The relationship between maternal perfluoroalkylated substances exposure and low birth weight of offspring: a systematic review and meta-analysis

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Abstract
Some studies have shown that maternal perfluoroalkylated substances (PFAS) exposure may be associated with low birth weight (LBW) of offspring. We conducted a meta-analysis to assess the association between maternal PFASs exposure and LBW in offspring. The researchers searched PubMed, Science Direct, Scopus, Google Scholar, Web of Science, and Embase to find all the articles before October 2020. The Newcastle-Ottawa Scale was used to evaluate the quality of the studies. Finally, six articles were included for meta-analysis. Our meta-analysis showed no significant correlation between maternal perfluorooctanoic acid (PFOA) exposure and LBW of offspring: odds ratio (OR) = 0.90, 95% confidence interval (95% CI) = 0.80–1.01, with low heterogeneity ($I^2 = 18.4\%$, $P = 0.289$); there was a significant positive correlation between maternal perfluorooctane sulfonate (PFOS) exposure and LBW of offspring (OR = 1.32, 95% CI = 1.09–1.55) with no heterogeneity ($I^2 = 0.00\%$, $P = 0.570$). The grouping analysis of PFOS showed was a significant positive correlation between maternal PFOS exposure and LBW of offspring in American (OR = 1.44, 95% CI = 1.15–1.72). This study provided a systematic review and meta-analysis evidence for the relationship between maternal PFASs exposure and LBW of offspring through a small number of studies. Researchers should conduct further studies between different regions.

Keywords perfluoroalkylated substances · low birth weight · Meta-analysis · offspring · maternal exposure · systematic review

Introduction
In the early stage of human development, the interference of environmental endocrine disruptors (EEDs) on natural hormones in the body may not lead to apparent structural changes of organs. However, it may bring delayed physiological dysfunction and even diseases. Perfluoroalkylated substances (PFASs) are environmental endocrine disruptors (Woods et al. 2017), which exist widely in the environment and organisms and have long-lasting toxicity. PFASs contain thousands of compounds; the most typical and the most widely used are perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS). Various fields of production and life, such as textile, paper making, tableware coating, food packaging, carpet, antifouling agent, foam extinguishing agent, aviation, and electroplating, widely use PFASs (Calafat et al. 2007, Woods et al. 2017). The results show that the final metabolites of PFASs in the environment are PFOS and PFOA (Lau et al. 2004). In recent years, PFASs have been detected in a variety
of environmental media around the world, including water, atmosphere, and soil (Zhang et al. 2016, Harrad and Wemken 2019, Shigei et al. 2020). Even in various foods, including animal-derived foods (aquatic products, meat, eggs, milk) and plant-derived foods, the presence of PFASs have been detected (Dalalmeh et al. 2018, Sznejder-Katarzyńska et al. 2018, Ghisi et al. 2019). Therefore, ingestion through the digestive tract is the main route of human PFASs exposure.

By analyzing the mass balance of fluorine atoms, researchers can calculate the abundance and concentration of different forms of fluoride in the natural environment (Ruan and Jiang 2017). According to the ratio of known PFASs to extractable adsorbed organic fluorine (EOF) (PFASs/EOF), the overall content of PFASs in the sample can be calculated. For example, the PFASs/EOF in the Liaodong Bay of China and the Koshi River of Nepal were 0.77% and 0.39%, respectively (Wang, Wang et al. 2013, Tan et al. 2014).

Given that PFASs have hazards such as environmental persistence, long-distance migration, bioaccumulation, and multiple toxicities, which seriously threaten the ecological environment and human health, several countries or regions worldwide have successively issued relevant regulations to restrict the production and use of PFASs. In 2009, the United Nations Environment Programme (UNEP) adopted the Stockholm Convention on Persistent Organic Pollutants (Pinney et al. 2014). The world had successively published the implementation of related detection methods standards in recent years (Wei et al. 2014).

Because of the long half-life of PFASs in the human body, the accumulated PFASs in the body can transmit to the fetus through the placental barrier after pregnancy. Moreover, PFASs can also be accumulated in the baby through breast milk after delivery (Liu et al. 2011). Some studies have shown that the longer the time of breast milk intake in infancy, the higher concentrations of PFOA and PFOS in children’s serum (Pinney et al. 2014).

In the early stage of a person’s life, especially in embryo and infant, it is the fragile period of growth and development. At this time, any unnatural interference may have adverse effects on the development of the embryo sometimes and the body physiological function of the infant, sometimes even irreversible changes. Birth weight is one of the cardinal indicators of fetal growth and development. The World Health Organization defines low birth weight (LBW) as 2499 g or less at birth, which is the fundamental cause of the increase in neonatal mortality and the incidence rate of various diseases. In 2003, the Developmental Origins of Health and Disease (DOHaD) hypothesis was officially put forward in the word (Kajee and Sobngwi 2018). DOHaD refers to that if human beings experience adverse factors (uterine placental dysfunction, malnutrition) in the early stage of development (including the fetus, infant, and childhood), it will affect the birth weight of offspring and eventually cause adult diseases, such as diabetes, cardiovascular disease, asthma, tumor, osteoporosis, and neuropsychiatric disease. This hypothesis has attracted extensive attention from scholars, and many investigators carry out epidemiological studies and animal experiments. Active research in this field can reduce the incidence of adult diseases, which is of great significance to the quality of life of society, families and individuals.

Currently, researchers had found that exposure to PFASs can inhibit fetal growth in animals (Takahashi et al. 2014, Chen and Yin 2017). PFASs could disrupt sex hormone or thyroid hormone function (Zhou et al. 2016, Li et al. 2017a, b) and activate peroxisome proliferator-activated receptor-α (Wolf et al. 2014). These were all potential mechanisms of effect on fetal growth. PFASs could also change epigenetic states, such as reducing methylation levels of insulin-like growth factor-2 in cord blood or placental tissue, leading to LBW of offspring (Kobayashi et al. 2017).

At present, more and more studies have used epidemiological methods to study the relationship between maternal PFASs exposure and birth weight of offspring. According to the research report in Japan, there was a significant negative correlation between maternal PFOS exposure level before birth and neonatal birth weight, especially in female newborns (Kishi et al. 2015). A birth cohort study of 1400 pregnant women and their newborns in Denmark also found a significant negative correlation between maternal PFOS exposure and neonatal birth weight (Fei et al. 2008). Chen et al. also observed a negative correlation between the level of PFOS in cord blood and fetal growth (Chen and Yin 2017). A recent epidemiological survey of 321 pairs of mothers and infants from Guangzhou, China, further confirmed these findings (Li et al. 2017a, b). However, some studies had not found a significant association between maternal PFASs exposure and birth weight of offspring. For example, a study of 1507 mothers and their children from the Aarhus birth cohort (2008–2013) showed no consistent association between maternal PFASs exposure and birth weight of offspring (Bach et al. 2016).

We can see that the relationship between maternal PFASs exposure and low birth weight of offspring is still controversial, so it is necessary to carry out a comprehensive meta-analysis to explore the relationship between the two.

The basic question was “Is there a relationship between maternal PFASs exposure and LBW of offspring?” This study aimed to systematically explore and review all the published articles to investigate and identify the association between LBW of offspring and maternal PFASs exposure. Through
this meta-analysis, we can understand the adverse effects of PFASs on fetal growth, and development is of great significance for public health decision-making. Meanwhile, we can improve the birth quality and population quality of the newborns and provide a theoretical basis for the control of PFASs pollution.

Method

Search strategy

We searched the electronic databases including PubMed, Web of Science, Embase, and Google Scholar for all studies published before October 2020. We used the following keywords: “Perfluorinated,” “Alkanesulfonic Acids,” “Fluorine,” “Fluorine Compounds,” “Halothane,” “perfluorooctane sulfonate,” “perfluorooctanoate,” “polyfluoroalkyl compounds,” “Polyfluoroalkyl chemicals,” “Perfluorinated chemicals,” “Perfluorooctanoic acid,” “perfluorooctane sulfonic acid,” “perfluorinated acid,” “fluorocarbons,” “Perfluorinated alkyl substances,” “Perfluorohexane sulfonate,” “perfluoroalkyl acids,” “fluorinated organic compounds,” “PFOA,” “PFOS,” “PFNA,” “PFC,” “PFHxS,” “PFOSA,” “Body Mass Index,” “Birth Weight,” “Birth Weights,” “Weight, Birth,” “Weights, Birth,” “Infant, Low Birth Weight,” “Low-Birth-Weight Infant,” “Infant, Infants, Low-Birth-Weight,” “Low Birth Weight Infant,” “Low-Birth-Weight Infants,” “Low Birth Weight,” “Birth Weight, Low,” “Birth Weights, Low,” “Low Birth Weight,” “Very-Low-Birth-Weight Infant,” “Infants, Very-Low-Birth-Weight,” “Very Low Birth Weight Infant,” “Very Low Birth Weight Infants,” “Very Low Birth Weight,” “Infant, Extremely Low Birth Weight,” “Extremely Low Birth Weight Infant,” “birth outcome,” “pregnancy outcome,” “birth weight,” “low birth weight,” “premature birth,” “small for gestational age,” “fetal growth,” “IUGR,” and “intrauterine growth retardation.”

We used the search syntax including three strategy: the first is Perfluorinated or “perfluorooctane sulfonate” or perfluorooctanoate or “polyfluoroalkyl compounds” or “Polyfluoroalkyl chemicals” or “Perfluorinated chemicals” or “Perfluorooctanoic acid” or “perfluorooctane sulfonic acid” or “perfluorinated acid” or fluorocarbons or “Perfluorinated alkyl substances” or “Perfluorohexane sulfonate” or “fluorinated organic compounds” or “PFOA” or PFOS or PFNA or PFC or PFHxS or PFOSA and “Birth Weight” or “Birth Weights” or “Birth, Weight” or “Weighes, birth” or “Infant, Low Birth Weight” or “Infant, Low-Birth-Weight” or “Low-Birth-Weight Infant” or “Infant, Low-Birth-Weight” or “Infants, Very-Low-Birth-Weight” or “Very Low Birth Weight Infant” or “Very Low-Birth-Weight Infants” or “Very Low Birth Weight” or “Infant, Extremely Low Birth Weight” or “Extremely Low Birth Weight Infant”; the second is Perfluorinated or “perfluorooctane sulfonate” or perfluorooctanoate or “polyfluoroalkyl compounds” or “Polyfluoroalkyl chemicals” or “Perfluorinated chemicals” or “Perfluorooctanoic acid” or “perfluorooctane sulfonic acid” or “perfluorinated acid” or fluorocarbons or “Perfluorinated alkyl substances” or “Perfluorohexane sulfonate” or “fluorinated organic compounds” or “PFOA” or PFOS or PFNA or PFC or PFHxS or PFOSA and “birth outcome” or pregnancy outcome or “birth weight” or “low birth weight” or “premature birth” or “small for gestational age” or “fetal growth” or “IUGR” or “intrauterine growth retardation”; the third is Fluorocarbons or “Alkanesulfonic Acids” or Fluorine or “Fluorine Compounds” or Halothane and “Body Mass Index” not rat mouse.

Besides, we also manually searched references of related articles for further research. The studies only include English or Chinese.

Study selection criteria

To begin with, we screened articles based on their titles and abstracts. We excluded the studies which did not address the correlation between maternal PFASs exposure and LBW of offspring. Then, two investigators independently and critically reviewed and assessed all identified papers (the titles, abstract, and full text) for eligibility. This article was guided by a checklist to assess research clarity. From this list, the published articles which evaluated the effect of PFASs on LBW of offspring were identified.

Inclusion criteria were as follows: (a) the study design was the cohort, cross-sectional, or case-control; (b) the study examined the correlation between maternal PFASs exposure and LBW of offspring; (c) the study provided the odds ratio (OR) and its 95% confidence intervals (CI) of LBW or provided sufficient data to allow adequate estimation of the OR and 95% CI; and (d) logistic regression model was used in the study.

Exclusion criteria were as follows: (a) the research with no full text; (b) the study did not provide raw data or incomplete data; (c) the repeated publication or used of the same data in a publication; and (d) low-quality research.

Data extraction and quality assessment

The data were extracted independently from the publication by two researchers in a standard format, and disagreements
were resolved by a third researcher. We extracted the following information from each study: first authors, year of publication, country, sample size, exposure type, exposure substances, adjustment variables, adjusted OR or RR; and its 95% CI. For the study of PFASs concentration divided into three or four levels, the fixed-effect model was used to merge the data, and the meta-analysis used final combined results (Table 1).

Methodological quality of the included studies was examined using the Newcastle-Ottawa Scale (NOS) by two researchers (Wells et al. 2014). The total score of NOS was 0–9. Studies with a total score of NOS higher than or equal to seven were considered to be of high quality, while studies with a NOS score below seven were considered to be of low quality Liu et al. (2017). The results of the quality assessment are shown in Table 2. All of them were of high quality.

### Statistical analysis

The aim of this meta-analysis was to examine the relationship between maternal PFASs exposure and LBW of offspring. The effect of these associations included OR.

The researchers used the $I^2$ and $P$-value to test the heterogeneity of the included studies. A $P$-value < 0.05 was considered to be heterogeneous. $I^2$ statistic >50% indicated high, 25–50% moderate, and <25% low heterogeneity. The analysis

| Author          | Year | Country | Research type | Study size | Exposure type | Exposure substances | Result          | Adjustment variables                          |
|-----------------|------|---------|---------------|------------|---------------|---------------------|-----------------|-----------------------------------------------|
| Lyndsey A. Darrow | 2013 | America | Cohort Studies | 1629       | Maternal blood | PFOA                | OR=0.94(0.45,1.98) | Maternal age, educational level, smoking status, parity, BMI, self-reported diabetes, time between conception and serum measurement |
|                 |      |         |               |            |               | OR=0.99(0.48,2.05) |                 |                                               |
|                 |      |         |               |            |               | OR=1.25(0.63,2.46) |                 |                                               |
|                 |      |         |               |            |               | OR=0.92(0.44,1.95) |                 |                                               |
|                 |      |         |               |            |               | PFOS                | OR=1.48(0.71,3.08) |                                               |
|                 |      |         |               |            |               | OR=1.23(0.57,2.65) |                 |                                               |
|                 |      |         |               |            |               | OR=1.31(0.59,2.94) |                 |                                               |
|                 |      |         |               |            |               | OR=1.33(0.60,2.96) |                 |                                               |
| David A. Savitz  | 2012 | America | Case-control studies | 3616     | Maternal blood | PFOA                | OR=0.90(0.70,1.20) | Maternal age, education, parity, smoking status, exposure year, state of residence, gestational age |
|                 |      |         |               |            |               | OR=1.00(0.80,1.30) |                 |                                               |
|                 |      |         |               |            |               | OR=1.00(0.80,1.30) |                 |                                               |
|                 |      |         |               |            |               | PFOS                | OR=0.90(0.50,1.70) |                                               |
|                 |      |         |               |            |               | OR=1.60(1.00,2.80) |                 |                                               |
|                 |      |         |               |            |               | OR=0.90(0.50,1.70) |                 |                                               |
| Cheryl R. Stein | 2009 | America | Cohort studies | 1589       | Maternal blood | PFOA                | OR=1.00(0.60,1.70) | Maternal age, parity, educational level at interview, smoking status at interview, and PFOS in the analysis of PFOA and PFOS in the analysis of PFOS |
|                 |      |         |               |            |               | OR=0.30(0.10,0.90) |                 |                                               |
|                 |      |         |               |            |               | OR=0.80(0.30,1.90) |                 |                                               |
|                 |      |         |               |            |               | OR=1.30(0.90,1.80) |                 |                                               |
|                 |      |         |               |            |               | OR=1.60(1.10,2.30) |                 |                                               |
|                 |      |         |               |            |               | OR=1.80(1.20,2.80) |                 |                                               |
| Cyntia B. Manzano-Salgado | 2017 | Spain   | Cohort studies | 1202  | Maternal blood | PFOA, PFOS, PFHxS, PFNA | OR=0.90(0.63,1.29) | Maternal age, parity, pre-pregnancy BMI, and fish intake during pregnancy |
|                 |      |         |               |            |               | OR=1.06(0.71,1.58) |                 |                                               |
| Mei-Huei Chen   | 2012 | Taiwan  | Cohort studies | 429    | Maternal blood | PFOA, PFOS, PFUA, PFNA | OR=0.53(0.18,1.55) | Maternal age,  low birth weight index, education level, low (Ln)-transformed cord blood cotinine levels, type of delivery, parity and infant sex, and gestational age of low birth weight |
|                 |      |         |               |            |               | OR=2.61(0.85,8.03) |                 |                                               |
|                 |      |         |               |            |               | OR=1.01(0.53,1.91) |                 |                                               |
|                 |      |         |               |            |               | OR=0.76(0.47,1.23) |                 |                                               |
| Youn Ju Lee     | 2012 | Korea   | Cohort studies | 59      | Maternal blood | PFOA, PFOS, PFHxS | OR=0.54(0.17,3.03) | Gestational age and maternal age |
|                 |      |         |               |            |               | OR=0.98(0.32,3.03) |                 |                                               |
|                 |      |         |               |            |               | OR=0.57(0.19,1.75) |                 |                                               |

PFOA perfluorooctanoic acid, PFOS perfluorooctane sulfonate, PFHxS perfluorohexane sulfonate, PFNA perfluorononanoic acid, PFUA perfluoroundecanoic acid, OR odds ratio, BMI body mass index

\[a\] The result for the low level of exposure quantile

\[b\] The result for the medium level of exposure quantile

\[c\] The result for the high level of exposure quantile

\[d\] The result for the highest level of exposure quantile
### Table 2: Methodological quality of studies included in the meta-analysis

| Study                                | Selection | Representativeness of the exposed cohort | Outcome of interest not present at start of study | Control for important factor or additional factor | Outcome assessment | Follow-up long enough for outcome to occur | Adequacy of follow-up of cohorts |
|--------------------------------------|-----------|------------------------------------------|-------------------------------------------------|-------------------------------------------------|--------------------|--------------------------------------------|---------------------------------|
| Darrow et al. 2013                   | *         | *                                        | *                                               | *                                               | *                  | *                                         | *                               |
| Stein et al. 2009                    | *         | *                                        | *                                               | *                                               | *                  | *                                         | *                               |
| Manzano-Salgado et al. 2017          | *         | *                                        | *                                               | *                                               | *                  | *                                         | *                               |
| Chen et al. 2012                     | *         | *                                        | *                                               | *                                               | *                  | *                                         | *                               |
| Lee et al. 2013                      | *         | *                                        | *                                               | *                                               | *                  | *                                         | *                               |
| Case-control studies                 | Selection | Representativeness of the exposed cohort | Outcome of interest not present at start of study | Control for important factor or additional factor | Outcome assessment | Follow-up long enough for outcome to occur | Adequacy of follow-up of cohorts |
| Savitz et al. 2012                   | *         | *                                        | *                                               | *                                               | *                  | *                                         | *                               |

Score: 8
was performed using the fixed effect model when there was no significant heterogeneity ($I^2 < 50\%$ or $P$-value > 0.05). Otherwise, the analysis was performed using the random effect model. To eliminate publication bias, Begg’s test and Egger’s regression asymmetry tests were used and presented in the form of funnel plots. To observe the stability of the comprehensive results, we performed several sensitivity analyses. The meta-analysis was conducted using Stata version 11 for windows.

Result

Study characteristics

The systematic search scheme of literature was shown in Fig. 1. According to the search strategy, investigators searched 790 articles from PubMed, Web of science, Embase databases and Google Scholar. After excluding the duplicate items, there were 485 remaining articles.

Then, 82 articles were selected for further evaluation by screening the titles and abstracts. According to the inclusion and exclusion criteria, researchers excluded 76 articles, of which nine articles were no full text, one article was a meta-analysis, 28 articles were no complete data, 33 articles used multiple linear regression model, four articles studied the relationship between maternal PFASs exposure and overweight of offspring, and one article was inappropriate data. Finally, the meta-analysis included six articles, of which five prospective birth cohort studies (Stein et al. 2009, Chen et al. 2012, Darrow et al. 2013, Lee et al. 2013, Manzano-Salgado et al. 2017) and one case-control study (Savitz et al. 2012). These studies were all of the high quality. The specific information of the articles was shown in Table 1.

Maternal PFOA exposure and LBW of offspring

There were six articles related to the relationship between maternal PFOA exposure and LBW of offspring. Savitz et al. included two groups of different exposure people (Savitz et al. 2012), so there were seven groups of data for meta-analysis. Meta-analysis was performed using a fixed effect model. The result showed no correlation between maternal PFOA exposure and LBW of offspring (OR = 0.90, 95% CI = 0.80–1.01) with low heterogeneity ($I^2 = 18.4\%$, $P = 0.289$). The result was shown in Fig. 2. To further understand the impact of different regions on the result, the researchers conducted a grouping analysis according to regions. The result showed that regions had no impact on the final results. The result was presented in Fig. 3.

Maternal PFOS exposure and LBW of offspring

There were five articles related to the relationship between maternal PFOS exposure and LBW in offspring. Meta-analysis was performed using a fixed-effect model. The result showed a positive correlation between maternal PFOS exposure and LBW of offspring (OR = 1.32, 95% CI = 1.09–1.55) without heterogeneity ($I^2 = 0.00\%$, $P = 0.570$). The result was shown in Fig. 2. To further understand the impact of different regions on the result, the researchers conducted a grouping analysis according to regions. The result showed a positive correlation between maternal PFOS exposure and LBW of offspring in American (OR = 1.44, 95% CI = 1.15–1.72). The result was presented in Fig. 4.

Publication bias and sensitivity analysis

The results of Begg’s tests showed no evidence of material publication bias (P = 0.133 for PFOA) (P = 1.000 for PFOS) (Fig. 5). In order to know whether the results were stable, the researchers conducted sensitivity analysis (Fig. 6). The result showed that the relationship between maternal PFOA exposure and LBW of offspring had changed after excluding study one of Savitz et al. (Savitz et al. 2012). It showed a negative correlation between the two (OR = 0.82, 95% CI = 0.65–0.98). The result was shown in Fig. 7. There was no statistical significance between maternal PFOS exposure and LBW of offspring after excluding Stein et al. (Stein et al. 2009) (OR = 1.16, 95% CI = 0.83–1.49). The result was shown in Fig. 8. Researchers obtained the opposite conclusion after the exclusion, which indicated that the sensitivity was high, and the robustness of the results was low. Researchers argued that further clarify the source of controversy was needed.

Discussion

The results of the meta-analysis showed that there was no correlation between maternal PFOA exposure and LBW of offspring (OR = 0.90, 95% CI = 0.80–1.01). However, there was a significant positive correlation between maternal PFOS exposure and LBW of offspring (OR = 1.32, 95% CI = 1.09–1.55). Further grouping analysis showed that maternal PFOS exposure was associated with LBW of offspring in American (OR = 1.44, 95% CI = 1.15–1.72). The study was the first meta-analysis to explore the relationship between maternal PFASs exposure and LBW of offspring. Our findings were of great significance for the protection of women and children who were in PFASs-contaminated areas.

At present, there were several possible mechanisms to link maternal PFASs exposure with LBW of offspring. The first mechanism was the role of thyroid hormone, which was essential for the natural growth and development of the fetus.
PFASs exposure could change thyroid hormone signal and interfere with thyroid hormone function and homeostasis (Long et al. 2013), which might cause maternal hypothyroidism and lead to LBW (Blazer et al. 2003). The second mechanism was the effect of estrogen. Kaijser et al. had proved that estrogen was very important in promoting fetal growth (Kaijser et al. 2000). PFASs could interfere with the estrogen receptor of the human body (Kjeldsen and Bonefeld-Jørgensen 2013). PFASs could also affect the expression of the estrogen response gene and cause the change of estrogen synthesis (Benninghoff et al. 2011). Exposure to PFASs might affect the estrogen homeostasis and fetal growth during pregnancy (Wang et al. 2019), resulting in LBW. Other mechanisms included that PFASs could interfere with average placental metastasis and reduce the nutritional intake of the fetus, resulting in LBW of offspring. PFASs could also directly produce toxicity to the fetus to cause fetal thyroid dysplasia and lead to LBW (Nolan, Nolan et al. 2009). At the same time, maternal immunotoxicity and susceptibility to infection might also be a potential mechanism of fetal LBW. The adverse effects of immune system had been confirmed in vitro experiments, animal experiments, and children’s experiments (DeWitt et al. 2012). In conclusion, it was reasonable that PFASs might lead to LBW of offspring. However, its mechanism has not been determined in human, so it needs to be further studied.

Given that maternal PFASs exposure can lead to LBW of offspring, pregnant women are cautioned against exposure to such substances. Social media should enhance publicity and education. For instance, they can use personal protection installations and breathing mask when going out; try to avoid contact with carpet, antifouling agent, and foam extinguishing agent in daily life; and do not wear clothes containing PFASs. Meanwhile, they should eat less food containing PFASs, use glass tableware when eating, and drink the tap water which boiled after performing filter disinfection treatment.
Moreover, the country should establish a strict control mechanism to manage PFASs.

This meta-analysis found no significant correlation between maternal PFOA exposure and LBW of offspring, which was the same as that of Nolan et al (Nolan, Nolan et al. 2009). In this review, 14 articles were evaluated by researchers. In most studies, higher PFOA concentration exposure was associated with mean birth weight loss, but only some results were statistically significant (Bach et al. 2015). In another meta-analysis, the results showed that early exposure to PFOA was associated with an increased risk of childhood obesity (Liu et al. 2018). By comparison, researchers found that no large number of studies had shown that PFOA was associated with LBW in offspring. Also, the results of this

| Study ID | OR (95% CI) | Weight |
|----------|-------------|---------|
| PFOA     |             |         |
| Lyndsey A. Darrow (2013) | 1.01 (0.61, 1.41) | 7.49 |
| David A. Savitz (2012 1)  | 0.97 (0.82, 1.11) | 56.98 |
| David A. Savitz (2012 2)  | 1.03 (0.64, 1.41) | 8.08 |
| Cheryl R. Stein (2009)    | 0.58 (0.28, 0.88) | 13.31 |
| Cynthia B. Manzano-Salgado (2017) | 0.90 (0.63, 1.29) | 11.00 |
| Mei-Huei Chen (2012)      | 0.53 (0.18, 1.55) | 2.55 |
| Youn Ju Lee (2012)        | 0.54 (0.17, 3.03) | 0.59 |
| Subtotal (I-squared = 18.4%, p = 0.289) | 0.90 (0.80, 1.01) | 100.00 |

| PFOS     |             |         |
|----------|-------------|---------|
| Lyndsey A. Darrow (2013) | 1.33 (0.76, 1.90) | 16.68 |
| Cheryl R. Stein (2009)    | 1.47 (1.15, 1.80) | 51.31 |
| Cynthia B. Manzano-Salgado (2017) | 1.06 (0.71, 1.58) | 26.84 |
| Mei-Huei Chen (2012)      | 2.51 (0.85, 8.03) | 0.42 |
| Youn Ju Lee (2012)        | 0.98 (0.32, 3.03) | 2.95 |
| Subtotal (I-squared = 0.0%, p = 0.570) | 1.32 (1.09, 1.55) | 100.00 |

Fig. 2 Association between maternal PFASs exposure and LBW of offspring

Fig. 3 Association between maternal PFOA exposure and LBW of offspring in different regions
meta-analysis showed that there was a significant positive correlation between maternal PFOS exposure and LBW of offspring. By consulting relevant articles, researchers found that most studies only believed that maternal PFOS exposure was related to a birth weight loss of offspring. For example, Kishi et al. concluded that maternal PFOS exposure was associated with birth weight loss in girls (Kishi et al. 2015). Meng et al. reported that every doubling of PFOS exposure was associated with a 45 g reduction in birth weight (Meng et al. 2018). This study concluded that maternal PFOS exposure would increase the birth weight of male infants (de Cock et al. 2016). Researchers found that no large number of studies had shown that PFOS was associated with LBW in offspring. In summary, this meta-analysis had great clinical significance, which can provide a theoretical basis for the prevention of LBW and the improvement of birth quality and population quality.

According to the results of sensitivity analysis, there was a negative correlation between maternal PFOA exposure and LBW of offspring after excluding study one of Savitz et al (Savitz et al. 2012). Through analysis, the researchers found that this study population’s self-reported residences locations were inaccurate, and it was unable to accurately predict the PFOA levels at a given place and time. Investigators estimated the selected PFOA exposure index through the relevant model, and it was not accurately measured, resulting in inaccurate exposure. Also, PFOA pharmacokinetics had individual differences. These limitations led to significant errors in the estimation of PFOA exposure and made the result errors larger. There was no statistical significance between maternal PFOS exposure and LBW of offspring in different regions.

| Study ID | OR (95% CI) | Weight |
|----------|-------------|--------|
| American |             |        |
| Lyndsey A. Darrow (2013) | 1.33 (0.76, 1.90) | 24.53 |
| Cheryl R. Stein (2009) | 1.47 (1.15, 1.80) | 75.47 |
| Subtotal (I-squared = 0.6%, p = 0.676) | 1.44 (1.15, 1.72) | 100.00 |
| Non-American |             |        |
| Cynthia B. Manzano-Salgado (2017) | 1.06 (0.71, 1.58) | 89.47 |
| Mei-Huei Chen (2012) | 2.61 (0.85, 8.03) | 1.31 |
| Youn Ju Lee (2012) | 0.98 (0.32, 3.03) | 9.22 |
| Subtotal (I-squared = 0.0%, p = 0.696) | 1.07 (0.65, 1.48) | 100.00 |

Fig. 4 Association between maternal PFOS exposure and LBW of offspring in different regions

Fig. 5 Analysis of publication bias between maternal PFASs exposure and LBW of offspring a PFOA; b PFOS
exposure and LBW of offspring after excluding Stein et al (Stein et al. 2009). Through analysis, the researchers found that this study only relied on the maternal self-report to assess whether the offspring were LBW infants. It did not accurately assess the birth weight according to the hospital’s birth records. So, the final result had large errors. Therefore, the sensitivity of the results of meta-analysis increased after the inclusion of those studies. The elevated sensitivity of the results made the results of this meta-analysis had some degree of unreliability. Moreover, the interpretation of the results should be more rigorous.

There was a positive correlation between maternal PFOS exposure and LBW of offspring in American. To a certain extent, this proved that the region impacted the birth weight of offspring. In this article, researchers randomly selected 1400 mothers and infants from the Danish birth cohort for analysis. They did not observe a statistically significant relationship between maternal PFOS exposure and LBW of offspring (Fei et al. 2007). Chen et al. concluded that maternal PFOS exposure showed an inverse relationship with a birth weight of offspring by analyzing 429 pairs of mothers and infants in the Taiwan birth cohort (Chen and Yin 2017). Thus, we could see that the results of maternal PFOS exposure and LBW of offspring were different in different regions. Therefore, we should conduct more studies in the future.

Our research had many advantages. First of all, the included studies were prospective cohort studies and retrospective case-control studies, all of which were high-quality articles. Secondly, all the included literature made the logistic regression model and the results of meta-analysis without heterogeneity. The effect estimates of the included studies might be highly comprehensive, which can availably explore the relationship between maternal PFASs exposure and LBW in offspring. Thirdly, there was no publication bias in the meta-

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**Fig. 6** Sensitivity analysis of maternal PFASs exposure a PFOA; b PFOS

**Fig. 7** Association between maternal PFOA exposure and LBW of offspring

| Study                      | %     |
|----------------------------|-------|
| ID | OR (95% CI) | Weight |
|----|-------------|--------|
| PFOA | | |
| Lyndsey A. Darrow (2013) | 1.01 (0.61, 1.41) | 17.40 |
| David A. Savitz (2012) | 1.03 (0.64, 1.41) | 18.79 |
| Cheryl R. Stein (2009) | 0.58 (0.28, 0.88) | 30.94 |
| Cyntia B. Manzano-Salgado (2017) | 0.90 (0.63, 1.29) | 25.57 |
| Mei-Huei Chen (2012) | 0.53 (0.18, 1.55) | 5.93 |
| Youn Ju Lee (2012) | 0.54 (0.17, 3.03) | 1.36 |
| Subtotal (I-squared = 9.6%, p = 0.355) | 0.82 (0.65, 0.98) | 100.00 |
analysis, which made the results credible. However, there were still limitations in this paper. The meta-analysis included few studies: six studies on the relationship between maternal PFOA exposure and LBW risk of offspring and five studies on the relationship between maternal PFOS exposure and LBW risk of offspring. The number of included literature was small, which might have a definite impact on the final results. Also, some studies did not report the relationship between maternal PFASs exposure and LBW of offspring and did not report its OR value. Some studies reported that PFASs was associated with LBW, but the reported data were incomplete, which might lead to some bias in the final results.

The results of this meta-analysis had definite scientific value and significance. By exploring the relationship between maternal PFASs exposure and LBW of offspring, we obtained a certain degree of the positive correlation between the two, which suggested that PFASs had adverse effects on fetal growth and development and provided distinct information for clinical. Given the prevalence of environmental PFASs pollution and its potential threat to the general population, understanding the adverse effects of PFASs on fetal growth and development was of great significance to public health decision-making. The present meta-analysis had definite reference value.

This study only included a small number of studies and only solved the relationship between PFOA and PFOS and LBW of offspring. We did not explore the relationship between exposure to perfluorononanoic acid (PFNA), perfluorohexane sulfonate (PFHxS), and LBW of offspring. Therefore, future studies should focus on maternal exposure to PFASs other than PFOA and PFOS with LBW of offspring. Moreover, we should further explore the effect of gender difference to know whether different outcomes would result in the association between maternal PFASs exposure and LBW of offspring. Also, we found that regional variability could also have different effects on the results. Further research should be conducted in different regions.

**Conclusion**

The present meta-analysis showed a significant positive association between maternal prenatal PFOS exposure and LBW of offspring, but no association between maternal PFOA exposure and LBW of offspring. Meanwhile, we observed regional factors might influence the occurrence of LBW.

These findings expand our knowledge on the association between PFASs exposure and fetal birth outcomes and underline that reducing environmental PFASs pollution and decreasing maternal PFASs exposure is essential to improve birth outcomes. More studies should be further encouraged to understand the mechanisms.

**Availability of data and materials** The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Author contribution** Conceived and designed the experiments, XLZ, XHL, and SJS; performed the experiments, ZXL, WJW, RL, XW, and YXN; analyzed the data, TRC and ABQ; contributed analysis tools, XLZ; wrote the paper, XHL, TRC, and ABQ. All authors read and approved the final manuscript.
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Declarations

Ethics approval and consent to participate  Not applicable.

Consent for publication  Not applicable.

Competing interests  The authors declare no competing interests.

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