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 were 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 America (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.

1. 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, Lanphear 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 perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA). 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, Wong et al. 2007, Woods, Lanphear et al. 2017). The results show that the final metabolites of PFASs in the environment are PFOS and PFOA (Lau, Butenhoff et al. 2004). 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, Li 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, Biro 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. World Health Organization defines Low birth weight (LBW) as 2499 grams 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, tumour, osteoporosis, neuropsychiatric disease. This hypothesis has attracted extensive attention from scholars, and many investigators carry out epidemiology 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.

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, Nakajima 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, McLaughlin et al. 2008). Chen et al. also observed a negative correlation between the level of PFOS in cord blood and fetal growth (Chen, Ng et al. 2017). A recent epidemiological survey of 321 pairs of mothers and infants from Guangzhou, China further confirmed these findings (Li, Zeng et al. 2017).

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, Bech 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. To our knowledge, there is no systematic review or meta-analysis of the relationship between maternal PFASs exposure and low birth weight of offspring. In light of the wide range of PFASs pollution, understanding the adverse effects of PFASs on fetal growth and development is of great significance for public health decision-making. Through this meta-analysis, we can improve the birth quality and population quality of the newborns, meanwhile provide a theoretical basis for the prevention and control of PFASs pollution.

2. Method

2.1 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”, “PFAA”, “PFNA”, “PFC”, “PFHxS”, “PFOSA”, “Body Mass Index”, “Birth Weight”, “Birth Weights”, “Weight, Birth”, “Weights, Birth”, “Infant, Low Birth Weight”, “Low-Birth-Weight Infant”, “Infant, Low-Birth-Weight”, “Infants, Low-Birth-Weight”, “Low Birth Weight Infant”, “Low-Birth-Weight Infants”, “Low Birth Weight”, “Birth Weight, Low”, “Birth Weights, Low”, “Low Birth Weights”, “Infant, Very Low Birth Weight”, “Very-Low-Birth-Weight Infant”, “Infant, Very-Low-Birth-Weight”, “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”, “premature birth”, “small for gestational age”, “fetal growth”, “IUGR”, “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 “perfluoroalkyl acids” or “fluorinated organic compounds” or PFOA or PFOS or PFAA or PFNA or PFC or PFHxS or PFOSA) and (“Birth Weight” or “Birth Weights” or “Weight, Birth” or “Weighes, birth” or “Infant, Low Birth Weight” or “Low-Birth-Weight Infant” or “Infant, Low-Birth-Weight” or “Infants, Low-Birth-Weight” or “Low Birth Weight Infant” or “Low-Birth-Weight Infants” or “Low Birth Weight” or “Birth Weight, Low” or “Birth Weights, Low” or “Low Birth Weights” or “Infant, Very Low Birth Weight” or “Very-Low-Birth-Weight, Infant” or “Infant, Very-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 “perfluoroalkyl acids” or “fluorinated organic compounds” or PFOA or PFOS or PFAA 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 not mouse.

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

2.2 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. The remaining studies were marked as potentially qualified.

Inclusion criteria: (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) or the risk ratio (RR) and its 95% confidence intervals (CI) of LBW, or provided sufficient data to allow adequate estimation of the or/RR and 95% CI; (d) logistic regression model was used in the study.

Exclusion criteria: (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; (d) low-quality research.

2.3 Data extraction and quality assessment

The data were extracted independently from the publication by researchers in a standard format. 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 it's 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). 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. The results of the quality assessment are shown in Table 2. All of them were of high quality.

2.4 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 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.

3. Result

3.1 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 and Embase databases. 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, Savitz et al. 2009, Chen, Ha et al. 2012, Darrow, Stein et al. 2013, Lee, Kim et al. 2013, Manzano-Salgado, Casas et al. 2017) and one case-control study (Savitz, Stein et al. 2012). These studies were all of the high quality. The specific information of the articles was shown in Table 1.

3.2 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, Stein 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.

3.3 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 America (OR = 1.44, 95% CI = 1.15-1.72). The result was presented in Fig. 4.

3.4 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, Stein et al. 2012). It showed a negative correlation between 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, Savitz 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.

4. 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 America (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, Ghisari et al. 2013), which might cause maternal hypothyroidism and lead to LBW (Blazer, Moreh-Waterman 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, Granath 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, Bisson et al. 2011). Exposure to PFASs might affect the estrogen homeostasis and fetal growth during pregnancy (Wang, Du 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, Peden-Adams 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.

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, Bech 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, Yang 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 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, Nakajima et al. 2015). Meng et al. reported that every doubling of PFOS exposure was associated with a 45 grams reduction in birth weight (Meng, Inoue et al. 2018). This study concluded that maternal PFOS exposure would increase the birth weight of male infants (de Cock, De Boer 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, Stein 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 after excluding Stein et al (Stein, Savitz 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 America. 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, McLaughlin et al. 2007). Chen et al. concluded that maternal PFOS exposure showed an inverse relationship with a birth weight of offspring by analysing 429 pairs of mothers and infants in the Taiwan birth cohort (Chen, Ng et al. 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-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 acute 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.

5. 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.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Conceived and designed the experiments: XLZ XHL SJS; Performed the experiments: ZXL WJW RL XW YXN; Analyzed the data: TRC ABQ; Contributed analysis tools: XLZ; Wrote the paper: XHL TRC ABQ. All authors read and approved the final manuscript.

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References

Bach, C. C., B. H. Bech, N. Brix, E. A. Nohr, J. P. Bonde and T. B. Henriksen (2015). "Perfluoroalkyl and polyfluoroalkyl substances and human fetal growth: a systematic review." Crit Rev Toxicol **45**(1): 53-67.https://doi.org/10.3109/10408444.2014.952400

Bach, C. C., B. H. Bech, E. A. Nohr, J. Olsen, N. B. Matthiesen, E. C. Bonefeld-Jorgensen, R. Bossi and T. B. Henriksen (2016). "Perfluoroalkyl Acids in Maternal Serum and Indices of Fetal Growth: The Aarhus Birth Cohort." Environ Health Perspect **124**(6): 848-854.https://doi.org/10.1289/ehp.1510046

Benninghoff, A. D., W. H. Bisson, D. C. Koch, D. J. Ehresman, S. K. Kolluri and D. E. Williams (2011). "Estrogen-like activity of perfluoroalkyl acids in vivo and interaction with human and rainbow trout estrogen receptors in vitro." Toxicol Sci **120**(1): 42-58.https://doi.org/10.1093/toxsci/kfq379

Blazer, S., Y. Moreh-Waterman, R. Miller-Lotan, A. Tamir and Z. Hochberg (2003). "Maternal hypothyroidism may affect fetal growth and neonatal thyroid function." Obstet Gynecol **102**(2): 232-241.https://doi.org/10.1016/s0029-7844(03)00513-1

Calafat, A. M., L. Y. Wong, Z. Kuklenyik, J. A. Reidy and L. L. Needham (2007). "Polyfluoroalkyl chemicals in the U.S. population: data from the National Health and Nutrition Examination Survey (NHANES) 2003-2004 and comparisons with NHANES 1999-2000." Environ Health Perspect **115**(11): 1596-1602.https://doi.org/10.1289/ehp.10598

Chen, M. H., E. H. Ha, T. W. Wen, Y. N. Su, G. W. Lien, C. Y. Chen, P. C. Chen and W. S. Hsieh (2012). "Perfluorinated compounds in umbilical cord blood and adverse birth outcomes." PLoS One **7**(8): e42474.https://doi.org/10.1371/journal.pone.0042474

Chen, M. H., S. Ng, C. J. Hsieh, C. C. Lin, W. S. Hsieh and P. C. Chen (2017). "The impact of prenatal perfluoroalkyl substances exposure on neonatal and child growth." Sci Total Environ **607-608**: 669-675.https://doi.org/10.1016/j.scitotenv.2017.06.273

Darrow, L. A., C. R. Stein and K. Steenland (2013). "Serum perfluorooctanoic acid and perfluorooctane sulfonate concentrations in relation to birth outcomes in the Mid-Ohio Valley, 2005-2010." Environ Health Perspect **121**(10): 1207-1213.https://doi.org/10.1289/ehp.1206372

de Cock, M., M. R. De Boer, M. Lamoree, J. Legler and M. Van De Bor (2016). "Prenatal exposure to endocrine disrupting chemicals and birth weight-A prospective cohort study." J Environ Sci Health A Tox Hazard Subst Environ Eng **51**(2): 178-185.https://doi.org/10.1080/10934529.2015.1087753

DeWitt, J. C., M. M. Peden-Adams, J. M. Keller and D. R. Germolec (2012). "Immunotoxicity of perfluorinated compounds: recent developments." Toxicol Pathol **40**(2): 300-311.https://doi.org/10.1177/0192623311428473

Fei, C., J. K. McLaughlin, R. E. Tarone and J. Olsen (2007). "Perfluorinated chemicals and fetal growth: a study within the Danish National Birth Cohort." Environ Health Perspect **115**(11): 1677-1682.https://doi.org/10.1289/ehp.10506

Fei, C., J. K. McLaughlin, R. E. Tarone and J. Olsen (2008). "Fetal growth indicators and perfluorinated chemicals: a study in the Danish National Birth Cohort." Am J Epidemiol **168**(1): 66-72.https://doi.org/10.1093/aje/kwn095

Kaijser, M., F. Granath, G. Jacobsen, S. Cnattingius and A. Ekbom (2000). "Maternal pregnancy estriol levels in relation to anamnestic and fetal anthropometric data." Epidemiology **11**(3): 315-319.https://doi.org/10.1097/00001648-200005000-00015

Kajee, N. and E. Sobngwi (2018). "The Developmental Origins of Health and Disease and Sustainable Development Goals: mapping the way forward." **9**(1): 5-9.https://doi.org/10.1017/s2040174417000630

Kishi, R., T. Nakajima, H. Goudarzi, S. Kobayashi, S. Sasaki, E. Okada, C. Miyashita, S. Itoh, A. Araki, T. Ikeno, Y. Iwasaki and H. Nakazawa (2015). "The Association of Prenatal Exposure to Perfluorinated Chemicals with Maternal Essential and Long-Chain Polyunsaturated Fatty Acids during Pregnancy and the Birth Weight of Their Offspring: The Hokkaido Study." Environ Health Perspect **123**(10): 1038-1045.https://doi.org/10.1289/ehp.1408834

Kjeldsen, L. S. and E. C. Bonefeld-Jørgensen (2013). "Perfluorinated compounds affect the function of sex hormone receptors." Environ Sci Pollut Res Int **20**(11): 8031-8044.https://doi.org/10.1007/s11356-013-1753-3

Lau, C., J. L. Butenhoff and J. M. Rogers (2004). "The developmental toxicity of perfluoroalkyl acids and their derivatives." Toxicol Appl Pharmacol **198**(2): 231-241.https://doi.org/10.1016/j.taap.2003.11.031

Lee, Y. J., M. K. Kim, J. Bae and J. H. Yang (2013). "Concentrations of perfluoroalkyl compounds in maternal and umbilical cord sera and birth outcomes in Korea." Chemosphere **90**(5): 1603-1609.https://doi.org/http://dx.doi.org/10.1016/j.chemosphere.2012.08.035

Li, M., X. W. Zeng, Z. M. Qian, M. G. Vaughn, S. Sauve, G. Paul, S. Lin, L. Lu, L. W. Hu, B. Y. Yang, Y. Zhou, X. D. Qin, S. L. Xu, W. W. Bao, Y. Z. Zhang, P. Yuan, J. Wang, C. Zhang, Y. P. Tian, M. Nian, X. Xiao, C. Fu and G. H. Dong (2017). "Isomers of perfluorooctanesulfonate (PFOS) in cord serum and birth outcomes in China: Guangzhou Birth Cohort Study." Environ Int **102**: 1-8.https://doi.org/10.1016/j.envint.2017.03.006

Liu, J., J. Li, Y. Liu, H. M. Chan, Y. Zhao, Z. Cai and Y. Wu (2011). "Comparison on gestation and lactation exposure of perfluorinated compounds for newborns." Environ Int **37**(7): 1206-1212.https://doi.org/10.1016/j.envint.2011.05.001

Liu, P., F. Yang, Y. Wang and Z. Yuan (2018). "Perfluorooctanoic Acid (PFOA) Exposure in Early Life Increases Risk of Childhood Adiposity: A Meta-Analysis of Prospective Cohort Studies." Int J Environ Res Public Health **15**(10).https://doi.org/10.3390/ijerph15102070

Long, M., M. Ghisari and E. C. Bonefeld-Jørgensen (2013). "Effects of perfluoroalkyl acids on the function of the thyroid hormone and the aryl hydrocarbon receptor." Environ Sci Pollut Res Int **20**(11): 8045-8056.https://doi.org/10.1007/s11356-013-1628-7

Manzano-Salgado, C. B., M. Casas, M. J. Lopez-Espinosa, F. Ballester, C. Iniguez, D. Martinez, O. Costa, L. Santa-Marina, E. Pereda-Pereda, T. Schettgen, J. Sunyer and M. Vrijheid (2017). "Prenatal exposure to perfluoroalkyl substances and birth outcomes in a Spanish birth cohort." Environ Int **108**: 278-284.https://doi.org/10.1016/j.envint.2017.09.006

Meng, Q., K. Inoue, B. Ritz, J. Olsen and Z. Liew (2018). "Prenatal Exposure to Perfluoroalkyl Substances and Birth Outcomes; An Updated Analysis from the Danish National Birth Cohort." **15**(9).https://doi.org/10.3390/ijerph15091832

Nolan, L. A., J. M. Nolan, F. S. Shofer, N. V. Rodway and E. A. Emmett (2009). "The relationship between birth weight, gestational age and perfluorooctanoic acid (PFOA)-contaminated public drinking water." Reprod Toxicol **27**(3-4): 231-238.https://doi.org/10.1016/j.reprotox.2008.11.001

Pinney, S. M., F. M. Biro, G. C. Windham, R. L. Herrick, L. Yaghjyan, A. M. Calafat, P. Succop, H. Sucharew, K. M. Ball, K. Kato, L. H. Kushi and R. Bornschein (2014). "Serum biomarkers of polyfluoroalkyl compound exposure in young girls in Greater Cincinnati and the San Francisco Bay Area, USA." Environ Pollut **184**: 327-334.https://doi.org/10.1016/j.envpol.2013.09.008

Savitz, D. A., C. R. Stein, B. Elston, G. A. Wellenius, S. M. Bartell, H. M. Shin, V. M. Vieira and T. Fletcher (2012). "Relationship of Perfluorooctanoic Acid Exposure to Pregnancy Outcome Based on Birth Records in the Mid-Ohio Valley." Environmental Health

Perspectives **120**(8): 1201-1207.https://doi.org/10.1289/ehp.1104752

Stein, C. R., D. A. Savitz and M. Dougan (2009). "Serum levels of perfluorooctanoic acid and perfluorooctane sulfonate and pregnancy outcome." Am J Epidemiol **170**(7): 837-846.https://doi.org/10.1093/aje/kwp212

Wang, H., H. Du, J. Yang, H. Jiang, K. O, L. Xu, S. Liu, J. Yi, X. Qian, Y. Chen, Q. Jiang and G. He (2019). "PFOS, PFOA, estrogen homeostasis, and birth size in Chinese infants." Chemosphere **221**: 349-355.https://doi.org/10.1016/j.chemosphere.2019.01.061

Woods, M. M., B. P. Lanphear, J. M. Braun and L. C. McCandless (2017). "Gestational exposure to endocrine disrupting chemicals in relation to infant birth weight: a Bayesian analysis of the HOME Study." Environ Health **16**(1): 115.https://doi.org/10.1186/s12940-017-0332-3

Tables

Table 1 Characteristics of studies entered in the meta-analysis.

Author	Year	Country	Study size	Exposure type	Exposure substances	Result	Adjustment variables
Lyndsey A. Darrow	2013	America	1629	Maternal blood	PFOA	OR=0.94(0.45,1.98)[a] OR=0.99(0.48,2.05)[b] OR=1.25(0.63,2.46)[c]	maternal age, educational level, smoking status, parity, BMI, self-reported diabetes, time between conception and serum measurement.
					PFOS	OR=0.92(0.44,1.95)[d] OR=1.48(0.71,3.08)[a] OR=1.23(0.57,2.65)[b] OR=1.31(0.59,2.94)[c]	
David A. Savitz	2012	America	3616	Maternal blood	PFOA	OR=1.33(0.60,2.96)[d] OR=0.90(0.70,1.20)[a] OR=1.00(0.80,1.30)[b]	maternal age, education, parity, smoking status, exposure year, state of residence, gestational age.
			4043	Maternal blood	PFOA	OR=1.00(0.80,1.30)[c] OR=0.90(0.50,1.70)[a] OR=1.60(1.00,2.80)[b]	maternal age, education, parity, smoking status, exposure year, state of residence, gestational age.
	2009	America	1589	Maternal blood	PFOA	OR=0.90(0.50,1.70)[c] OR=1.00(0.60,1.70)[a] OR=0.30(0.10,0.90)[b]	
Cheryl R. Stein			4561		PFOS	OR=0.80(0.30,1.90)[c] OR=1.30(0.90,1.80)[a] OR=1.60(1.10,2.30)[b] OR=1.80(1.20,2.80)[c]	maternal age, parity, educational level at interview, smoking status at interview, and PFOS in the analysis of PFOA and PFOA in the analysis of PFOS.
Cyntia B. Manzano-Salgado	2017	Spanish	1202	Maternal blood	PFOA PFOS PFHxS PFNA	OR=0.90(0.63,1.29) OR=1.06(0.71,1.58) OR=0.94(0.71,1.23) OR=0.86(0.63,1.17)	maternal age, parity, pre-pregnancy BMI, and fish intake during pregnancy.
Mei-Huei Chen	2012	Taiwan	429	Maternal blood	PFOA PFOS PFUA PFNA	OR=0.53(0.18,1.55) OR=2.61(0.85,8.03) OR=1.01(0.53,1.91) OR=0.76(0.47,1.23)	maternal age, prepregnancy body mass index, education level, log (Ln)-transformed cord blood cotinine levels, type of delivery, parity and infant sex and gestational age for low birth weight.
Youn Ju Lee	2012	Korea	59	Maternal blood	PFOA PFOS PFHxS	OR=0.54(0.17,3.03) OR=0.98(0.32,3.03) OR=0.57(0.19,1.75)	gestational age and maternal age.

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.

Cohort studies	Selection				Comparability	Outcome			Score
	Representativeness of the exposed cohort	Selection of the unexposed cohort	Ascertainment of exposure	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	
Lyndsey A. Darrow 2013	*	*	*	*	*	*	*	*	8
Cheryl R. Stein 2009	*	*	*	*	*	*	*	*	8
Cyntia B. Manzano-Salgado 2017	*	*	*	*	*	*	*	*	8
Mei-Huei Chen 2012	*	*	*	*	*	*	*	*	8
Youn Ju Lee 2012	*	*	*	*	*	*	*	*	8

Case-control studies	Selection				Comparability	Exposure			Score
	Case definition	Representativeness	Control selection	Control definition	Control for important factor or additional factor	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-Response rate	
David A. Savitz 2012	*	*	*	*	*	*	*	*	8

Figures

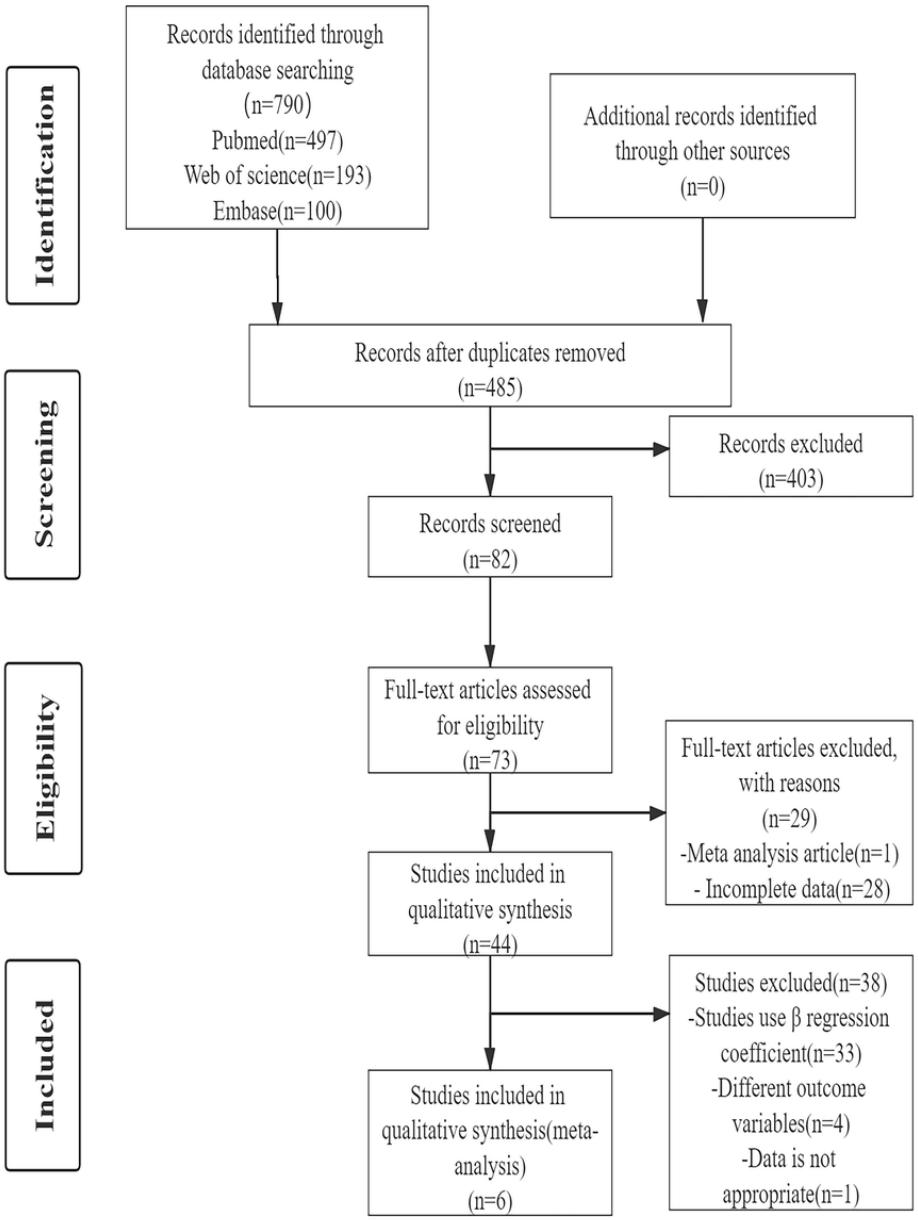

Figure 1

Flow chat of selecting studies for meta-analysis

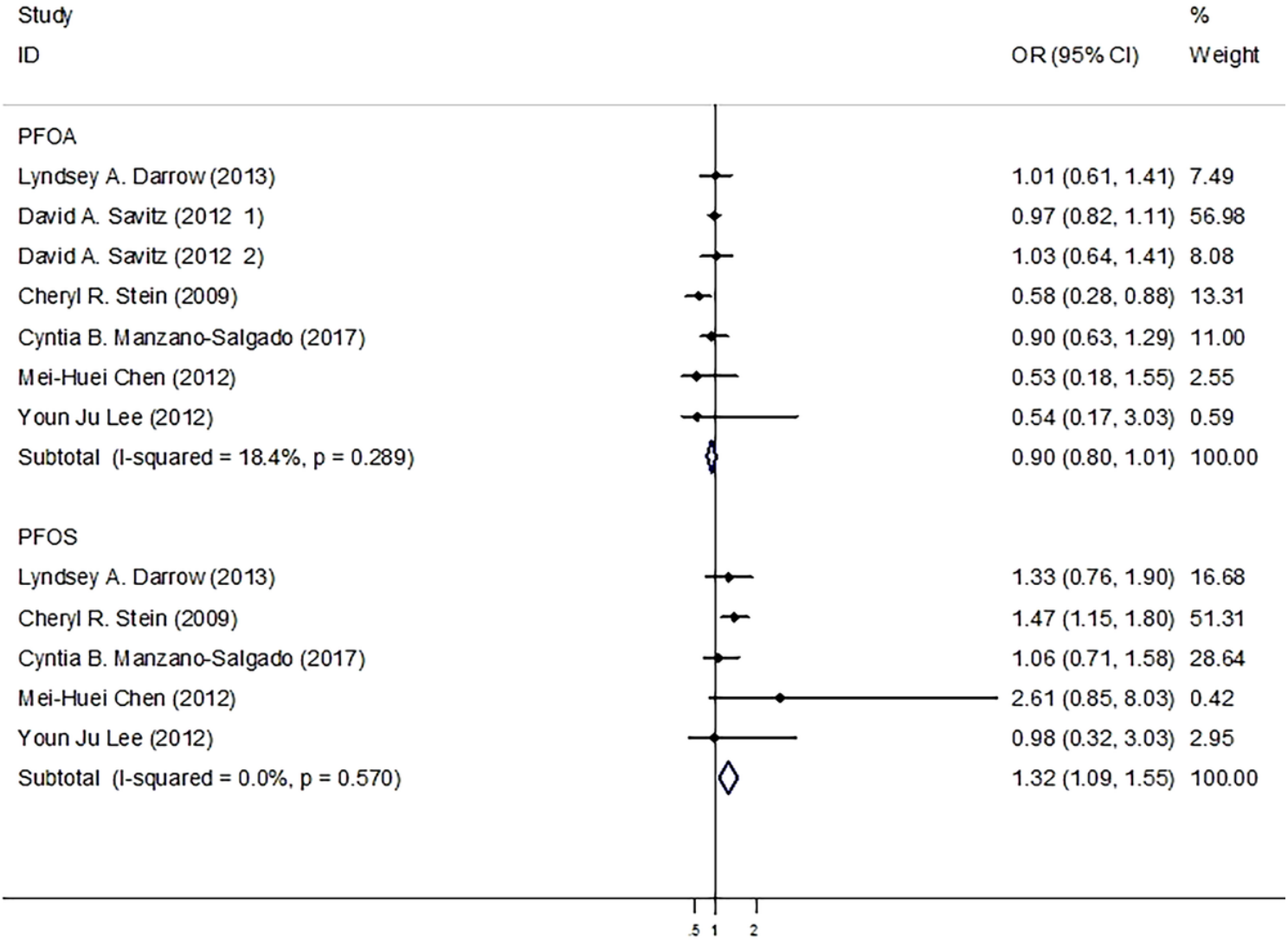

Figure 2

Association between maternal PFASs exposure and LBW of offspring

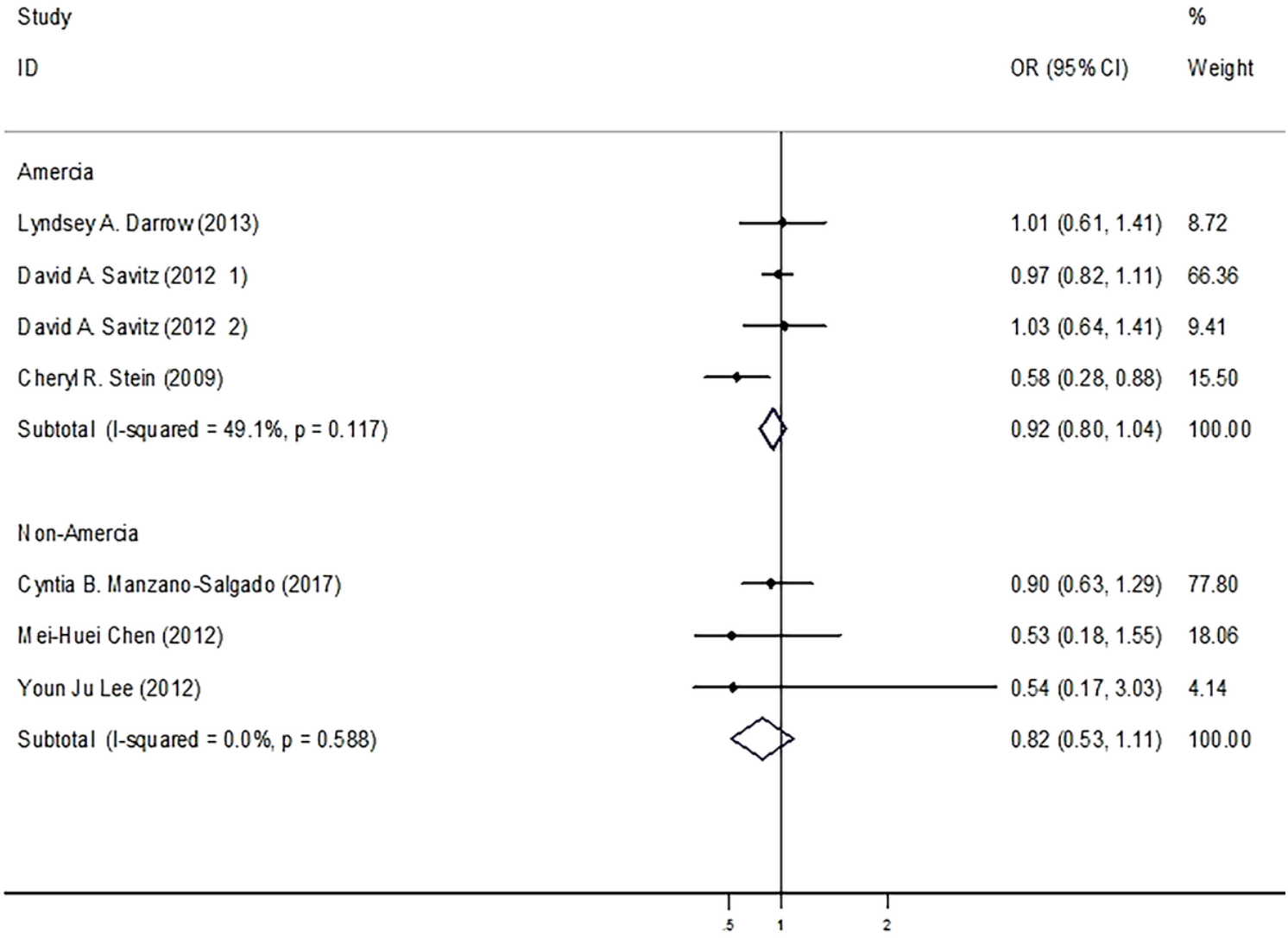

Figure 3

Association between maternal PFOA exposure and LBW of offspring in different regions

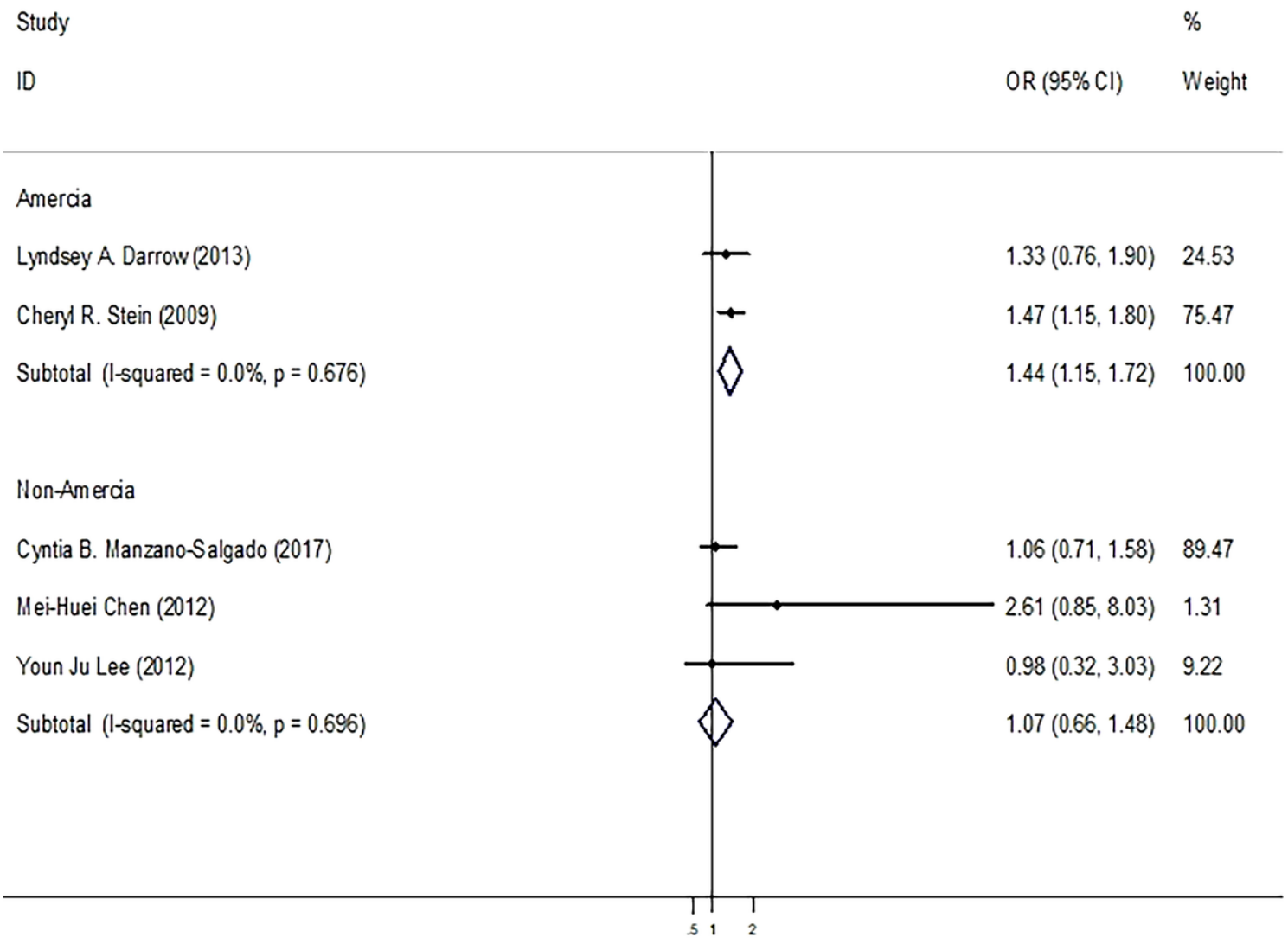

Figure 4

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

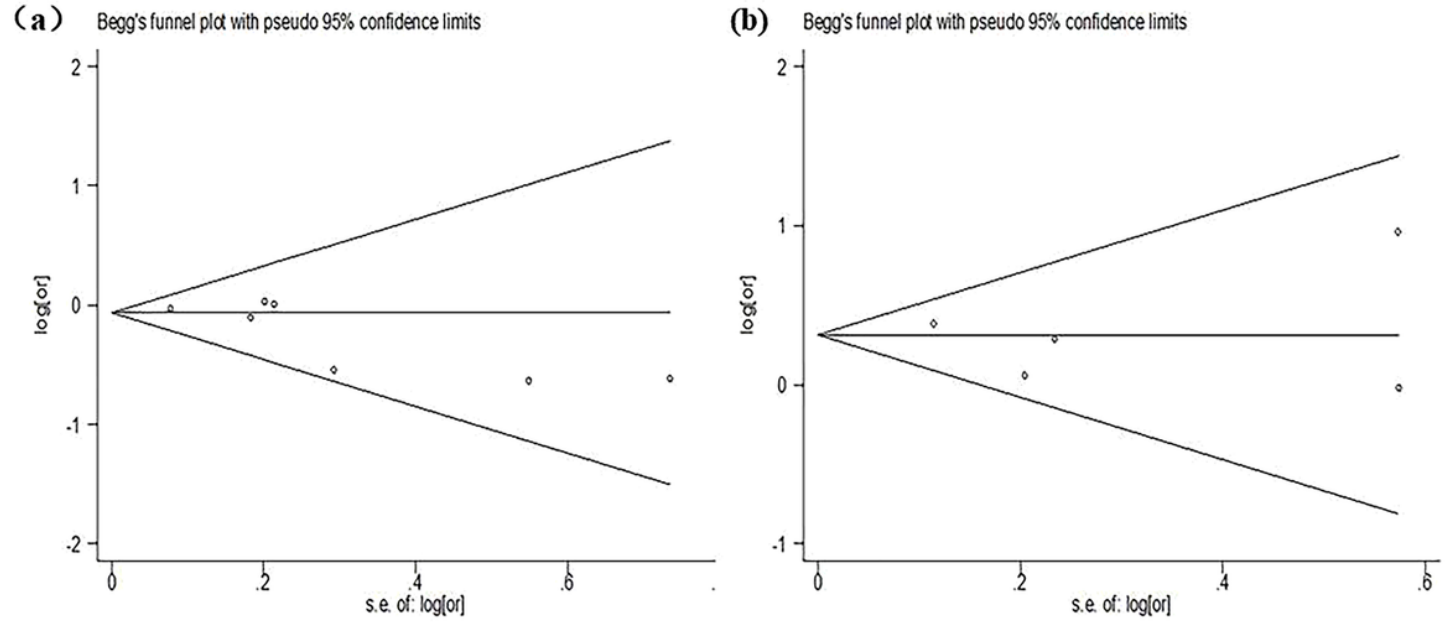

Figure 5

Analysis of publication bias between maternal PFASs exposure and LBW of offspring (a) PFOA; (b) PFOS

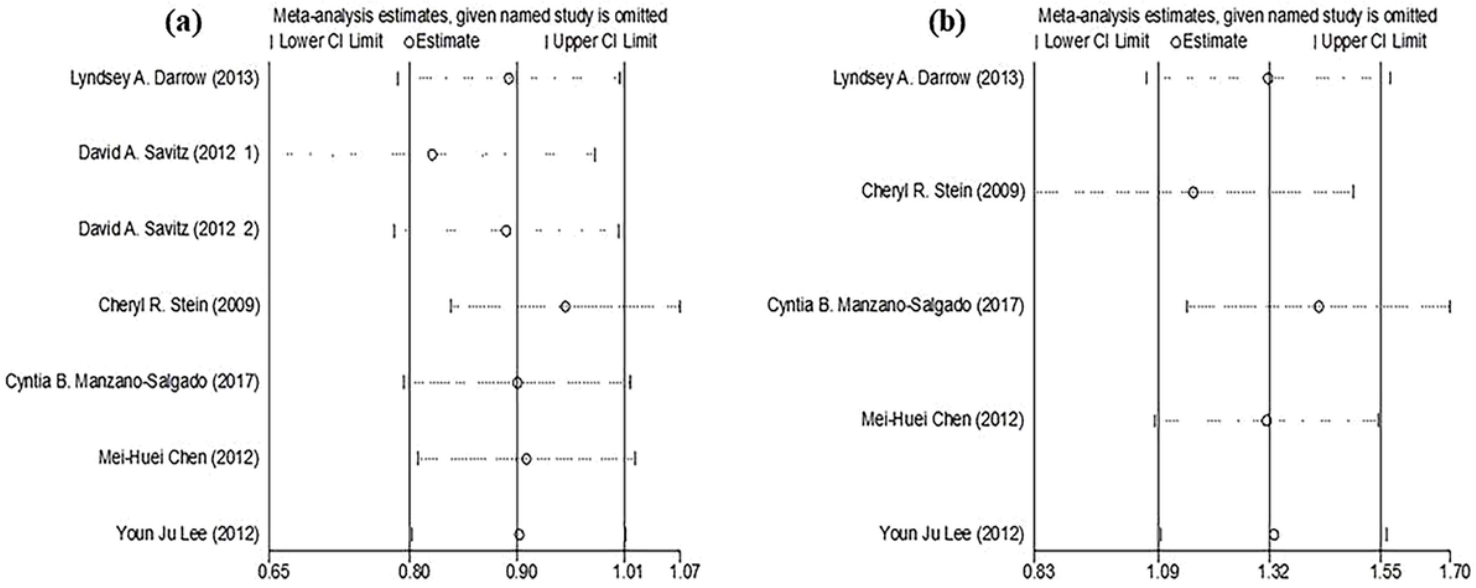

Figure 6

Sensitivity analysis of maternal PFASs exposure (a) PFOA; (b) PFOS

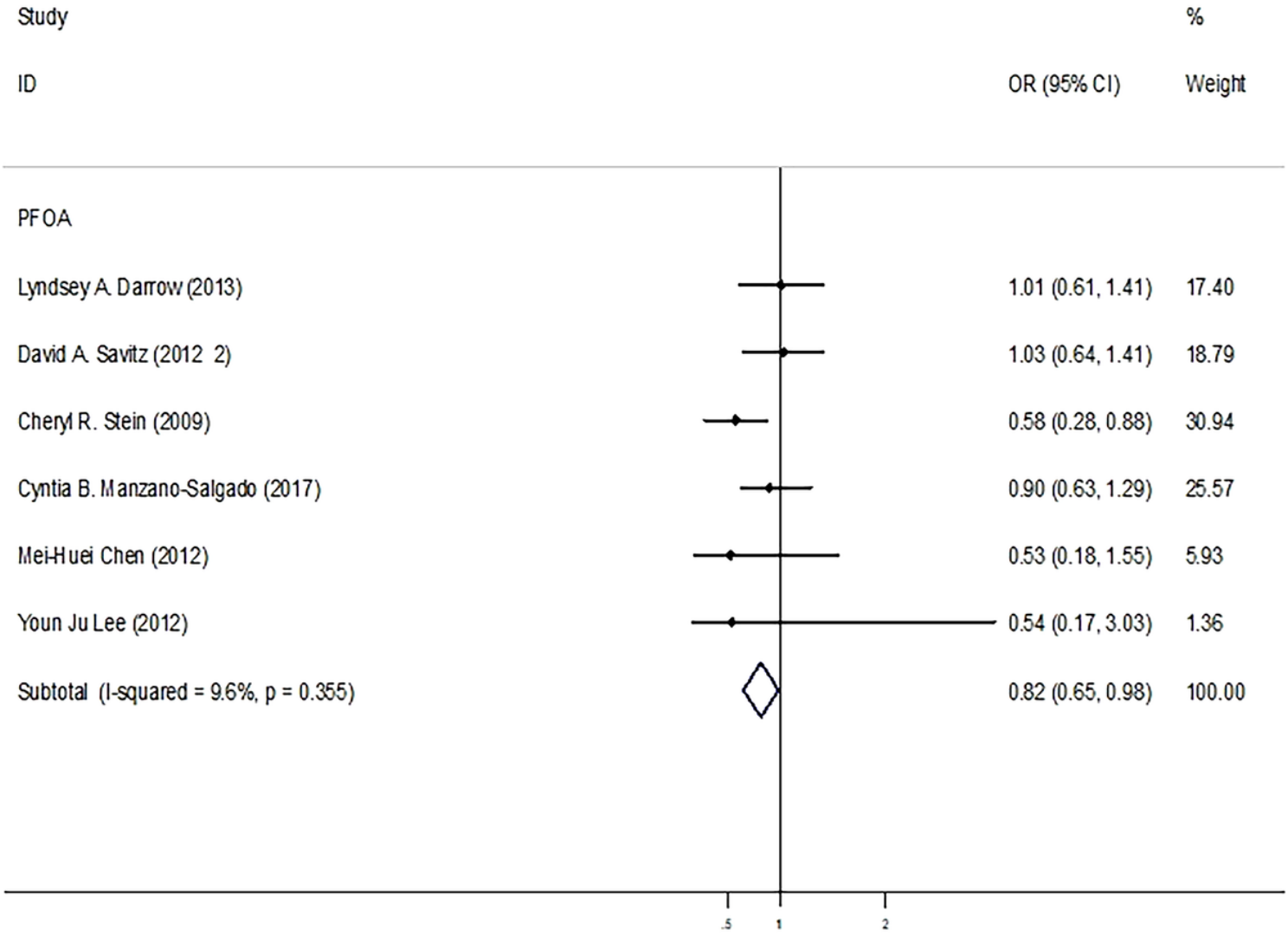

Figure 7

Association between maternal PFOA exposure and LBW of offspring

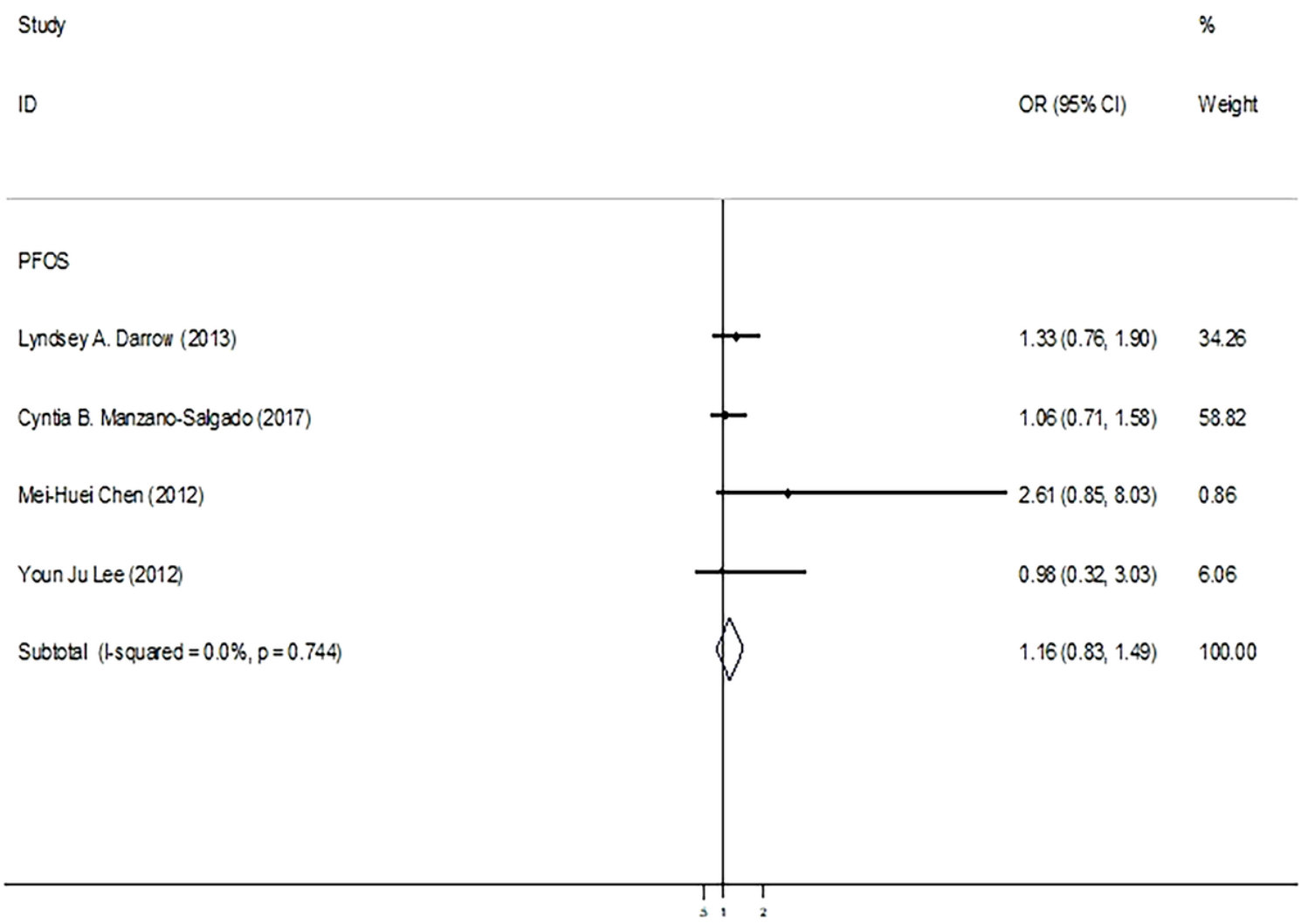

Figure 8

Association between maternal PFOS exposure and LBW of offspring