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Maternal perfluoroalkyl and polyfluoroalkyl substances (PFAS) exposure and preeclampsia: a systematic review and meta-analysis

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Abstract

Polyfluoroalkyl and perfluoroalkyl substances (PFAS) are persistent organic pollutants and exposure have been suggested with the risk of developing preeclampsia. Yet, evidence on the associations of PFAS with preeclampsia is still conflicting. Thus, the current study conducted a systematic review and meta-analysis of the epidemiological evidence linking maternal PFAS exposure to preeclampsia. This research methodology involved searching three electronic databases for epidemiological studies, and then conducting a meta-analysis using a random-effects model to analyse the heterogeneity between the studies. The quality and strength of evidence for each exposure-outcome pair was also evaluated, as well as the risk of bias. The search identified 10 potentially eligible studies related to maternal PFAS blood level with preeclampsia, which 7 were ultimately selected. Meta-analysis demonstrated evidence of association between combined PFAS compounds in pregnant mother with preeclampsia with zero heterogeneity (I2=0.0%, Q= 3.09, df= 6, p=0.798). Preeclampsia was found to have moderate association with maternal perfluorooctanoic acid (PFOA) exposure (Test for overall effect: z=2.2, p=0.03; Test for heterogeneity: I2=0.0%, Q= 3.49, df= 6, p=0.745) as well as maternal perfluorooctane sulfonate (PFOS) exposure (Test for overall effect: z=2.5, p=0.01; Test for heterogeneity: I2=0.0%, Q= 3.70, df= 6, p=0.718). This study showed significant associations between PFOA and PFOS exposure with the risk of preeclampsia. However, in-depth investigation is imperative to elucidate the impact of the different concentration and types of PFAS on preeclampsia risk.

Keywords Perfluoroalkyl substances, Polyfluoroalkyl substances, PFOA, PFOS, PFHxS, Preeclampsia

Introduction

Preeclampsia is one of the most terrifying complications often presenting as new-onset hypertension and proteinuria during pregnancy and it may progress rapidly to serious issues, including mortality of both mother and fetus [1]. Preeclampsia has been categorised into two different disease entities: early-onset preeclampsia which develops before 34 weeks of gestation, and late-onset preeclampsia which develops at or after 34 weeks of gestation [2]. Perfluoroalkyl and polyfluoroalkyl substances (PFAS) are a group of chemical compound widely used in the manufacturing of products for household and industry [3].

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Several studies reported positive association between the risk of preeclampsia and maternal exposure of Perfluorooctane sulfonate PFOS [4–6], perfluorononanoic acid (PFNA) [7], Perfluoroheptanesulfonic acid (PFHpS) [5], perfluorobutane sulfonic acid (PFBS) [4, 8], perfluorohexane sulfonic acid (PFHxS) [9], and Perfluorodecanoic acid (PFDA) [6].

PFAS are known as persistent organic pollutant (POP) due to the presence of carbon and fluorine chains in the structure. These carbon (C) and fluorine (F) chains are the reason why PFAS have a half-life of more than years [10] and with the long-chain PFAS with more C-F chains, in some cases, their half-life may reach up to three years [11]. These C-F bonds contribute to the extremely stable properties of PFAS aside from other unique properties such as being hydrophobic and lipophobic [12]. Thus, they are ubiquitously being used as surface active agents in products such as fire-fighting foams [13]. The ubiquitous usage of PFAS in the environment may contribute to spreading of these chemicals and consequently in different media of environment including water and solid. Eventually could lead to uptake by animals and humans.

To date, PFAS have been detected in water systems, soil, air, as well as the food sources. However, the primary pathway of PFAS exposure in humans is by drinking contaminated water [14]. PFOS and perfluorooctanoic acid (PFOA) are the most well-studied entities among PFAS [15], and these substances have been linked to various health issues such as hepatocellular carcinoma [16], neurological diseases [17], kidney disorders [18] and immunotoxicity [19]. Besides, other chemicals belonging to PFAS such as PFNA, PFHxS and PFBS are also frequently detected in environment as emerging PFAS with potential risk to human beings [20]. The environmental contamination by PFAS has generated significant concern in the community regarding their potential long-term health effects [21]. These contaminant have been detected in human samples including breastmilk, blood and tissues extracted from different organs [22]. PFAS has been reported to be detected in human living in developed countries and is linked with the development of many diseases including metabolic related disorder. For the past few decades numerous studies reported an association of PFAS exposure with metabolic related disorder or metabolic syndrome [23] such as hypercholesterolemia [24], hypertension [25], hypothyroid [26] and diabetic mellitus [27].

In addition, there are increasing number of studies that reported on the associations between preeclampsia and higher serum levels of several PFASs especially PFOS and PFAS in human during pregnancy [28].

A recent review has discussed the exposure of PFAS and the risk of preeclampsia [29]. However, to date, no attempt has yet been made to synthesise the empirical findings into a clearer picture through meta-analysis. Thus, the aim of the present study was to provide meta-analytic evidence on the risk of preeclampsia from exposure of various PFAS.

Materials and methods

This meta-analysis was conducted according to the PRISMA guidelines for systematic reviews and meta-analyses.

Literature search

Three electronic databases namely Google Scholar, PubMed and Science Direct were searched for articles that evaluated and reported the association between PFAS exposure and preeclampsia between 2012 and 2022. For all PubMed and Science Direct, the search strategy was using keywords ("perfluoroalkyl" OR "polyfluoroalkyl") AND ("PFOA" OR "PFOS" OR "PFAS") AND ("Pre-eclampsia" OR "Preeclampsia"). For Google Scholar, a search feature 'Advance Search' was applied with; find articles with all the words 'per-fluoroalkyl PFAS PFOS preeclampsia', with at least one of the words 'PFAS PFOS PFOA polyfluoroalkyl, and without the word 'animal mice rat'.

Inclusion criteria

The studies had to meet the following conditions in order to be eligible:

1. Publication Type: Research articles were eligible. Review article, meta-analysis, and conference proceedings or abstracts were excluded.
2. Types of Studies: Randomised controlled trials (RCTs), case-controlled studies, cohort, as well as cross-sectional studies were eligible. Systematic reviews and narrative reviews were excluded.
3. Types of participants: Pregnant woman.
4. Types of interventions: Studies that compared PFAS exposure on pregnant woman with and without development of preeclampsia, studies that provided quantitative estimation on the association between PFAS exposure and preeclampsia, including odds ratios (ORs) with 95% confidence intervals (CIs) or mean, standard deviation (SD), were eligible.

Data extraction

Eligible studies were independently assessed by two reviewers using a structured form to abstract information about the country and year of publication, objectives of the study, study design, sample size, source of study subjects, PFAS investigated, sample type, detection method, and main conclusion.

Quality assessment

In order to assess the methodological quality of selection, comparability, and outcome of the included studies, Newcastle-Ottawa scale for observational studies was used [30]. The quality assessment and scoring of the studies according to the prespecified criteria were performed by two independent reviewers. A lower quality studies have higher risk of bias, and vice versa. A study considered to be poor quality if scored zero star for any of the three domains or scored one star for selection or outcome. Studies were regarded as fair quality if scored two stars for selection, and one or two stars for comparability, and two or three stars for outcome. Studies were considered to good quality if scored three or four stars for selection, and one or two stars for comparability, and two or three stars for outcome [31].

Statistical analysis

The review protocol consists of independent analysis maternal PFAS exposure for (1) association of maternal combined PFAS exposure with preeclampsia, (2) association of maternal PFOA exposure with preeclampsia, (3) association of maternal combined PFOS exposure with preeclampsia, and (4) association of maternal combined PFHxS exposure with preeclampsia. The AOR (adjusted odds ratio) from the median quartile of each PFAS exposure (PFOA, PFOS, and PFHxS) (95% CIs) in association with preeclampsia were selected in all included studies for meta-analysis. In order to calculate pooled effect estimates and ORs with 95% CIs from eligible studies in the investigation of the association between maternal PFAS exposure and preeclampsia, a random-effects model meta-analysis was performed using Comprehensive Meta-Analysis software V3. The magnitude of the overall effect size was calculated using ORs categorized into small (z = 1.5-2), moderate (z = 2–3), and large effect size (z > 3) [32]. In the determination of heterogeneity of the studies, I^2 statistics was used and the percentages of I^2 indicate the extend of heterogeneity which are 0.00-0.30% (no heterogeneity), 30–49% (moderate heterogeneity), 50–74% (substantial heterogeneity) and 75–100% (considerable heterogeneity). Significant heterogeneity indicated by a p-value ≤ 0.10 [33]. Publication bias was assessment was done by visual analysis of funnel plots which generated using Comprehensive Meta-Analysis V3 and 'Trim and Fill' method was applied to the Funnel Plot. Apparently, the significance of publication bias assessed by regression-based tests considered to be less dependent on the size of meta-analysis [34]. Therefore, Egger's linear regression test was used for the assessment of publication bias due to small number of included studies [35].

Results

Literature search

As illustrated in Fig. 1, the original database search resulted in a total of 193 records of which 61 from Google Scholar, 112 from Science Direct and 20 from PubMed. A total of 179 records were eligible for the first phase of screening after removal of 9 duplicate records. After further screening, another 54 records were removed for other reasons which are news ($n = 1$), book ($n = 11$), review ($n = 25$), webpage ($n = 1$), abstract ($n = 9$), conference proceeding ($n = 2$), citations ($n = 3$), and index ($n = 2$). A total of 125 records retrieved for second phase of screening from which 115 records were excluded, 30 due to publication type other than research articles or randomised controlled trial, 16 due to in vitro, in vivo, or in-silico studies, 4 articles in Spanish, and another 65 records were out of the scope of study. Therefore, 10 articles were left included for meta-analysis, 6 from Google Scholar [4–7, 36–37], 2 from PubMed [8, 38], and another 2 from Science Direct [9, 39].

Study characteristic

The 10 studies listed in Table 1 reported the association between maternal PFASs exposure and preeclampsia. Among the 10 studies, one study categorised preeclampsia into early onset and late onset [6], and two studies assessed the association between maternal PFASs exposure and hypertensive disorders of pregnancy (HDP), including gestational hypertension and preeclampsia [4, 39]. The studies were published between 2014 and 2022, and were conducted in Norway, Sweden, China, Canada, US, and Denmark. Sample size of the studies ranged between 122 and 3220 participants and the study design were mostly cohort ($n = 6$), while others were case-control ($n = 3$) and cross-sectional ($n = 1$) [8]. All 7 included studies evaluated OR with 95% CI for each PFAS compound selected and use maternal blood sample. In addition, in all included studies, the maternal blood level of PFASs of interest (PFOS, PFOA, and PFHxS) was analysed using liquid chromatography-tandem mass spectrometry (LC-MS/MS). There were 3 excluded studies due to placenta sample [38] and reported HR effect measure instead of OR [6, 37]. HR values in the two studies cannot be converted into OR by calculation due to the absence of baseline prevalence information or data to derive ACR (assumed control risk) in the studies.

The quality of included studies

All included studies in the meta-analysis are observational studies which are cohort, case-control and cross-sectional studies. Table 2 presents the quality rating of each included study according to Newcastle-Ottawa scale (NOS), a preferred tool for quality assessment of observational or nonrandomised studies. Six out of seven

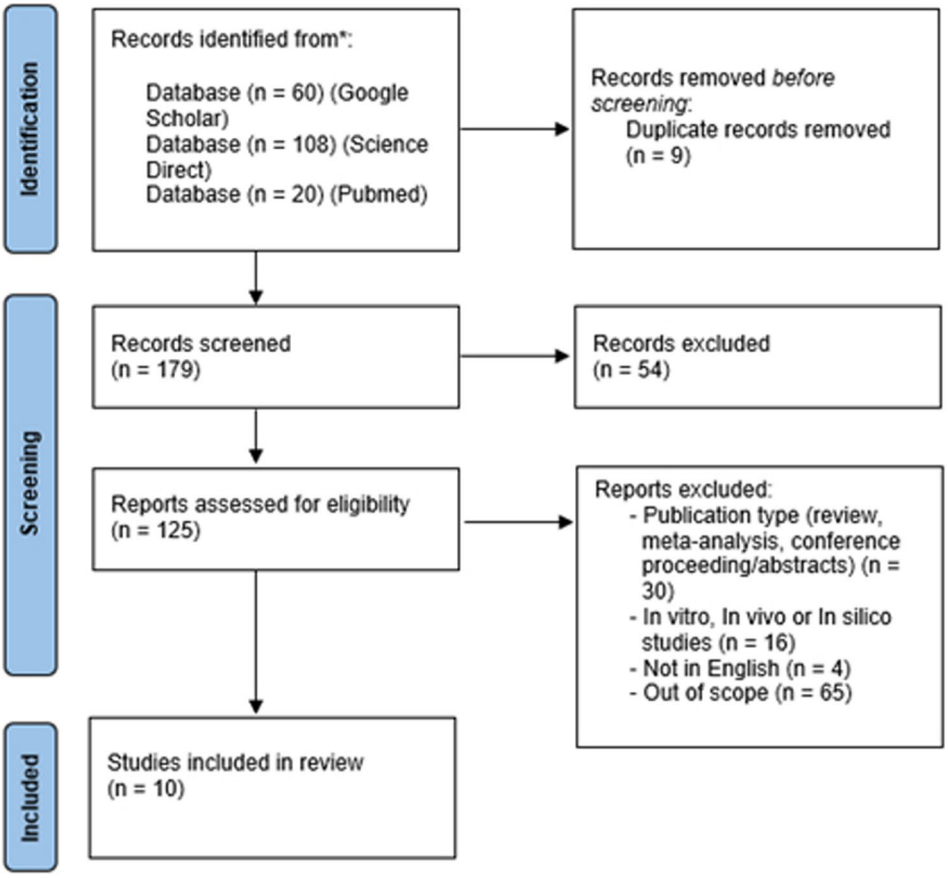

Fig. 1 The flowchart of identification and selection of study

included studies scored high quality and only a single study [8], scored fair quality in the assessment. Among these observational studies, three were rated 8 stars, three were rated 7 stars and one was rated 6 stars.

The association between maternal PFAS exposure and preeclampsia

A total of seven studies provided data for the meta-analysis. Figure 2 illustrates the results of combined meta-analysis which suggested little evidence of association between maternal PFAS and preeclampsia ($z = 1.9$, $p = 0.05$) with zero heterogeneity ($I^2 = 0.0\%$, $Q = 3.09$, $df = 6$, $p = 0.798$). The results in Fig. 3 showed that PFOA ($z = 2.2$, $p = 0.03$) exposure might be associated with moderate overall effect on preeclampsia with zero heterogeneity ($I^2 = 0.0\%$, $Q = 3.49$, $df = 6$, $p = 0.745$). In Fig. 4, the similar moderate overall effect on preeclampsia was demonstrated by PFOS exposure ($z = 2.5$, $p = 0.01$) with zero heterogeneity ($I^2 = 0.0\%$, $Q = 3.70$, $df = 6$, $p = 0.718$). However, as shown in Fig. 5, no evidence of association between maternal PFHxS exposure and preeclampsia with overall effect ($z = 0.28$, $p = 0.78$) and substantial heterogeneity ($I^2 = 68.8\%$, $Q = 19.21$, $df = 6$, $p = 0.004$) were noticed.

Analysis of publication bias

The analysis of publication bias was done using funnel plot by applying "Trim and Fill" method and Egger's linear regression test. For the association between combined PFAS and preeclampsia, the funnel plot with "trim and fill" method applied in Fig. 6 suggested no missing studies. Under the random-effects model, the point estimate and 95% CI for combined studies was 1.20 (1.00-1.44) and the values unchanged when using the "trim and fill" method. Egger's regression test ($p = 0.326$) showed insignificant publication bias. As shown in Fig. 7, the funnel plot with "trim and fill" method applied does not indicate any missing studies for the association between PFOA and preeeclampsia. The point estimate and 95% CI under the random-effects model was 1.24 (1.02–1.50) and these values remained unchanged when using the "trim and fill" method. However, Egger's regression test ($p = 0.909$) indicates insignificant publication bias. For the association between PFOS and preeclampsia, the funnel plot with "trim and fill" method applied suggested no missing studies as illustrated in Fig. 8. Under the random-effects model, the point estimate and 95% CI was 1.26 (1.05–1.51) and the values unchanged using "trim and fill" method. Egger's regression test ($p = 0.008$)

Table 1 Summary of PFAS investigated in association with preeclampsia

Main author, year and study design	PFAS investigated in association with preeclampsia	Country	Comment	Ref
Starling, 2014, cohort	PFOS, PFOA, PFHxS, PFNA, PFUnDA, PFHpS, PFDA.	Norway	Excluded, Effect measure; HR	[5]
Wikström, 2019, cohort	PFOS, PFOA, PFHxS, PFNA, PFDA, PFUnDA, PFHpA, PFDoDA	Sweden	Included	[7]
Huang, 2019, cross-sectional	PFOA, PFOS, PFNA, PFUA, PFDA, PFHxS, PFDoDA, PFBS	China	Included	[8]
Rylander, 2020, case-control	PFOS, PFOA, PFHxS, PFNA	Sweden	Included	[36]
Huo, 2020, cohort	PFOA, PFOS, PFDA, PFUnDA, PFNA, PFHxS, PFHpA, PFBS, PFDoA, PFOSA	China	Included	[39]
Borghese, 2020, cohort	PFOA, PFOS, PFHxS	Canada	Included	[9]
Bangma, 2020, cohort	PFPeS, PFHxS, PFHpS, PFOS, PFHxA, PFOA, PFNA, PFDA, PFUnA, PFTriA, PFTA	US	Excluded, Placenta sample	[38]
Bommarito, 2021, case-control	PFHxS, PFOS, PFOA, PFNA, PFDA, PFUnDA, PFOSA, MeFOSAA	US	Included	[6]
Birukov, 2021, cohort	PFHxS, PFOS, PFOA, PFNA, PFDA	Denmark	Excluded, Effect measure; HR	[37]
Liu, 2022, case-control	PFHxS, PFHpA, PFOS, PFOA, PFNA, PFDA, PFUnA, PFBF, PFDoA	China	Included	[4]

suggested the presence of publication bias. Finally, for the association between PFHxS and preeclampsia, two studies were trimmed in the "trim and fill" analysis as shown in the funnel plot in Fig. 9. Under the random-effects model, the point estimate and 95% CI was 1.05 (0.73, 1.51). These values were adjusted when using 'trim and fill' and the imputed point estimate is 0.87 (0.61, 1.25). Egger's regression test ($p = 0.759$) indicated no significant publication bias.

Discussion

Preeclampsia is characterised by new-onset or exacerbated hypertension, with numerous individual or overlapping aetiologies such as endocrine disorders and environmental expsoure. In developed countries, the incidence of preeclampsia and maternal mortality has decreased significantly in the past 50 years. However, the incidence rates of preeclampsia and maternal mortality are still very high in developing countries [40]. It was reported that the global incidence of preeclampsia is 4.6% [95% confidence interval (CI), 2.7–8.2], and it is varied among different regions, for example 5.6% in Africa and 1.0% the eastern Mediterranean [41]. Exposure to environmental pollutants such as PFAS have been reported associated with the development of preeclampsia. There are limited observational studies available in the literature that investigated the association between maternal PFAS exposure and preeclampsia in pregnancy, and the results of these studies are conflicting. A recent review suggested that maternal exposure to two PFAS which are PFOS and PFOA is weakly linked with the risk of preeclampsia [29]. Therefore, a systematic review and meta-analysis study is necessary to assess the relationship between PFAS exposure and preeclampsia. Thus, this study was done to perform meta-analysis and determine the association between maternal PFAS exposure and preeclampsia.

In this review, among all seven included studies, six evaluated maternal blood sample and one study [8] evaluated cord blood sample for the analysis of PFAS level. It was suggested that in the cord blood, the PFOS level is well representative of the maternal blood level [8]. Seven types of PFAS was detected in samples of maternal and matched cord blood in the Norwegian study [42]. The maternal and foetal levels exhibited a substantial correlation for all studied PFAS such as PFOA, PFOS, PFHxS, PFUA, and PFNA, the concentration of these PFAS in the cord plasma was reported to be within the range between of 30 to 79% of maternal blood concentrations [42]. Five out of seven included studies reported an association between PFAS exposure and preeclampsia [5–9].

Table 2 Quality assessment using Newcastle-Ottawa scale (NOS) for the studies included in the meta-analysis

Source	Selection	Comparability	Outcome	Total stars	Quality	Ref
Wikström, 2019	★★★	★	★★★	7	Good	[7]
Huang, 2019	★★	★	★★★	6	Fair	[8]
Rylander, 2020	★★★	★★	★★★	8	Good	[36]
Huo, 2020	★★★	★	★★★	7	Good	[39]
Borghese, 2020	★★★	★★	★★★	8	Good	[9]
Bommarito, 2021	★★★	★★	★★★	8	Good	[6]
Liu, 2022	★★★	★	★★★	7	Good	[4]

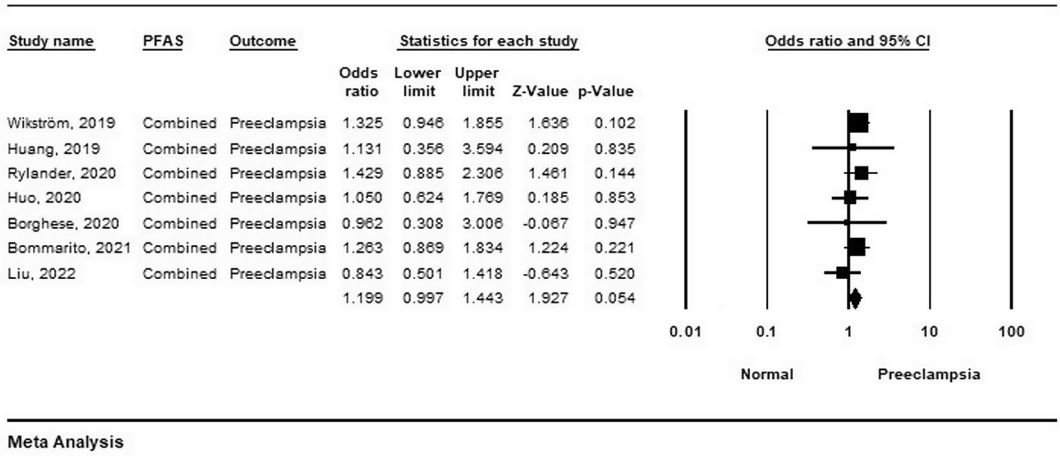

Fig. 2 Association of combined PFAS maternal exposure with preeclampsia. Meta-analysis conducted using random-effects model, ordered by date of publication. PFAS combined = PFOA, PFAS, and PFHxS. Test for overall effect: z = 1.9, $p = 0.05$; Test for heterogeneity: I2 = 0.0%, Q = 3.09, df = 6, $p = 0.798$

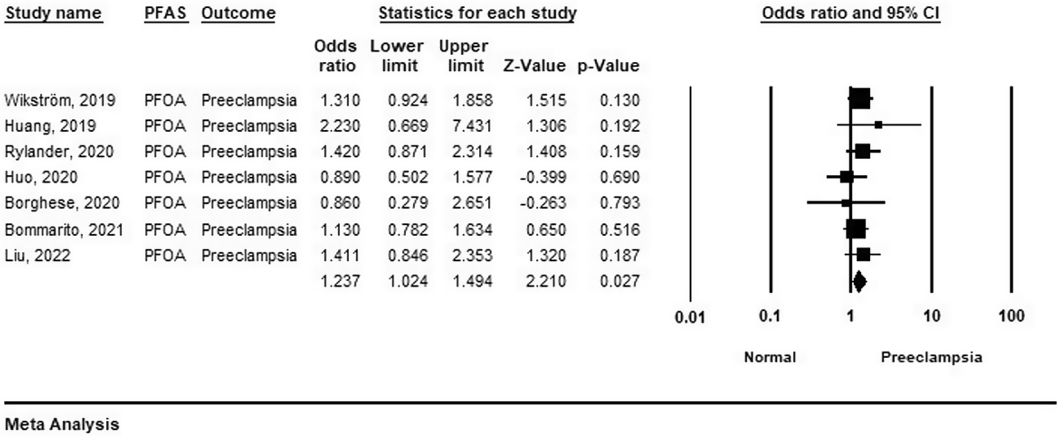

Fig. 3 Association of maternal PFOA exposure with preeclampsia. Meta-analysis conducted using random-effects model, ordered by date of publication. Test for overall effect: z = 2.2, $p = 0.03$; Test for heterogeneity: I2 = 0.0%, Q = 3.49, df = 6, $p = 0.745$

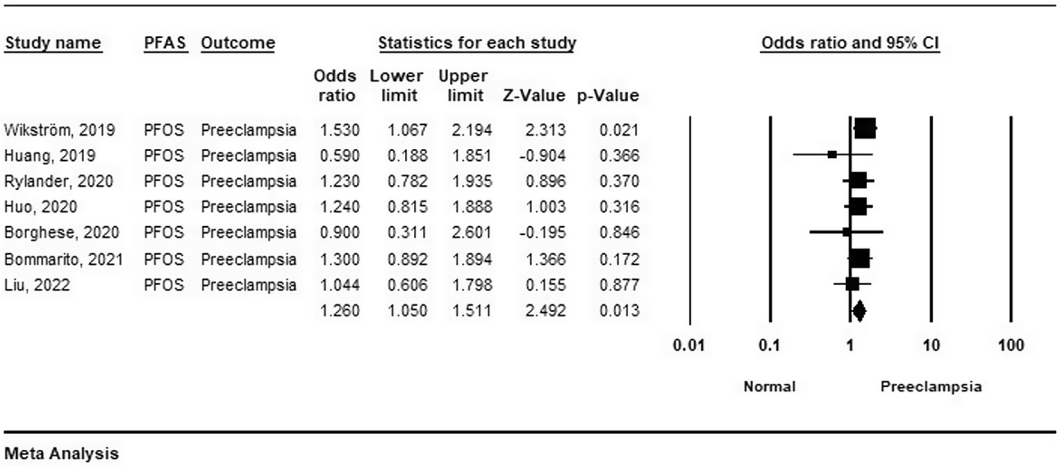

Fig. 4 Association of maternal PFOS exposure with Preeclampsia Meta-analysis conducted using random-effects model, ordered by date of publication. Test for overall effect: z = 2.5, $p = 0.01$; Test for heterogeneity: I2 = 0.0%, Q = 3.70, df = 6, $p = 0.718$

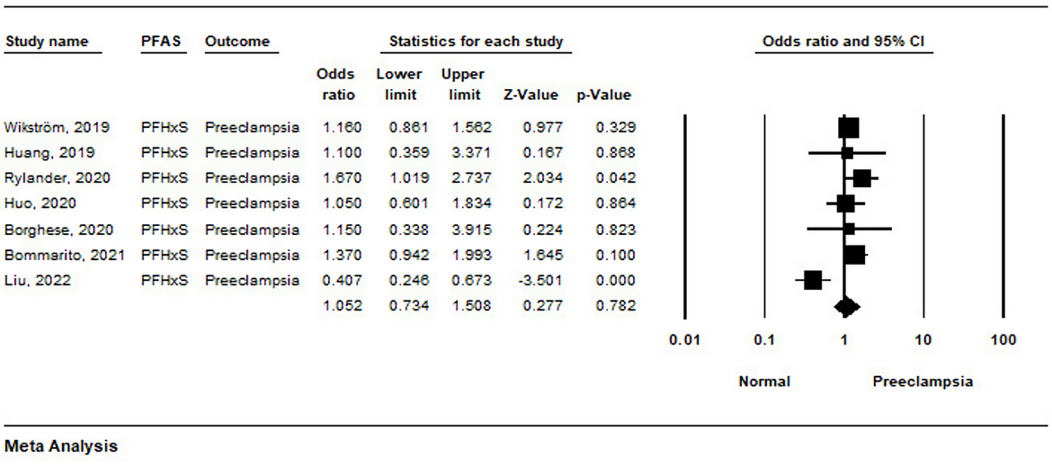

Fig. 5 Association of maternal PFHxS exposure with preeclampsia Meta-analysis conducted using random-effects model, ordered by date of publication. Test for overall effect: z = 0.28, $p = 0.78$; Test for heterogeneity: I2 = 68.8%, Q = 19.21, df = 6, $p = 0.004$

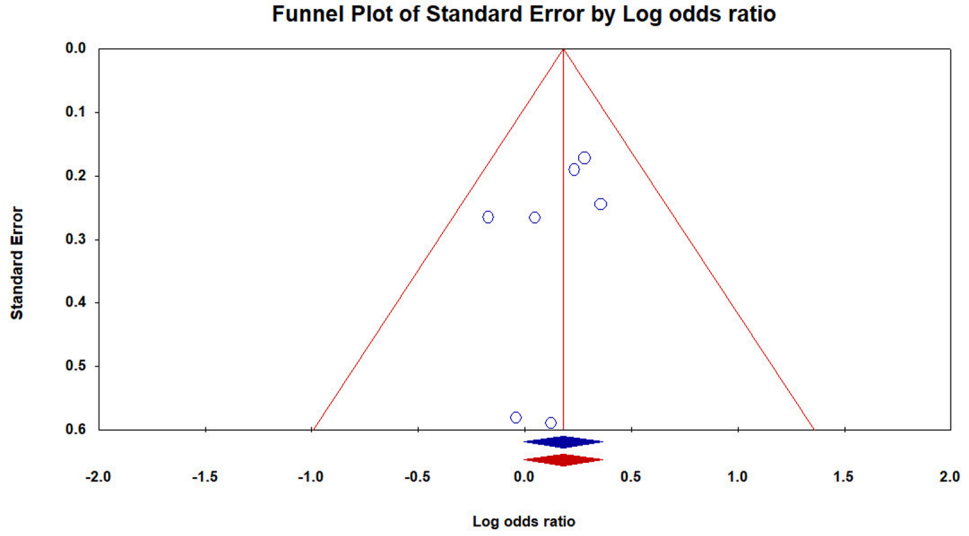

Fig. 6 Funnel plots of observational studies of the association of combined PFAS maternal exposure with preeclampsia. The publication bias is adjusted by imputing the missing studies based on the asymmetry of the funnel plot. (Red circle) plot imputed and (blue circle) plot observed studies. Egger 's linear regression test ($p = 0.326$). Adjusted values 'Trim and Fill' test (1.20, CI = 1.00, 1.44)

In contrast, the other two studies reported no association between PFAS exposure and preeclampsia [36, 39]. Nonetheless, the conflicting findings could be contributed by many factors, for example, one study determined the level of PFAS in blood of early pregnancy subjects [36], while the other study was done on mid-pregnancy subjects [42]. It is also possible that the physiological changes occurring during mid-pregnancy, such as increased insulin resistance and hormonal shifts in mid to late pregnancy may interact with PFOS and PFUnDA exposure differently compared to earlier in pregnancy. The physiological changes during mid-pregnancy, including hormonal changes in mid to late pregnancy, may interact with PFAS exposure differently than in the earlier stages of pregnancy. Hence, it is crucial to understand the mechanism of PFAS exposure leading to development of preeclampsia.

The underlying mechanisms of association between PFAS exposure and preeclampsia is yet to be unravelled. Previous study suggested the association of PFOS and preeclampsia could be due to the induction of oxidative stress in epithelial cells and alteration of immune response by PFOS [7]. This could contribute to vascular disturbances which include endothelial dysfunction with oxidative stress and enhanced inflammatory response in the development of preeclampsia [7]. It is believed that the starting point in the pathogenesis of preeclampsia is due to shallow trophoblast invasion into the maternal decidual and spiral arteries in the early pregnancy leading to defective placentation [43]. Previous study

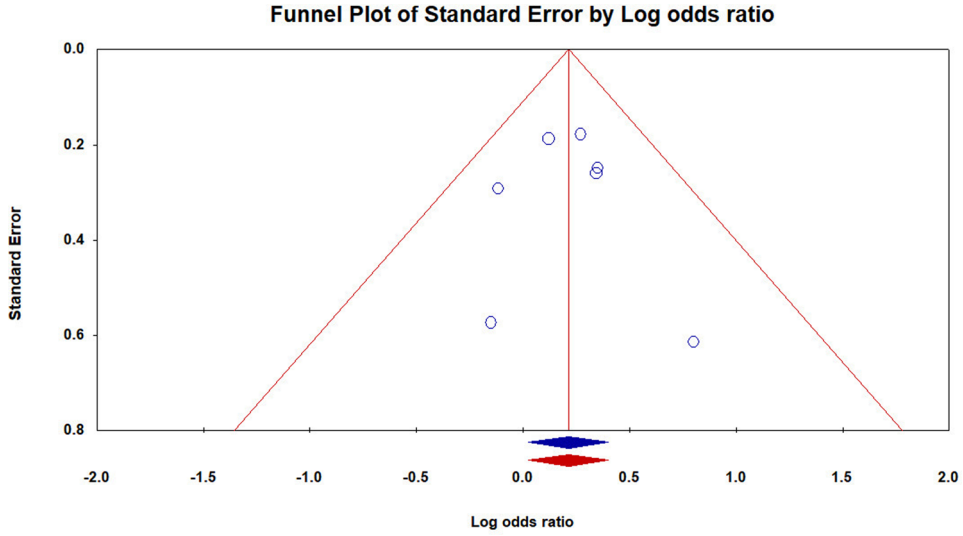

Fig. 7 Funnel plots of observational studies of the association of PFOA maternal exposure with preeclampsia. The publication bias is adjusted by imputing the missing studies based on the asymmetry of the funnel plot. (Red circle) plot Imputed and (blue circle) plot observed studies. Egger 's linear regression test ($p = 0.908$). Adjusted values 'Trim and Fill' test (1.24, CI = 1.02, 1.50)

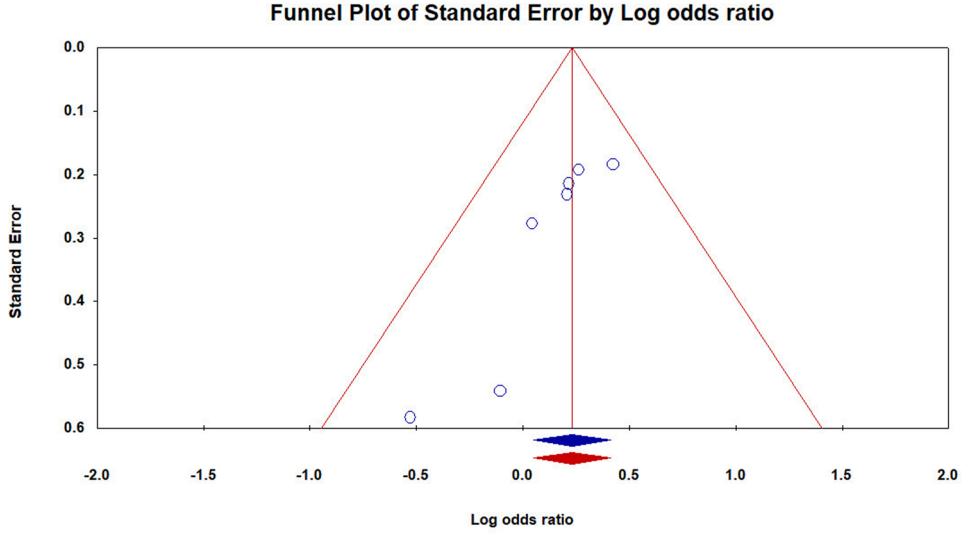

Fig. 8 Funnel plots of observational studies of the association of PFOS maternal exposure with preeclampsia. The publication bias is adjusted by imputing the missing studies based on the asymmetry of the funnel plot. (Red circle) plot imputed and (blue circle) plot observed studies. Egger 's linear regression test ($p = 0.008$). Adjusted values 'Trim and Fill' test (1.26, CI = 1.05, 1.51)

suggested that some PFAS might contribute to defective spiral artery remodelling by interfering with cytotrophoblast invasion, leading to the development of the initial stage of preeclampsia [9]. In addition, peroxisome proliferator-activated receptor gamma (PPARγ) is a regulator of placentation and trophoblast differentiation, thus, dysregulation of both placental PPARα and γ has been implicated in the pathophysiology of preeclampsia [44]. However, the relevance of PPAR-dependent pathways for PFAS in humans remain vague. Further study need to be done to understand the effect of PFAS level with placental PPAR signalling in human as its association could be contributed by genetic factors and maternal nutrition.

The primary route of PFAS exposure is via dietary intake and dermal exposure, therefore adopting modifications on lifestyle by using PFAS-free goods may help in mitigating the extent of exposure [3]. In addition, behaviour interventions which aim at reducing maternal exposure to PFAS may have the potential to mitigate the incidence of pre-eclampsia. Gaining insight into the impact of maternal PFAS exposure on pregnancy outcomes is crucial for addressing significant public health

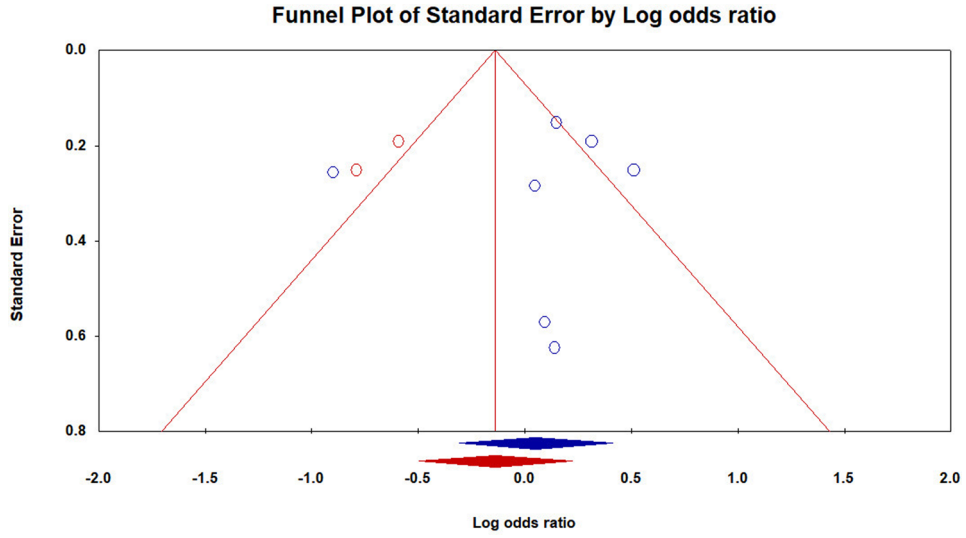

Fig. 9 Funnel plots of observational studies of the association of PFHxS maternal exposure with preeclampsia. The publication bias is adjusted by imputing the missing studies based on the asymmetry of the funnel plot. (Red circle) plot imputed and (blue circle) plot observed studies. Egger 's linear regression test ($p = 0.759$). Adjusted values 'Trim and Fill' test (0.87, CI = 0.61, 1.25)

inquiries regarding the reproductive harmful effects of this growing environmental contaminant. This understanding serves as a scientific foundation for implementing policies aimed at reducing exposure.

Our meta-analysis indicated that maternal exposure to PFOA and PFOS were moderately linked to preeclampsia, but no association found on PFHxS exposure. Although the current meta-analysis provided some evidence of association between maternal PFAS exposure and preeclampsia, it is not without limitations. Firstly, the number of studies included in this study was not large enough and this is due to limited studies in the literature for the past 10 years investigating the link between maternal PFAS exposure and preeclampsia. Second limitation is that this study was unable to separate the data into low and high levels of PFAS exposure to understand the relation of PFAS blood concentration at different levels and the risk of preeclampsia. Thirdly, limited number of included studies unable us to perform additional subgroup analyses to further explore the possible sources of heterogeneity among the included studies. Finally, all included studies were observational studies with no randomised trials available in the literature which might affect the power of conclusion from this meta-analysis. The inconsistency in confounding adjustments might affect the estimation of the actual association between maternal PFAS exposure and preeclampsia.

Currently, inadequate evidence hinders our understanding how a mixture of PFAS exposure in the environment leads to negative health effects. Recent investigations on PFAS toxicological profile have documented numerous detrimental health effects on the liver, cardiovascular system, immune system, and reproductive system. Yet those studies were mainly done on the most frequently identified PFAS in the environment, including PFOA, PFOAS, PFNA, and PFHxS. Nevertheless, the mixture of different PFAS with cause-and-effect linkages for many of these outcomes remain poorly understood. Furthermore, many factors such as the intensity and frequency of exposure were not considered. Thus, future studies need to exercise caution when interpreting the exposure data and should consider for factors such as age, presence of other disease, and intake of supplementation, which could potentially lead to confounding. The difficulty in establishing a dependable measurement of these substances arises from the fact that the length of exposures may fluctuate over the entire course of pregnancy. The model components may differ among subclasses of pregnant women, such as nulliparous, primiparous, or multiparous. Furthermore, lifestyles can have a significant impact, such as the contrast between sedentary and sporty, leading to expected differences in the duration of pregnancies. Accurate computer modelling can be beneficial, as long as it accurately describes the levels of exposure and the relevant populations. The ongoing objective should be to offer prognostic values for PFAS substances that do not have actual measurements, relying on chemical structures and reliable physiological characteristics. Many animal and epidemiological studies have reported the impact of in utero exposure to many environmental pollutants including PFAS. The adverse health effects could directly impact birth outcomes, and subsequent life stages. Recently, PFAS have been linked to a higher prevalence of childhood obesity [45] and metabolic syndrome [46] in the offspring. Due to the pervasive nature of PFAS

exposure, these findings may have ramifications for public health, necessitating more investigation.

Conclusion

In conclusion, current meta-analysis suggests that maternal exposure to PFOA and PFOS contributed to the risk of preeclampsia in pregnancy. Nevertheless, it is important for more observational studies to be carried out and in vivo as well as in vitro studies are needed to verify the potential relationship and biological mechanisms.

Abbreviations

PFAS	Perfluoroalkyl and polyfluoroalkyl substances
PFOS	Perfluorooctane sulfonate
PFOA	Perfluorooctanoic acid
PFNA	Perfluorononanoic acid
PFBA	Perfluorobutanoic acid
PFHxS	Perfluorohexane sulfonic acid
PFBS	Perfluorobutane sulfonic acid
OR	Odds ratio
CI	Confidence interval

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Author contributions

N. A. M. and S. H. S. A. K wrote the first draft and revised the drafts. J. Y., M. S. A. S and S. H. S. A. K. were involved in paper visualisation, supervision of the postgraduate students and project administration. All authors have read and agreed to the published version of the manuscript.

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Data availability

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

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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