRB*-TC/CC (Interaction term)	-0.038 (-0.238, 0.161)	0.706	-0.042 (-0.249, 0.164)	0.687
Oleic acid (μg/mL)	PFOS (ng/mL)	-0.110 (-0.234, 0.014)	0.082	-0.089 (-0.222, 0.044)	0.190
	LXRB-TC/CC (vs. TT)	0.088 (-0.074, 0.251)	0.285	0.092 (-0.077, 0.262)	0.285
	PFOS × *LXRB*-TC/CC (Interaction term)	-0.110 (-0.331, 0.111)	0.328	-0.116 (-0.346, 0.113)	0.320
Linoleic acid (μg/mL)	PFOS (ng/mL)	-0.703 (-0.968, -0.437)	<0.001	-0.681 (-0.964, -0.397)	<0.001
	LXRB-TC/CC (vs. TT)	-0.116 (-0.463, 0.231)	0.509	-0.077 (-0.439, 0.284)	0.673
	PFOS × *LXRB*-TC/CC (Interaction term)	0.339 (-0.133, 0.810)	0.158	0.296 (-0.194, 0.785)	0.235
Linolenic acid (μg/mL)	PFOS (ng/mL)	-0.619 (-0.934, -0.303)	<0.001	-0.594 (-0.930, -0.258)	0.001
	LXRB-TC/CC (vs. TT)	-0.081 (-0.492, 0.331)	0.700	-0.070 (-0.498, 0.357)	0.746
	PFOS × *LXRB*-TC/CC (Interaction term)	0.352 (-0.208, 0.913)	0.216	0.340 (-0.239, 0.920)	0.248
Arachidonic acid (μg/mL)	PFOS (ng/mL)	-0.438 (-0.711, -0.164)	0.002	-0.396 (-0.687, -0.105)	0.008
	LXRB-TC/CC (vs. TT)	-0.014 (-0.372, 0.343)	0.938	0.054 (-0.318, 0.425)	0.776
	PFOS × *LXRB*-TC/CC (Interaction term)	0.192 (-0.294, 0.678)	0.438	0.110 (-0.392, 0.613)	0.665
Eicosapentaenoic acid (μg/mL)	PFOS (ng/mL)	0.120 (-0.173, 0.413)	0.422	0.123 (-0.191, 0.436)	0.441
	LXRB-TC/CC (vs. TT)	0.130 (-0.253, 0.513)	0.503	0.086 (-0.313, 0.485)	0.671
	PFOS × *LXRB*-TC/CC (Interaction term)	-0.182 (-0.702, 0.339)	0.492	-0.143 (-0.684, 0.398)	0.602
Docosahexaenoic acid (μg/mL)	PFOS (ng/mL)	-0.189 (-0.491, 0.113)	0.220	-0.154 (-0.478, 0.170)	0.350
	LXRB-TC/CC (vs. TT)	0.022 (-0.373, 0.417)	0.913	0.053 (-0.361, 0.466)	0.801
	PFOS × *LXRB*-TC/CC (Interaction term)	0.195 (-0.342, 0.732)	0.475	0.154 (-0.405, 0.714)	0.587

The association between PFOS levels and maternal genotype *LXRB* (rs1405655) on fatty acid levels were tested using a multiple linear regression model.
Crude: Non-adjusted.
Adjusted for maternal age (continuous), pre-pregnancy BMI (continuous), maternal smoking in the third trimester (yes/no), maternal alcohol consumption during pregnancy (yes/no), parity (primiparous/multiparous), educational level (less than or equal to high school graduation/more than high school graduation), annual household income (less than 5 million Japanese yen/more than or equal to 5 million Japanese yen), and maternal blood sampling periods (during pregnancy/after delivery).
β (95% CI) represents the change in log_{10}-transformed fatty acid levels.
PFOS and fatty acid levels were log_{10}-transformed scales.
The PFOS-*LXRB* interaction term was defined as "log_{10}-transformed PFOS levels (continuous) × genotype (0 = TT and 1 = TC/CC)."

Supplementary Table 5. Sensitivity analysis of associations between PFOS and PFOA levels and birth outcomes stratified by the maternal genotype *LXRB* (rs1405655) in female infants, among participants whose maternal blood samples were collected during pregnancy (before delivery)

Outcome	Genotype	Crude β (95% CI)	*p* value	Adjusted β (95% CI)	*p* value
Exposure: PFOS (ng/mL)					
BW (g)	TT	-601.6 (-947.8, -255.4)	0.001	-641.6 (-976.3, -306.9)	<0.001
	TC/CC	279.7 (-112.1, 671.5)	0.157	259.4 (-164.0, 682.7)	0.222
BL (cm)	TT	-1.634 (-3.159, -0.108)	0.036	-1.774 (-3.293, -0.255)	0.023
	TC/CC	-0.162 (-2.303, 1.979)	0.880	-0.603 (-2.736, 1.529)	0.569
BCC (cm)	TT	-2.166 (-3.660, -0.672)	0.005	-2.348 (-3.845, -0.851)	0.003
	TC/CC	1.505 (-0.161, 3.171)	0.075	1.069 (-0.466, 2.605)	0.166
BHC (cm)	TT	-0.732 (-1.757, 0.292)	0.159	-0.841 (-1.964, 0.282)	0.140
	TC/CC	0.357 (-1.373, 2.087)	0.679	0.151 (-1.567, 1.869)	0.859
BPI (kg/m^3)	TT	-0.264 (-0.501, -0.028)	0.029	-0.267 (-0.525, -0.008)	0.044
	TC/CC	0.273 (-0.050, 0.596)	0.095	0.327 (-0.026, 0.680)	0.068
Exposure: PFOA (ng/mL)					
BW (g)	TT	-219.1 (-490.9, 52.7)	0.113	-164.2 (-463.9, 135.5)	0.278
	TC/CC	-92.0 (-357.6, 173.6)	0.488	-56.6 (-367.1, 253.8)	0.713
BL (cm)	TT	-0.076 (-1.242, 1.091)	0.897	-0.067 (-1.228, 1.362)	0.918
	TC/CC	-0.401 (-1.822, 1.020)	0.572	0.013 (-1.527, 1.553)	0.986
BCC (cm)	TT	-0.418 (-1.582, 0.746)	0.477	-0.327 (-1.637, 0.983)	0.620
	TC/CC	-1.136 (-2.233, -0.039)	0.043	-0.357 (-1.486, 0.772)	0.525
BHC (cm)	TT	0.015 (-0.757, 0.786)	0.970	-0.032 (-0.969, 0.905)	0.946
	TC/CC	-0.692 (-1.827, 0.442)	0.225	-0.115 (-1.350, 1.119)	0.851
BPI (kg/m^3)	TT	-0.195 (-0.371, -0.019)	0.030	-0.166 (-0.381, 0.049)	0.128
	TC/CC	-0.006 (-0.229, 0.216)	0.953	0.050 (-0.316, 0.216)	0.706

The associations between PFOS or PFOA levels and birth outcomes were tested using a multiple linear regression model.
Crude: Non-adjusted.
Adjusted for maternal age (continuous), pre-pregnancy BMI (continuous), maternal smoking in the third trimester (yes/no), maternal alcohol consumption during pregnancy (yes/no), parity (primiparous/multiparous), educational level (less than or equal to high school graduation/more than high school graduation), annual household income (less than 5 million Japanese yen/more than or equal to 5 million Japanese yen), cesarean section (yes/no), maternal blood sampling periods (during pregnancy/after delivery), and gestational age (continuous).
β (95% CI) represents the change in BW (g), BL (cm), BCC (cm), BHC (cm), and BPI (kg/m^3) for each 10-fold increase in PFOS or PFOA levels (ng/mL).

Supplementary Table 6. Associations of PFOS quartile levels with birth weight, birth chest circumference, and birth Ponderal index among female infants stratified by the maternal genotype *LXRB* (rs1405655)

Outcome	Maternal genotype	PFOS level (ng/mL)	n_{Female}	Crude β (95% CI)	*p* value	Adjusted β (95% CI)	*p* value
BW (g)	TT	Quartile 1 (<3.7)	38	0.0 (Reference)		0.0 (Reference)	
		Quartile 2 (3.7 to <5.2)	27	-12.9 (-204.4, 178.5)	0.894	-58.0 (-219.9, 103.8)	0.479
		Quartile 3 (5.2 to <7.2)	26	-51.3 (-244.9, 142.3)	0.601	-115.9 (-279.1, 47.4)	0.162
		Quartile 4 (≥7.2)	32	-219.5 (-402.0, -37.0)	0.019	-306.1 (-475.9, -136.2)	0.001
		p for trend (p_{trend})			0.021		0.001
	TC/CC	Quartile 1 (<3.7)	16	0.0 (Reference)		0.0 (Reference)	
		Quartile 2 (3.7 to <5.2)	16	-0.3 (-287.4, 286.9)	0.999	22.0 (-213.6, 257.7)	0.852
		Quartile 3 (5.2 to <7.2)	22	68.1 (-198.8, 335.0)	0.613	84.5 (-135.7, 304.7)	0.446
		Quartile 4 (≥7.2)	21	225.1 (-44.4, 494.6)	0.100	119.7 (-104.5, 344.0)	0.290
		p for trend (p_{trend})			0.075		0.232
BCC (cm)	TT	Quartile 1 (<3.7)	38	0.000 (Reference)		0.000 (Reference)	
		Quartile 2 (3.7 to <5.2)	27	-0.134 (-0.983, 0.715)	0.755	-0.379 (-1.152, 0.394)	0.334
		Quartile 3 (5.2 to <7.2)	26	-0.200 (-1.058, 0.658)	0.645	-0.491 (-1.271, 0.289)	0.215
		Quartile 4 (≥7.2)	32	-0.839 (-1.648, -0.030)	0.042	-1.242 (-2.054, -0.431)	0.003
		p for trend (p_{trend})			0.050		0.004
	TC/CC	Quartile 1 (<3.7)	16	0.000 (Reference)		0.000 (Reference)	
		Quartile 2 (3.7 to <5.2)	16	-0.069 (-1.625, 1.487)	0.930	-0.094 (-1.428, 1.241)	0.889
		Quartile 3 (5.2 to <7.2)	22	-0.198 (-1.644, 1.248)	0.785	-0.138 (-1.385, 1.109)	0.826
		Quartile 4 (≥7.2)	21	1.209 (-0.252, 2.669)	0.103	0.571 (-0.699, 1.841)	0.372
		p for trend (p_{trend})			0.369		0.175
BPI (kg/m^3)	TT	Quartile 1 (<3.7)	38	0.000 (Reference)		0.000 (Reference)	
		Quartile 2 (3.7 to <5.2)	27	-0.063 (-0.180, 0.053)	0.284	-0.079 (-0.194, 0.036)	0.175
		Quartile 3 (5.2 to <7.2)	26	-0.085 (-0.203, 0.033)	0.157	-0.093 (-0.209, 0.023)	0.116
		Quartile 4 (≥7.2)	32	-0.110 (-0.222, 0.001)	0.051	-0.144 (-0.265, -0.023)	0.020
		p for trend (p_{trend})			0.045		0.018
	TC/CC	Quartile 1 (<3.7)	16	0.000 (Reference)		0.000 (Reference)	
		Quartile 2 (3.7 to <5.2)	16	0.104 (-0.063, 0.271)	0.218	0.130 (-0.045, 0.304)	0.142
		Quartile 3 (5.2 to <7.2)	22	0.179 (0.024, 0.334)	0.024	0.221 (0.058, 0.384)	0.009
		Quartile 4 (≥7.2)	21	0.188 (0.031, 0.345)	0.019	0.203 (0.037, 0.369)	0.017
		p for trend (p_{trend})			0.013		0.011

The associations between PFOS levels and birth outcomes were tested using a multiple linear regression model.
Crude: Non-adjusted.
Adjusted for maternal age (continuous), pre-pregnancy BMI (continuous), maternal smoking in the third trimester (yes/no), maternal alcohol consumption during pregnancy (yes/no), parity (primiparous/multiparous), educational level (less than or equal to high school graduation/more than high school graduation), annual household income (less than 5 million Japanese yen/more than or equal to 5 million Japanese yen), cesarean section (yes/no), maternal blood sampling periods (during pregnancy/after delivery), and gestational age (continuous).
β (95% CI) represents the change in BW (g), BCC (cm), and BPI (kg/m^3) compared to the reference group.