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Federaal Kenniscentrum voor de Gezondheidszorg
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SUPPLEMENT

WHAT IS THE CLINICAL UTILITY OF PFAS TESTS? FOCUS ON PREGNANT AND BREASTFEEDING WOMEN, AND OCCUPATIONALLY EXPOSED INDIVIDUALS



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COLOPHON

Title:	What is the clinical utility of PFAS tests? Focus on pregnant and breastfeeding women, and occupationally exposed individuals – Supplement
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SUPPLEMENTS

1 SEARCH STRATEGY

1.1 Search strategy for the systematic reviews

1.1.1 Umbrella review

Search date	Search string in Pubmed	Results
Search date	Search string in Pubmed	Results
5/1/2026	("Fluorocarbons"[MeSH Terms] OR "PFAS"[All Fields] OR "perfluoroalkyl*"[All Fields] OR "polyfluoroalkyl*"[All Fields] OR "Per-and polyfluoroalkyl substances"[All Fields]) AND ("systematic review"[All Fields] OR "meta-analysis"[All Fields] OR ("meta analysis as topic"[MeSH Terms] OR ("meta-analysis"[All Fields] AND "topic"[All Fields]) OR "meta analysis as topic"[All Fields] OR "metaanalysis"[All Fields]))	285

1.1.2 Occupational exposure

Search date	Search string in Pubmed	Results
Search date	Search string in Pubmed	Results
Search date	Search string in Pubmed	Results
20/4/2026	(("Fluorocarbons"[MeSH Terms] OR "PFAS"[All Fields]) AND ("occupational exposure/analysis"[MeSH Major Topic] OR "worker*"[All Fields] OR "occupation*"[All Fields])) AND (review[Filter] OR systematicreview[Filter]))	130

1.2 Search strategy for primary studies

1.2.1 Preeclampsia

Search date	Search string in Pubmed	Results
Search date	Search string in Pubmed	Results
13/01/2026	*(("fluorocarbons"[MeSH Terms] OR "PFAS"[All Fields] OR "perfluoroalkyl*"[All Fields] OR "polyfluoroalkyl*"[All Fields] OR "per and polyfluoroalkyl substances"[All Fields]) AND ("pre eclampsia"[MeSH Terms] OR "pre eclampsia"[All Fields] OR "preeclampsia"[All Fields])) AND (2022:2026[pdat])*	34

1.2.2 Miscarriage

Search date	Search string in Pubmed	Results
21/4/2026	(("Fluorocarbons"[Mesh] OR PFAS OR Perfluoroalkyl* OR polyfluoroalkyl* OR "Per- and polyfluoroalkyl substances")) AND ("Abortion, Spontaneous"[Mesh] OR miscarriage))	44

1.2.3 Prematurity – preterm birth

Search date	Search string in Pubmed	Results
09/03/2026	(polyfluor* OR perfluor* OR PFAS) AND (prematurity OR premature OR preterm) NOT systematic, filter from 2021/3/1	80

1.2.4 Congenital abnormalities

Search date	Search string in Pubmed	Results
05/03/2026	(("Fluorocarbons"[Mesh] OR PFAS OR Perfluoroalkyl* OR polyfluoroalkyl* OR "Per-and polyfluoroalkyl substances")) AND ("Congenital Abnormalities"[Mesh] OR "congenital") NOT animal Filters: in the last 10 years Sort by: Most Recent	42

	((("Fluorocarbons"[MeSH Terms] OR "PFAS"[All Fields] OR "perfluoroalkyl*"[All Fields] OR "polyfluoroalkyl*"[All Fields] OR "Per-and polyfluoroalkyl substances"[All Fields]) AND ("Congenital Abnormalities"[MeSH Terms] OR "congenital"[All Fields])) NOT ("animals"[MeSH Terms:noexp] OR "animal"[All Fields])) AND (y_10[Filter])	

1.2.5 *Acute lymphoblastic leukemia (ALL)*

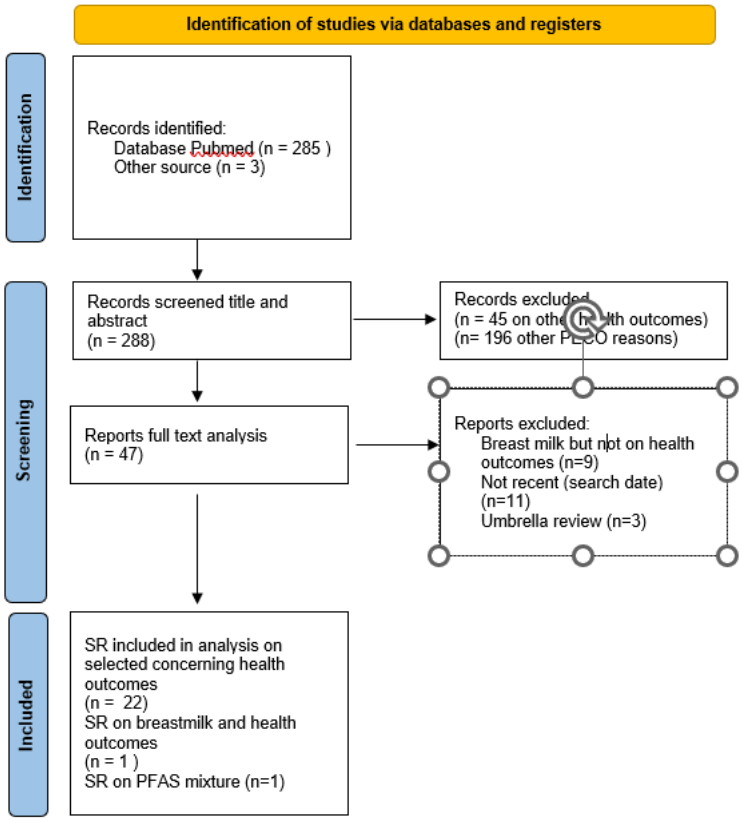
Search date	Search string in Pubmed	Results
21/04/2026	(("Fluorocarbons"[Mesh] OR PFAS OR Perfluoroalkyl* OR polyfluoroalkyl* OR "Per-and polyfluoroalkyl substances")) AND (acute lymphocytic leukemia[MeSH Terms])"	5

1.2.6 *Breast milk*

Search date	Search string in Pubmed	Results
02/04/2026	"Breast Feeding"[MeSH Terms] OR ("Breast Feeding"[MeSH Terms] OR ("breast"[All Fields] AND "feeding"[All Fields]) OR "Breast Feeding"[All Fields] OR "breastfeeding"[All Fields] OR "breastfeedings"[All Fields] OR "breastfeeders"[All Fields]) OR ("milk, human"[MeSH Terms] OR ("milk"[All Fields] AND "human"[All Fields]) OR "human milk"[All Fields] OR ("human"[All Fields] AND "milk"[All Fields]))) AND ("Fluorocarbons"[MeSH Terms] OR "PFAS"[All Fields] OR "perfluoroalkyl*"[All Fields] OR "polyfluoroalkyl*"[All Fields] OR "Per-and polyfluoroalkyl substances"[All Fields])) NOT ("animals"[MeSH Terms:noexp] OR "animal"[All Fields])) Filters: from 2018 - 2026	155

2 FULL TEXT ANALYSES

2.1 Flow chart umbrella review



2.2 Systematic reviews identified in umbrella review

Table 1 – Identified SRs for selected 'concerning' outcomes

Identified Systematic Reviews	Info - Exclusion
Preeclampsia and gestational hypertension	
Abs Mutalib 2025 - Maternal perfluoroalkyl and polyfluoroalkyl substances (PFAS) exposure and preeclampsia: a systematic review and meta-analysis	
Hirke 2023 - Exposure to endocrine-disrupting chemicals and risk of gestational hypertension and preeclampsia: A systematic review and meta-analysis	
Hu 2023- Perfluoroalkyl and polyfluoroalkyl substances and hypertensive disorders of pregnancy: A systematic review and meta-analysis	
Gestational diabetes	
Quan 2025- Associations of prenatal per- and polyfluoroalkyl substances exposure with glucose homeostasis and gestational diabetes mellitus: A systematic review and meta-analysis	
Wang 2025- Correlation of perfluoroalkyl and polyfluoroalkyl substance levels during pregnancy with gestational diabetes mellitus: a systematic review and meta-analysis	
Yao 2023 - Environmental pollutants exposure and gestational diabetes mellitus: Evidence from epidemiological and experimental studies	
Wang 2022- Association between per- and polyfluoroalkyl substances and risk of gestational diabetes mellitus	More recent available
Yan 2022 - Endocrine-disrupting chemicals and the risk of gestational diabetes mellitus: a systematic review and meta-analysis	More recent available
Immunology – Antibodies – vaccine response	
Antoniou and Dekant 2024 - Childhood PFAS exposure and immunotoxicity: a systematic review and meta-analysis of human studies	SR also relevant for outcome "infections"
Crawford 2023 - Systematic review and meta-analysis of epidemiologic data on vaccine response in relation to exposure to five principal perfluoroalkyl substances	
Zhang 2022 - Effects of exposure to per- and polyfluoroalkyl substances on vaccine antibodies: A systematic review and meta-analysis based on epidemiological studies	
Infections	
Lyrou 2025 - Association between prenatal exposure to perfluoroalkyl and polyfluoroalkyl substances and the incidence of infant and childhood respiratory infections: A systematic review	Outcome: acute respiratory infection Search date 2015-Feb 2025
Rosen et al 2025 - Systematic review and meta-analysis of epidemiologic data on infectious disease in relation to exposure to twelve perfluoroalkyl substances (PFAS)	Several studies included on children/neonates Outcomes: lower respiratory tract infections, upper respiratory tract infections, not specified respiratory infections, gastointestinal Search date: June 11, 2024
Low birth weight or small for gestational age	
Fu 2025 - The association between maternal perfluoroalkylated substances exposure and neonatal birth weight: a system review and meta-analysis	Outcome: Birth outcomes determined through clinical assessments, registration data, or medical records based on the International Classification of Diseases (ICD Search date: March 2024
Wright 2025 - Birth weight in relation to maternal and neonatal biomarker concentration of perfluorooctane sulfonic acid: a meta-analysis and meta-regression from a systematic review	
Wright 2023 - Systematic review and meta-analysis of birth weight and PFNA exposures	

Identified Systematic Reviews	Info - Exclusion
Ru 2024- Systematic review and meta-analysis of birth weight and perfluorohexane sulfonate exposures: examination of sample timing and study confidence	
Lan 2023 - Associations between maternal exposure to perfluoroalkylated substances (PFASs) and infant birth weight: a meta-analysis	More recent available
Cao 2021 - The relationship between maternal perfluoroalkylated substances exposure and low birth weight of offspring: a systematic review and meta-analysis	More recent available
Lee 2021 - Early-Life Exposure to Per- and Poly-Fluorinated Alkyl Substances and Growth, Adiposity, and Puberty in Children: A Systematic Review	More recent available
Steenland 2018 - Serum Perfluorooctanoic Acid and Birthweight An Updated Meta-analysis With Bias Analysis	More recent available
Negri 2017 - Exposure to PFOA and PFOS and fetal growth: a critical merging of toxicological and epidemiological data	More recent available
Johnson 2014 - The Navigation Guide - evidence-based medicine meets environmental health: systematic review of human evidence for PFOA effects on fetal growth	More recent available
Bach 2015 - Perfluoroalkyl and polyfluoroalkyl substances and human fetal growth: a systematic review	More recent available
Congenital malformations/birth defects	
Bernardo 2025 - Association between endocrine disruptors and surgical congenital malformations: Systematic review and meta-analysis	
Elhassan 2024 - The Relationship Between Maternal Exposure to Endocrine-Disrupting Chemicals and the Incidence of Congenital Heart Diseases: A Systematic Review and Meta-Analysis	
More general Pregnancy outcomes – preterm birth - miscarriage	
Deji 2021 - Association between maternal exposure to perfluoroalkyl and polyfluoroalkyl substances and risks of adverse pregnancy outcomes: A systematic review and meta-analysis	More recent available Outcomes: miscarriage, stillbirth, preterm birth Search date: up to 2020
Gao 2021 - Per- and polyfluoroalkyl substances exposure during pregnancy and adverse pregnancy and birth outcomes: A systematic review and meta-analysis	Outcomes: preterm birth, miscarriage, gestational diabetes, preeclampsia, small for gestational age, low birth weight, intrauterine growth restriction Search date: feb 2021 For miscarriage more recent available
Gui 2022 - Association Between Exposure to Per- and Polyfluoroalkyl Substances and Birth Outcomes: A Systematic Review and Meta-Analysis	Outcomes: birth weight, birth length, head circom, preterm birth, miscarriage Search date: 13 Feb 2021
Yang 2022 - Associations between exposure to perfluoroalkyl substances and birth outcomes: A meta-analysis	Outcomes: premature birth (PTB), low birth weight (LBW), small for gestational age (SGA) and miscarriage Search date March 21, 2021 For miscarriage more recent available
Haimbaugh 2024 - Environmental Exposure to Per- and Polyfluorylalkyl Substances (PFASs) and Reproductive Outcomes in the General Population: A Systematic Review of Epidemiological Studies	Outcomes: fertility, preterm birth, miscarriage, ovarian health, menstruation, menopause, sperm health, and in utero fetal growth

Identified Systematic Reviews	Info - Exclusion
	Search date: between 2017-2022
Liu 2024 - Influence of maternal endocrine disrupting chemicals exposure on adverse pregnancy outcomes: A systematic review and meta-analysis	Outcomes: miscarriage, small for gestational age (SGA), low birth weight (LBW) and preterm birth (PTB) Search date: before 2023
Pang 2024 - Association between prenatal perfluorinated compounds exposure and risk of pregnancy complications: A meta-analysis	Outcomes: gestational diabetes, hypertensive disorders, preeclampsia Search date 28 nov 2023
General health outcomes (including pregnant, children)	
Kemp 2025 – Evaluating health impacts of exposure to PFAS mixtures: a systematic review of epidemiological studies using mixture methods	Focus mixtures, on high quality primary studies Search date: 17 June 2025
Rocabois 2024 - Chemical exposome and children health: Identification of dose-response relationships from meta-analyses and epidemiological studies	Exclusion: Overview/umbrella SR. Focus on whether or not there are dose-response relationships. Based on SR by Colzin 2024 PFAS related to immune system, birth weight, behaviour, miscarriage
Xing 2024 - Per- and polyfluoroalkyl substances and human health outcomes: An umbrella review of systematic reviews with meta-analyses of observational studies	Exclusion: Umbrella review.
Colzin 2024 - A plausibility database summarizing the level of evidence regarding the hazards induced by the exposome on children health	Exclusion: Overview/Not specific for PFAS

Table 2 –SR relevant on breastfeeding, but excluded because not on health outcomes

Author - title	Relevant info	
O'Connor 2026 - Arsenic, cadmium, lead, mercury, and PFAS exposure during pregnancy or lactation and respective concentrations in human milk: Systematic review[1]	SR on exposure Included 10 studies	Higher exposure to PFOA, and PFOS during pregnancy or lactation correlated with concentrations of these contaminants in human milk (moderate certainty of evidence).
Ahmadpourmir 2025 - Early-Life Dietary Exposure to Perfluorooctanoic Acid (PFOA) Through Milk Consumption: A Systematic Review[2]	SR on PFOA exposure 49 studies on PFOA in breast milk 25 studies on PFOA in infant formula and commercial milk	The highest concentration of PFOA in infant formula and commercial milk was reported from Spain (2490 ng/kg) and the highest level of PFOA in breast milk from Belgium (3.5 ng/mL).
Dunn 2025- Endocrine Disrupting Chemicals in Human Milk: A Systematic Review of Concentrations and Potential Health Implications[3]	12 studies on PFAS	The most commonly detected PFAS in human milk were PFOA (12 studies), PFOS (10 studies), and PFDA (7 studies). The levels at which each chemical was detected varied, with maxima reaching up to 1.1 ng/mL (PFOA) , 0.87 ng/mL (PFOS), and 1.1 ng/mL (PFDA)
Thoerig 2025 - Assessment of arsenic, cadmium, lead, mercury, and per- and	Focus exposure in US studies	

Author - title	Relevant info	
polyfluoroalkyl substances concentrations in human milk and infant formula in the United States: a systematic review[4]	4 US studies on breast milk 2 US studies on infant formula	
Thayagabalu 2024 - A systematic review of contaminants in donor human milk [5]	Narrative reporting on exposure 4 European studies	
Timmermann 2023 - Per- and Polyfluoroalkyl Substances and Breastfeeding as a Vulnerable Function: A Systematic Review of Epidemiological Studies [6]	6 studies included (5 European and 1 US)	five out of six studies found shorter total duration of breastfeeding with higher PFAS exposure, while the US study identified an inverse association
Gonzalez and Domingo 2025* - PFC/PFAS concentrations in human milk and infant exposure through lactation: a comprehensive review of the scientific literature[7]	Narrative reporting on exposure per geographical area	reviewed studies suggest a decline in the concentrations of legacy PFAS (e.g., PFOS, PFOA) in breast milk in Europe and North America, which would be attributed to stricter regulations and reduced use of these compounds
LaKind 2023 *Per- and polyfluoroalkyl substances (PFAS) in breast milk and infant formula: A global issue* [8]	SR on exposure 49 publications with measured breast milk PFAS concentrations	
Van Noy 2018 - Breastfeeding as a Predictor of Serum Concentrations of Per- and Polyfluorinated Alkyl Substances in Reproductive-Aged Women and Young Children: A Rapid Systematic Review	SR on exposure	*We concluded there was "sufficient" evidence supporting an association between breastfeeding and serum PFASs concentrations among women, and "limited" evidence of an association among children due to issues with sample size, confounding, and exposure assessment*

** Note: These SRs reviews were identified outside the umbrella review search*

Table 3 – Excluded SRs because not the outcomes selected as "concerning health outcomes"

Author -title	Info
Thyroid	
Zhang 2025 - The Association Between Per- and Polyfluoroalkyl Substances Exposure and Thyroid Hormones in Men and Non-Pregnant Women: A Systematic Review and Meta-Analysis	Not on pregnant women, on thyroid biomarkers (link with FT3 but not with other markers)
Du et al 2024 - Association between PFAS exposure and thyroid health: A systematic review and meta-analysis for adolescents, **pregnant** women, adults and toxicological evidence	On thyroid biomarkers, no clinical diagnosis. MA on 14 studies in pregnant. No clear pattern
Zhang 2023 - Contact to perfluoroalkyl substances and thyroid health effects: A meta-analysis directing on pregnancy	On thyroid biomarkers (MA of 13 studies - association between PFOS, PFOA and PFDA exposure and TSH, not on other biomarkers/effects) *Our data recommend verifying the relationship between PFAS exposure and thyroid health effects in a large sample population cohort in future studies*

Author -title	Info
Sun 2022 - Prenatal exposure to endocrine-disrupting chemicals and thyroid function in **neonates**: A systematic review and meta-analysis	On thyroid biomarkers, not specific on PFAS (PFAS mentioned when TT4 was analysed)
Ballesteros 2017 - Exposure to perfluoroalkyl substances and thyroid function in **pregnant women and children**: A systematic review of epidemiologic studies	On thyroid biomarkers
Reproductive hormones	
Li et al 2024- Association between exposure to per- and perfluoroalkyl substances (PFAS) and reproductive hormones in human: A systematic review and meta-analysis.	
Tzouma 2025 - Associations Between Endocrine-Disrupting Chemical Exposure and Fertility Outcomes: A Decade of Human Epidemiological Evidence	
Cavicchio et al 2025 - Exposure to per- and polyfluoroalkyl substances (PFAS) and timing of menarche: A systematic review and meta-analysis	
Wang et al 2023 - The effects of perfluoroalkyl and polyfluoroalkyl substances on female fertility: A systematic review and meta-analysis	
Wang et al 2023 - Association between per- and polyfluoroalkyl substances and semen quality	
Childhood neurodevelopment	
Xu et al 2025 - The association between environmental endocrine disruptors and the risk of attention deficit and hyperactivity disorder in children: A systematic review and meta-analysis	Not specific on PFAS, no link with PFAS
Liu et al 2024-Association of prenatal exposure to perfluorinated and polyfluoroalkyl substances with childhood neurodevelopment: A systematic review and meta-analysis.	Inconsistent findings (sex-specific relationship)
Yang 2024 - Prenatal endocrine-disrupting chemicals exposure and impact on offspring neurodevelopment: A systematic review and meta-analysis	Not specific on PFAS
Stübner 2023 - Early-Life Exposure to Perfluoroalkyl Substances (PFAS) and Child Language and Communication Development: A Systematic Review	Inconsistent findings - No systematic effect of early-life PFAS exposure
Yao 2023 - The Association between Prenatal Per- and Polyfluoroalkyl Substances Exposure and Neurobehavioral Problems in Offspring: A Meta-Analysis	Inconsistent findings (PFOA positive link, PFOS negative link)
Qu et al 2021 - The association between maternal perfluoroalkyl substances exposure and early attention deficit hyperactivity disorder in children: a systematic review and meta-analysis	
Roth 2014 - Neurodevelopmental and neurobehavioural effects of polybrominated and perfluorinated chemicals: a systematic review of the epidemiological literature using a quality assessment scheme	
Childhood obesity	
Frangione 2024 Exposure to perfluoroalkyl and polyfluoroalkyl substances and pediatric obesity: a systematic review and meta-analysis	No link
Frigerio 2023 - Prenatal and childhood exposure to per-/polyfluoroalkyl substances (PFASs) and its associations with childhood overweight and/or obesity: a systematic review with meta-analyses -	Heterogeneity among studies
Stratakis 2022 - Prenatal exposure to persistent organic pollutants and childhood obesity: A systematic review and meta-analysis of human studies	
Asthma/ allergy in childhood	
Aeraki 2024 - Exposure to Poly- and Perfluoroalkyl Substances During Pregnancy and Asthma in Childhood: A Systematic Review	
Yin et al 2025 - Prevalence and Risk Factors of Asthma in Children: A Systematic Review and Meta-analysis	
Hatem et al 2025 - Exposure to per-and poly-fluoroalkyl substances and respiratory and skin effects in children and adolescents: A systematic review and meta-analysis	

Author -title	Info
Rafiee 2024 - Asthma and decreased lung function in children exposed to perfluoroalkyl and polyfluoroalkyl substances (PFAS): An updated meta-analysis unveiling research gaps	
Luo et al 2020 - Exposure to perfluoroalkyl substances and allergic outcomes in children: A systematic review and meta-analysis	
Smit 2015 - Prenatal exposure to environmental chemical contaminants and asthma and eczema in school-age children	
Cardiovascular diseases	
AbdullahSoheimi 2021 - Understanding the Impact of Perfluorinated Compounds on Cardiovascular Diseases and Their Risk Factors: A Meta-Analysis Study	
Yang 2023 - The Association of Hypertension with Perfluoroalkyl and Polyfluoroalkyl Substances	
Xiao 2023 - Association between per- and polyfluoroalkyl substances and risk of hypertension: a systematic review and meta-analysis	
Lipid concentrations in blood	
Ho et al 2022 - Perfluoroalkyl substances and lipid concentrations in the blood: A systematic review of epidemiological studies	
Zheng 2024- The effect of PFAS exposure on glucolipid metabolism in children and adolescents: a meta-analysis	
Hussey et al 2025 - The relationship between PFAS exposure and dyslipidemia: an updated review, meta-analysis, and evaluation of bias	This is of relevance for occupational exposure as there is a dedicated subanalysis.
Ji et al 2025 - Global Serum Per- and Polyfluoroalkyl Substances Exposures and Their Correlation with Lipids: A Systematic Review and Meta-Analysis	
Song et al 2025 - Association between exposure to per- and polyfluoroalkyl substances and levels of lipid profile based on human studies	
Cancer	
Sassano 2025 - Exposure to per- and poly-fluoroalkyl substances and hematological cancer: A systematic review and meta-analysis	This is of relevance for occupational exposure as there is a dedicated subanalysis.
Sassano 2025 - Exposure to per- and poly-fluoroalkyl substances and lung, head and neck, and thyroid cancer: A systematic review and meta-analysis	This is of relevance for occupational exposure as there is a dedicated subanalysis.
Seyyedsalehi 2023 - Per- and Poly-fluoroalkyl Substances (PFAS) Exposure and Risk of Kidney, Liver, and Testicular Cancers: A Systematic Review and Meta-Analysis	This is of relevance for occupational exposure as there is a dedicated subanalysis.
Seyyedsalehi 2024 - Per- And Poly-Fluoroalkyl Substances (PFAS) Exposure and Risk of Breast, and Female Genital Cancers: A Systematic Review and Meta-Analysis.	This is of relevance for occupational exposure as there is a dedicated subanalysis.
Sezavar 2024 - Examining the relationship between per-and polyfluoroalkyl substances and breast, colorectal, prostate, and ovarian cancers: a meta-analysis.	
Spyrakis 2025 - PFOA biomonitoring and kidney cancer risk: a meta-analysis of serum levels **+ correction**	
Van Gerwen 2024 - Per- and polyfluoroalkyl substances (PFAS) exposure and thyroid cancer: Systematic review and meta-analysis	
Wang et al 2025 - The association between per-fluoroalkyl and poly-fluoroalkyl substances exposure and thyroid cancer: a meta-analysis	
Yang 2024 - Perfluoroalkyl and polyfluoroalkyl substances and Cancer risk: results from a dose-response Meta-analysis **+ correction**	
Yang 2025 - Exposure to Per- and Polyfluoroalkyl Substances and the Risk of Prostate and Ovarian Cancer: An Epidemiologic Meta-Analysis	
Zhang 2025 - Per- and poly-fluoroalkyl substances exposure and risk of gastrointestinal cancers: a systematic review and meta-analysis	

2.3 Primary studies: Preeclampsia

The search for primary studies after 2022 (search date of SR Hirke 2023) identified 34 hits. Among them 8 were assessed for eligibility based on title and abstract, and 4 were excluded.

Author - title	Reason for exclusion
Save-Söderberg, 2025[9] - Per- and polyfluoroalkyl substances (PFAS) in drinking water, gestational diabetes mellitus, hypertension and preeclampsia: A nation-wide register-based study on PFAS in drinking water	Ecological study
Zhou, 2024[10] - Potential causal associations between perfluoroalkyl substances exposure and adverse pregnancy outcomes: A bidirectional two-sample mendelian randomization study	No direct measurement of PFAS in the blood/use of databases
Ebel, 2023[11] - Gestational hypertension, preeclampsia, and gestational diabetes mellitus after high exposure to perfluoroalkyl substances from drinking water in Ronneby, Sweden	Ecological study
Kaiser, 2023[12]- Prenatal exposure to per- and polyfluoroalkyl substances and pregnancy outcome in Austria	No measure of the association

2.4 Primary studies: Miscarriage

The search identified 44 references. Among them, 35 were excluded based on title/abstract, and 9 selected for full text analysis. Four studies were excluded and five included.

Author - title	Reason for exclusion
Wang 2026 - Exposure to per- and poly-fluoroalkyl substances and associations with embryo quality and adverse pregnancy outcomes: a prospective cohort study	Specific IVF:ICSI population and Exposure measured in Follicular fluid samples
Fang 2024 - Association of coexposure to perfluoroalkyl and polyfluoroalkyl compounds and heavy metals with pregnancy loss and reproductive lifespan: The mediating role of cholesterol	Focus on co-exposure of PFAS and lead and mercury, and genes
Hasegawa 2024 - Maternal Exposure to Per- and Polyfluoroalkyl Substances and Offspring Chromosomal Abnormalities: The Japan Environment and Children's Study	Outcome: chromosomal abnormalities (addressed as separate outcome)
Savitz 2012 - Perfluorooctanoic acid exposure and pregnancy outcome in a highly exposed community	PFAS Exposure based on estimation/modeling

2.5 Primary studies: Prematurity

Among the 80 primary studies published after March 2021, 70 were excluded on title/abstract, and four additional studies were excluded after reading full text.

Author-title	Reason for exclusion
Dioniso et al. 2026[13] Associations of PFAS exposure with obstetric and birth outcomes in the Japan Environment and Children's Study (JECS): Is maternal endometriosis an effect modifier?	Results are on threatened premature labor (20.5%), not PTB
Mullin et al.2025[14] - Perfluoroalkyl substances and preterm birth	Only an abstract is available
Qin et al., 2023[15]- Prenatal Exposure to PFAS, Associations with Preterm Birth and Modification by Maternal Estrogen Levels: The Maoming Birth Study	-Nested case-control, Maoming Birth Study (China) with differences between groups (controls were younger, more educated, more often female, more often in first pregnancy) -Blood sample taken at mean gestational age: 32 wk, range: 7–40 wk
Zhang et al., 2024[16] - Maternal and Paternal Preconception Serum Concentrations of Per and Polyfluoroalkyl Substances in Relation to Birth Outcomes	Preconception cohort of subfertile couples

2.6 Primary studies: Congenital abnormalities

The search identified 42 references, of which 21 were excluded on title/abstract, and 11 were excluded after full text review.

Author -title	Reason for exclusion
Platel 2025 - Environmental Contaminants and Congenital Heart Defects: Focus on PFAS, PAHs, and Other Emerging Exposures	Narrative review
Bianchi F 2025 - Interesting new findings on the relationship between PFAS and congenital malformations	Italian
Nunez Garcia Bernardo and Alvarez-Garcia Natalia 2025 - Association between endocrine disruptors and surgical congenital malformations: Systematic review and meta-analysis	No specific analysis for PFAS. 10 primary studies included on PFAS and congenital heart disease
Save- Soderbergh 2025 - Fetal exposure to perfluoroalkyl substances (PFAS) in drinking water and congenital malformations: A nation-wide register-based study on PFAS in drinking water	Exposure via “estimated one-compartment toxicokinetic model” (not via PFAS blood measure)
Elhassan 2024 - The Relationship Between Maternal Exposure to Endocrine-Disrupting Chemicals and the Incidence of Congenital Heart Diseases: A Systematic Review and Meta-Analysis	No specific focus on PFAS, only 2 primary study included (Ou 2021 ; Sainan Li 2024)
Bianchi F 2024 - Congenital heart disease and PFAS: a relationship to be studied in contaminated areas	Italian
Boyer 2023 - Prenatal exposure to persistent organic pollutants and molar-incisor hypomineralization among 12-year-old children in the French mother-child cohort PELAGIE	No outcome of interest

Author -title	Reason for exclusion
Abuduxukuer 2025 - Prenatal exposure to per-and polyfluoroalkyl substances and its association with Developmental Defects of Enamel (DDE) and dental caries in 4 years old children: Findings from Shanghai birth cohort	No outcome of interest
Tian 2022 - Associations of single and multiple perfluoroalkyl substances exposure with folate among adolescents in NHANES 2007-2010	No population of interest
Desalegn 2021 - A case-cohort study of perinatal exposure to potential endocrine disrupters and the risk of cryptorchidism in the Norwegian HUMIS study	INCLUDE Exposure via breast milk samples
Petersen 2020 - Per- and polyfluoroalkyl substances and male reproductive health: a systematic review of the epidemiological evidence	No population/outcome of interest

2.7 Primary studies: Acute Lymphoblastic leukemia

The search for primary studies resulted in 5 references, of which three were excluded based on title/abstract, and one based on full text review.

Author-title	Reason for exclusion
Metayer 2024 - Exposure to per- and polyfluoroalkyl substances in residential settled dust and risk of childhood acute lymphoblastic leukemia	Exposure via quantification in house dust collected in vacuum bags in homes of 178 children with ALL and 204 health controls

2.8 Primary studies on breast milk and health outcomes

The search for primary studies after 2018 (search date of Hoadley 2023) identified 155 references, of which 14 were selected for full text review. Nine studies were included and five excluded.

Table 4 – Excluded primary studies on association of PFAS exposure through breastmilk and health outcomes

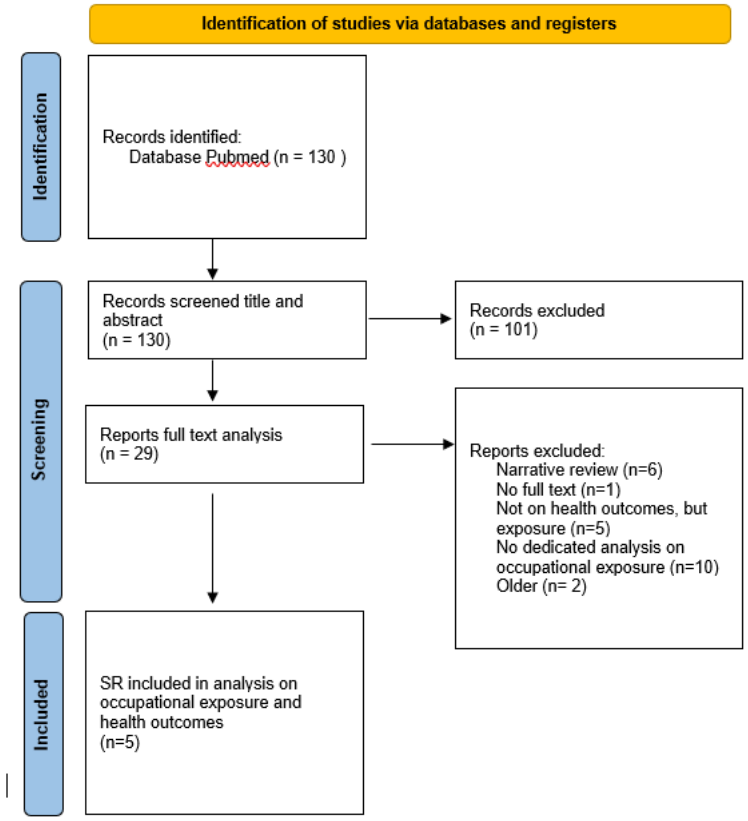
Author - title	Reason for exclusion
Gyllenhammar 2019, Perfluoroalkyl Acids (PFAAs) in Children's Serum and Contribution from PFAA-Contaminated Drinking Water	No measurement in breast milk
Colles 2020 Perfluorinated substances in the Flemish population (Belgium): Levels and determinants of variability in exposure	No direct measurement of PFAS in breast milk. Breastfeeding identified as reason why maternal plasma concentration is lower
Abraham 2020 , Internal exposure to perfluoroalkyl substances (PFASs) and biological markers in 101 healthy 1-year-old children: associations between levels of perfluorooctanoic acid (PFOA) and vaccine response	No direct measurement of PFAS in breast milk. Plasma levels of PFOA and PFOS of 3.8 ± 1.1 and 6.8 ± 3.4 µg/L, respectively, in the 21 formula-fed children, and of 16.8 ± 6.6 and 15.2 ± 6.9 µg/L in the 80 children exclusively breastfed for at least 4 months

Author - title	Reason for exclusion
	Vaccin response but no further link with breastfeeding
Forns 2020 , Early Life Exposure to Perfluoroalkyl Substances (PFAS) and ADHD: A Meta-Analysis of Nine European Population-Based Studies	Already included in SR by Hoadley 2023. Forns synthetized data of 9 European studies, of which 2 studies with measurement in breast milk • PCB cohort (Slovakia) • HUMIS (Norway)
Mahfouz 2023 Maternal Serum, Cord and Human Milk Levels of Per- and Polyfluoroalkyl Substances (PFAS), Association with Predictors and Effect on Newborn Anthropometry	41 women with breast milk but no health effects linked

2.9 Systematic reviews on occupational exposure

The search identified 130 references, of which 29 were selected for full text analysis. Twenty-four full text were excluded because not on occupational cohorts and health effects (see table 5 below). Five SRs were included because somewhere in their analysis they reported on occupational cohorts.

2.9.1 Flowchart SR on occupational exposure



2.9.2 Excluded reviews

Table 5 – Excluded reviews on occupational exposure during full text review.

Author/Title	Reason of exclusion
Schutte 2026 - Firefighter Cancer Risks: A Systematic Review and Proposal for a Volunteer-Specific Decontamination Model[17]	Narrative - No primary studies on occupational exposure and cancer risk. PFAS is listed as one of the potential hazards, in addition to combustion byproducts, diesel particles. Referral to IARC carcinogenic to humans (group 1) based on 'sufficient evidence for cancer in humans due to exposure to a variety of hazards (such as combustion products from fires such as polycyclic aromatic hydrocarbons, building material such as asbestos, diesel exhaust and PFAS)'.[18, 19]
He et al 2025 - A Critical Review of Populations with Occupational Exposure to Per-and Polyfluoroalkyl Substances: External Exposome, Internal Exposure Levels, and Health Effects	Narrative review –partial overview of available studies on health effects in occupational exposure. The authors highlight the importance of changes in levels of serum biochemical markers relevant for liver (aspartate transaminase, alanine transaminase, glutamyl transferase), kidney (creatinine and uric acid) and lipid homeostasis (total cholesterol, triglycerides). US: Ubel 1980 ,Gilliland 1993, Gilliland 1996, Lundin 2009, Sakr 2009, Leonard 2008, Alexander 2003, Alexander 2007 Europe: Costa 2009, Olsen 2007 (Antwerp), Sakr 2007 China: Fu 2016, Wang 2012, Zhou 2014
Crawford and Hartmann 2024 - Respiratory Exposure to Highly Fluorinated Chemicals via Application of Ski Wax and Related Health Effects.[20]	Narrative review
Mazumder 2023 - Firefighters' exposure to per-and polyfluoroalkyl substances (PFAS) as an occupational hazard: A review	Narrative review
Lee 2026 - Distribution and Concentration of Airborne Per- and Polyfluoroalkyl Substances (PFAS) in Indoor and Outdoor Environments: A Systematic Review	Systematic review - On measurement of PFAS in environment
Chistensen and Calkins 2023 - Occupational exposure to per- and polyfluoroalkyl substances: a scope review of the literature from 1980-2021.[21]	Systematic review but limited to exposure assessement 92 studies covering both manufacturing and non-manufacturing work environments
Phillipson and Bartell 2026 - Exposure to per- and polyfluoroalkyl substances and inflammatory bowel disease: review and meta-analysis	No specific analysis for occupational exposure 2 studies included, but Agrawal not included in meta-analysis • Steenland 2015 worker cohort" • Agrawal et al 2024 nested case-control study of military personnel with Crohn's disease (CD), ulcerative colitis (UC),
Tanghal 2026 - Exposure to Per- and Polyfluoroalkyl Substances and Liver Cancer: A Systematic Review of Animal and Epidemiological Studies	No dedicated analysis for occupational exposure.

Author/Title	Reason of exclusion
	7 studies focused on population in highly exposed and occupational cohorts with two studies on PFAS measurement in blood Girardi 2019 Leonard 2008
Spyrakis 2025 - PFOA biomonitoring and kidney cancer risk: a meta-analysis of serum levels	Included 3 studies of which none specific for occupational exposure
Zhang 2024 - Per- and poly-fluoroalkyl substances exposure and risk of gastrointestinal cancers: a systematic review and meta-analysis	Included studies on occupational exposure but no dedicated analysis
Wu 2025 - Relationship between PFAS and attention-deficit/hyperactivity disorder or autism spectrum disorder: Epidemiological and experimental evidence	Narrative review
Sezavar 2024 - Examining the relationship between per-and polyfluoroalkyl substances and breast, colorectal, prostate, and ovarian cancers: a meta-analysis	No dedicated analysis on occupational exposure
Du 2024 - Association between PFAS exposure and thyroid health: A systematic review and meta-analysis for adolescents, pregnant women, adults and toxicological evidence	No dedicated analysis on occupational exposure
Chang 2024 - Exposure to per- and polyfluoroalkyl substances and breast cancer risk: a systematic review and meta-analysis of epidemiologic studies	Only included Feng 2022 and Rayleigh 2014 but no dedicated analysis on occupational exposure
Xiao 2023 - Association between per- and polyfluoroalkyl substances and risk of hypertension: a systematic review and meta-analysis	No dedicated to occupational cohort studies, nor analysis
Paris-Davilla et al 2023 - Occupational exposures to airborne per- and polyfluoroalkyl substances (PFAS)-A review.	Systematic review on exposure
Lucas et al 2023 - Occupational exposure and serum levels of per- and polyfluoroalkyl substances (PFAS): A review.	Systematic review on exposure
Kim 2018 - Association between perfluoroalkyl substances exposure and thyroid function in adults: A meta-analysis	no included studies on occupational exposure
Gebbink and van Leeuwen 2020 - Environmental contamination and human exposure to PFASs near a fluorochemical production plant: Review of historic and current PFOA and GenX contamination in the Netherlands	Review on exposure
Chang 2014 - A critical review of perfluorooctanoate and perfluorooctanesulfonate exposure and cancer risk in humans	Narrative - Many positive associations with PFOA exposure were detected in community settings without occupational exposure and were not supported by results in exposed workers.

Author/Title	Reason of exclusion
Steenland 2010 - Epidemiologic evidence on the health effects of perfluorooctanoic acid (PFOA)	Two occupational cohort studies do not provide consistent evidence for chronic disease; both are limited by sample size and reliance on mortality data
Bach 2016 - Perfluoroalkyl and polyfluoroalkyl substances and measures of human fertility: a systematic review	- No focus on occupational exposure
Olsen 2009 - Perfluoroalkyl chemicals and human fetal development: an epidemiologic review with clinical and toxicological perspectives	2 included studies on occupational exposure but no blood samples collected (Grice et al 2007, Olsen et al 2004) No association with self-reported birth weight and occupational exposure to PFOS materials was observed among female perfluorochemical production workers
Nakayama 2005 - Distributions of perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) in Japan and their toxicities	No full text available One epidemiological study conducted by 3M revealed an increase in prostate cancer mortality [3.3-fold increase (95% CI, 1.02-10.6)] among workers exposed to PFOA. Another study conducted by 3M revealed an increase in bladder cancer mortality (SMR 12.77, 95% CI 2.63-37.35) among workers exposed to PFOS

3 CRITICAL APPRAISAL

3.1 Critical appraisal of Systematic Reviews

3.1.1 AMSTAR Methodology – critical domains

The paper by Shea et al 2017 provides guidance on how to interpret the individual criteria of AMSTAR and come to an overall rating.[22] In this report, we took existing guidance into account, but we considered a systematic review to be of good quality as long as it did not contain a critical limitation. The presence of a critical limitation depends on both the health outcome and the specific systematic review, and is explicitly mentioned when rating the overall quality.

Box 1: AMSTAR 2 critical domains

- Protocol registered before commencement of the review (item 2)
- Adequacy of the literature search (item 4)
- Justification for excluding individual studies (item 7)
- Risk of bias from individual studies being included in the review (item 9)
- Appropriateness of meta-analytical methods (item 11)
- Consideration of risk of bias when interpreting the results of the review (item 13)
- Assessment of presence and likely impact of publication bias (item 15)

3.1.2 Appraisal of SR on preeclampsia

3.1.2.1 Abd Mutalib et al, 2025[23]

Abd Mutalib et al, 202523	Comments
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes • **Population:** pregnant women • **Exposure/ Comparator:** 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), no comparator defined • **Outcomes:** preeclampsia • **Timeframe:** 2012-2022 • **Studies:** research articles
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No protocol mentioned and the review was not registered.
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Not applicable because in this field there are only observational studies in humans. No explanation/ scientific justification is provided (just “research article” mentioned).
4. Did the review authors use a comprehensive literature search strategy?	Partial yes • Consulted databases (Google Scholar, Pubmed, Science Direct), search strategy and restrictions criteria are mentioned. Full-strategy do not include the numbers of hits. • No justification for language restrictions (exclusion of articles in Spanish), no consultation of trial/study registries, no consultation of experts, no grey literature listed.
5. Did the review authors perform study selection in duplicate?	Yes (unclear if applicable for the second-level selection on full text). Strategy to decide on discrepancies between the 2 reviewers is not explained.
6. Did the review authors perform data extraction in duplicate?	Probably yes (quality assessment performed by two independent reviewers)
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No list available
8. Did the review authors describe the included studies in adequate detail?	No (see Table 1 with limited information; no data on the types and levels of exposure; no detail on the control groups, no information on the adjustments of the odds ratio,…)

Abd Mutalib et al, 202523	Comments
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes (Newcastle-Ottawa scale- NOS). 6 out of 7 studies scored high quality and one study scored fair quality
10. Did the review authors report on the sources of funding for the studies included in the review?	No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Partial yes : random-effect models no justification on the combination of data heterogeneity absent for two PFAS on three no mention of combined effect estimates from studies that were adjusted for confounding
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Yes
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	No heterogeneity for two PFAS (PFOA, PFOS) and some explanations given for the third (PFHxS)
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes

Critical domains according to Shea 2017:

- items 2 (no protocol)
- item 4 are ‘‘partial yes’
- item 7 is answered ‘no’
- 11 is answered ‘partial yes’
- 9, 13 and 15 are answered ‘yes’

Conclusion: low quality (critical limitations: not enough details on the pooling of the data, other concerns: no protocol, no list of excluded studies, no comprehensive description of the studies,)

3.1.2.2 Hirke et al, 2023[24]

Hirke et al, 2023[24]	Comments
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Partly:- discrepancy with protocol? • **Population:** Pregnant women aged between 16 to 45 years with singleton live birth with gestational week between 8 to 37 weeks, who have been exposed to endocrine disrupting chemicals • **Exposure:** endocrine disrupting chemicals is associated with risk of development of gestational hypertension and preeclampsia • **Comparator:** Non-hypertensive Pregnant Women having exposure to various classes of endocrine disrupting chemicals • **Outcomes:** preeclampsia, hypertensive disorders • **Timeframe:** all English-language articles published up to January 2022 (**different from the dates in the protocol)** • **Studies:** case-control, cohort, and cross-sectional studies
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes. The review was registered CDR 42022298243. Review question, search strategy, inclusion/exclusion criteria, risk of bias assessment and statistical analysis were defined
3. Did the review authors explain their selection of the study designs for inclusion in the review?	No explanation is provided (case-control, cohort, and cross-sectional studies) However, in this field of research only observational studies in humans
4. Did the review authors use a comprehensive literature search strategy?	Partial yes • Consulted databases (PubMed + Google Scholar), search strings are mentioned but no full-strategy with numbers. • No justification for language restrictions (exclusion of articles in Spanish), no consultation of trial/study registries, no consultation of experts, no grey literature listed.
5. Did the review authors perform study selection in duplicate?	Yes for screening on titles and abstracts and full text. Strategy to decide on discrepancies between the 2 reviewers is not explained.
6. Did the review authors perform data extraction in duplicate?	Yes (but the protocol mentioned only one reviewer for extraction)
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No

Hirke et al, 2023[24]	Comments
8. Did the review authors describe the included studies in adequate detail?	Yes (type of exposure not mentioned)
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes (Newcastle-Ottawa scale- NOS). All studies considered high quality (score >6 on total of 9)
10. Did the review authors report on the sources of funding for the studies included in the review?	No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Partial yes : Fixed or random-effect models (according to heterogeneity) no justification on the combination of data no mention of combined effect estimates from studies that were adjusted for confounding
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Not applicable, all studies were considered high quality
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Yes
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Partly (few information on sensitivity analysis but it was performed by excluding studies one by one to examine the influence on each individual study in the pooled result)
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes

Critical domains according to Shea 2017:

- items 2 protocol ‘yes’
- item 4 ‘partial yes’
- item 7 is answered ‘no’

- 11 is answered 'partial yes'
- 9, 13 and 15 are answered 'yes'

Conclusion: Low (critical limitation: not enough details on the pooling of the data)

3.1.2.3 Hu et al, 2023[25]

Hu et al, 2023[25]	Comments
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes : • **Population:** Female humans who were pregnant at exposure • **Exposure:** Exposure to PFASs, including the species of PFAS (e.g., PFOA, PFOS, PFHxS, PFNA, PFDA, etc.) and PFAS measured or modeled that estimate PFAS concentration • **Comparator:** A comparison population exposed to lower levels (or no exposure/ exposure below detection levels) of PFASs • **Outcomes:** Gestational hypertension, preeclampsia, hypertensive disorders of pregnancy, pregnancy-induced hypertensive disorders • **Studies/ Timeframe:** Only human studies that are published between up to November 2022, in peer-reviewed journal articles and written in English. Studies that reported a quantitative measure of association and measure of precision.
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No • Review question, search strategy, inclusion/exclusion criteria, risk of bias assessment present) provided in the Appendix with a PRISMA list but no registered protocol mentioned • Although discussed in the article, there is no protocol for meta-analysis plan and investigation of the heterogeneity
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Not applicable because in this field there are only observational studies in humans. Designs mentioned but no explanation is provided
4. Did the review authors use a comprehensive literature search strategy?	Partial yes • Consulted databases : PubMed, Web of Science, and EMBASE. • Search strategy provided • No consultation of registries, experts, grey literature..
5. Did the review authors perform study selection in duplicate?	Yes for screening on titles, abstracts and full texts. Strategy to decide on discrepancies between the 2 reviewers is not explained.
6. Did the review authors perform data extraction in duplicate?	Yes

Hu et al, 2023[25]	Comments
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No list of excluded studies
8. Did the review authors describe the included studies in adequate detail?	Partial yes (types of exposure is not mentioned, limited details on the control groups)
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes (NTP/OHAT)
10. Did the review authors report on the sources of funding for the studies included in the review?	Yes (it is mentioned that "*all studies included in this review were funded by public bodies, as well as no conflicts of interest were declared.*")
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Partial yes Method: random-effect meta-analysis Harmonisation of data No mention of combined effect estimates from studies that were adjusted for confounding No Forrest plots; for the meta-analysis on preeclampsia (11 studies were included). Sensitivity analysis is mentioned ("leave-one-out-method"). In Table 4, limited information on highest and lowest exposure, but analysis per 1 ln unit increase. "*This meta-analysis included only observational studies, resulting in an initial rating of "moderate confidence" in accordance with the NTP/OHAT framework.*" The number of included studies is mentioned in the Table 4 but no detail with Forrest plots of the included studies.
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No The authors noted inconsistency as the main reason for down-grading the association exposure-outcome, using GRADE framework. The review assessed the risk of bias of the included studies using NTP/OHAT but did not quantify the influence of this RoB on the pooled estimates.
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Yes (based on the quality) – GRADE framework
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Partial yes, this is discussed but no subgroup analysis
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes (Egger test)
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes

Critical domains according to Shea 2017:

- items 2 (no protocol)
- item 4 'partial yes'
- item 7 is answered 'no'
- 11 is answered 'partial yes'
- 9, 13 and 15 are answered 'yes'

Conclusion: Low - critical limitations: not enough details on the pooling; no registered protocol, partial comprehensive data search, unaccounted quantative analysis including study quality, no list of excluded studies

3.1.3 Appraisal of the SRs on gestational diabetes

3.1.3.1 Quan 2026[26]

Quan 2026[26]	Comments
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes • **Population:** pregnant women • **Exposure:** measured in serum or plasma PFASs (at least one PFAS • **Comparator:** An incremental increase in concentration of a specific PFAS compared with a lower concentration • **Outcomes:**. OGTT test or GDM diagnosis • **Timeframe:** before feb 2025 **Studies:** cohort, case-control, and cross-sectional
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes, registered at PROSPERO registration number ID: CRD420251045750
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Not applicable because in this field there are only observational studies in humans . Inclusion: studies with risk estimates or regression coefficient and 95%CI
4. Did the review authors use a comprehensive literature search strategy?	Partially Yes • PubMed, Web of Science, and Scopus, covering all records published before February 20, 2025. Search keywords in article • No Reference lists were checked.

Quan 2026[26]	Comments
	• No Grey literature check • No consultation of trial/study registries, no consultation of experts,
5. Did the review authors perform study selection in duplicate?	Yes: two independent reviewers conducted the literature search and screened the titles and abstracts for eligibility.
6. Did the review authors perform data extraction in duplicate?	Yes (performed independently by two reviewers using a standardized extraction form)
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Yes in text 4 studies no quantitative analysis and 1 on cord serum
8. Did the review authors describe the included studies in adequate detail?	No (see Table 2 and figure 2, table S5 is not complete), the figure gives an overview of the 28 studies but no link to the identity of the study. no individual ORs per study but the adjusted factors are communicated
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes (NOS) in table 2,3 and 4 in supplement. All are rated low risk of bias (score 8 or 9). but NOS not the most ideal tool to assess quality (see KCE guideline)
10. Did the review authors report on the sources of funding for the studies included in the review?	No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Yes reexpression such that all logarithmic results were on the natural log scale, and all results on the absolute scale on a per ng/ml difference They only pooled per exposure assessment: Per logarithmic increase Per absolute increase Categorical high vs low Sensitivity leave one out Subgroup analyses
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	They did not discuss quality of studies. All were rated via NOS and had scores of 7 or higher, implicitly high quality (but not discussed).
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	No quality of studies, no information on confounding but they discussed the subgroup analysis
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	In cases of high heterogeneity, sensitivity analysis or meta-regression was conducted to explore potential sources of heterogeneity. The source of heterogeneity for most substances was the literature by Xu 2022

Quan 2026[26]	Comments
	Subgroup analysis per study site, publication year, sampling period and methods of chemical analysis
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Publication bias was assessed using Egger's linear regression asymmetry; no publication bias
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes

Critical domains according to Shea 2017:

- item 2,7,9,11,15 'yes'
- item 4 adequacy of literature search 'partially yes'
- Item 13 consideration of risk of bias when interpreting study results 'no'

Conclusion: moderate to high – No critical limitations. The systematic review did not consideration risk of bias when interpreting study results as they were all considered high quality, and some details on primary studies including source of funding were not available, nor the risk estimates per individual study. The SR did provide a meta-analysis with rescaling to ln units, reported on separate pooling and performed several subgroup analyses.

3.1.3.2 Wang 2025 (gestational diabetes)

Wang 2025 (gestational diabetes)	Comments
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Partly Yes • **Population:** pregnant women • **Exposure:** PFAS, including but not limited to PFOA, PFNA, PFOS, PFDA, and PFHxS **(but no detail on which matrix)** • **Comparator: ?** • **Outcomes:**. GDM diagnosis • **Timeframe:** before oct 2023 • **Studies:** cohort, case-control, and cross-sectional
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes, registered at PROSPERO registration number CRD42023477293.

Wang 2025 (gestational diabetes)	Comments
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Not applicable because in this field there are only observational studies in humans - exclusion: studies without full text and lacking statistical data such as OR, HR, and 95%CI, animal studies, case reports, reviews, meta-analysis, repeated published literature, non English literature
4. Did the review authors use a comprehensive literature search strategy?	Partially Yes • Pubmed, EMBASE, Web of Science, and Cochrane Library Oct 16, 2023. Search string in appendix • No Reference lists were checked. • No Grey literature check • no consultation of trial/study registries, no consultation of experts,
5. Did the review authors perform study selection in duplicate?	No, Back-to-back searches were conducted by two investigators, but no info selection
6. Did the review authors perform data extraction in duplicate?	Yes (performed independently by two reviewers)
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No list of references: four articles were excluded for the following reasons: 1 was irrelevant to the research topic, and 3 were meta-analyses, and another 8 were excluded because incomplete statistics n=3, irrelevant exposure or outcome n=5
8. Did the review authors describe the included studies in adequate detail?	Partly Yes (see Table 2), no info on median PFAS levels per study, no info on which kind of exposure measurement was used, or details on rescaling, individual OR per study for SMD in appendix (study of Xu 2022 shows very large impact on PFOA)
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes (NOS) in table 3. but NOS not the most ideal tool to assess quality
10. Did the review authors report on the sources of funding for the studies included in the review?	No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	No OR was used to estimate risk for all studies while SMD was used to synthesize continuous data (without adjusting). The reporting was guided by the non-adjusted data (the SMD and univariate analysis) Statistical modeling was guided by the heterogeneity results (random or fixed) Sensitivity analyses showed the heterogeneity was derived from Zhang 2015 and Xu 2022 Subgroup analysis (study location, year of publication, timing of exposure, methods of chemical analysis)

Wang 2025 (gestational diabetes)	Comments
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Not applicable: All were rated via NOS, 3 had a score of 8 and 9 had a score of 9, all indicating high quality
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	No details on quality of studies, no information on confounding but they discussed the subgroup analysis and impact of Chinese studies. But they preferably reported non-adjusted analysis minimizing the adjusted
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes, Subgroup analysis to try to explain the large heterogeneity
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Publication bias was assessed indicating no publication bias
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes

Critical domains according to Shea 2017:

- item 2,9,15 ‘yes’
- item 4 adequacy of literature search ‘partially yes’
- item 7 justification of excluding studies: no
- item 11 , there was no focus on combining effect sizes adjusted for confounding
- Item 13 consideration of risk of bias when interpreting study results ‘no’

Conclusion: low - The systematic review has critical limitation (the reporting on the meta-analysis was not sufficiently clear - focus on univariate analysis?), no consideration of risk of bias when interpreting study results because all considered high quality, no justification of excluding studies, as well as lack of details on primary studies including source of funding. On the other hand, it did provide a meta-analysis reported on separate pooling and performed several subgroup analyses.

3.1.3.3 Pang 2024 (gestational diabetes)

Pang 2024 (gestational diabetes)	Comments
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Partly Yes • **Population:** pregnant women • **Exposure:** PFAS, including but not limited to PFOA, PFOS, PFHxS **in biological sample** • **Comparator: ?** • **Outcomes:**. GDM diagnosis • **Timeframe:** November 2023 • **Studies:** cohort, case-control, and cross-sectional
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Not applicable because in this field there are only observational studies in humans – Inclusion criteria: the study provided risk estimates to investigate the association of PFASs on pregnancy complications, such as odds ratio (OR), risk ratio (RR), or hazard ratio (HR) and corresponding 95% confidence interval English Exclusion when full text and sufficient original data was not available, SR, animal studies, RCTs,editorials, comments, repeat publication, and articles considered low quality
4. Did the review authors use a comprehensive literature search strategy?	Partially Yes • Pubmed, PubMed, Qvid Medline, Embase, and Web of Science • Search strategy in appendix • No Reference lists were checked. • No Grey literature check • no consultation of trial/study registries, no consultation of experts,
5. Did the review authors perform study selection in duplicate?	Two authors (PLY and LM) screened all articles independently
6. Did the review authors perform data extraction in duplicate?	PLY and LM separately extracted information from eligible articles using standardized data extraction forms and discussed to resolve disagreements.
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No list of references or justification

Pang 2024 (gestational diabetes)	Comments
8. Did the review authors describe the included studies in adequate detail?	Partly Yes (see appendix), no info on median PFAS levels per study, or individual OR per study nor on confounding/adjustments
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	STROBE tool in appendix table 3. scoring 15 or higher on 22 items is high quality. They all were high quality They excluded articles with low quality (exclusion criteria)
10. Did the review authors report on the sources of funding for the studies included in the review?	No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Yes, Odds Ratio (OR), Hazard Ratio (HR),the corresponding 95% Confidence Interval (95%CI) were extracted from **adjusted** covariance models Random effects model to account for heterogeneity Subgroup analysis (region, study type, sample size) and leave one out sensitivity analysis The included studies included PFAS concentrations as categorical variables, and calculated effect sizes by comparing the highest with the lowest categories
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	all studies were considered low risk of bias
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	No quality of studies, no information on confounding but they discussed the subgroup analysis
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	not fully transparent as they did not clearly state that the sub analyses on region, study type and sample size were not consistent. Although in their conclusion they soften However, the associations may vary depending on the region, study type, or inconsistencies in the trend could arise due to differences in study sample sizes
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	When analyzing ten or more articles, publication bias was assessed using the Begg test; for analyses involving fewer than ten articles, publication bias was not evaluated: the Begg test detected no publication bias
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes

Critical domains according to Shea 2017:

- Item 2 (no protocol)

- item 4 adequacy of literature search 'partially yes'
- item 9 yes
- item 7 justification of excluding studies: no
- item 11 yes
- Item 13 consideration of risk of bias when interpreting study results 'no'

Conclusion: moderate - The systematic review has limitations, though not critical (no protocol, no justification of excluding studies, no details on primary studies including adjusted risk estimates). The heterogeneity was addressed in the conclusion as the associations may vary depending on region, study type or sample size.

3.1.3.4 Yao 2023 (gestational diabetes)

Yao 2023 (gestational diabetes)	Comments
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes, in the protocol • **Population:** women with a live singleton birth provided urine, blood, meconium, and completed questionnaire on demographic and lifestyle. History of diabetes excluded • **Exposure:** environmental pollutants such as PFAS in biological samples • **Comparator:** participants with routine prenatal care • **Outcomes:**. GDM diagnosis, with Odds ratio and confidence interval • **Timeframe:** before sept 2022 • **Studies:** cohort, case-control, and cross-sectional
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes, registered at PROSPERO registration number CRD42022369993
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Not applicable because in this field there are only observational studies in humans; exclusion: 1) editorials, case reports, reviews, and conference abstracts; 2) the level of pollutants exposure was not examined through biological samples (plasma, serum, urine, or meconium); 3) reported exclusively the effects of occupational or acute exposure; 4) repeated cohort data; 5) the effect size with 95%CI could not be calculated; for experimental studies:
4. Did the review authors use a comprehensive literature search strategy?	Partially Yes • PubMed, Embase, Web of Science, Medline • and Cochrane Sept, 2022. Search string in appendix

Yao 2023 (gestational diabetes)	Comments
	• Reference lists were checked. • No Grey literature check • no consultation of trial/study registries, no consultation of experts,
5. Did the review authors perform study selection in duplicate?	Yes, two reviewers independently reviewed all articles and disagreements with third reviewer
6. Did the review authors perform data extraction in duplicate?	Not specified… the quality assessment via NOS was via two independent
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No list of references
8. Did the review authors describe the included studies in adequate detail?	Partly Yes (see appendix), no info on median PFAS levels , no ORs per individual study reported
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes (NOS) in table 3. but NOS not the most ideal tool to assess quality
10. Did the review authors report on the sources of funding for the studies included in the review?	No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	No, the overall pooling of the same studies but for different PFAS compounds into one overall estimate is not correct. For the pooling per single PFAS categorical and logarithmic scale were pooled. Random effects model because of heterogeneity Sensitivity analyses (leave one out) showed the heterogeneity was derived from Xu 2020 and Xu 2022 Subgroup analysis (country, exposure period, comparison category (ccategorical or continuous) , laboratory method, sample size, study design, used sample
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	They did not discuss quality of studies. All were rated via NOS and had scores of 8 or 9, implicitly high quality (but not discussed).
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	No quality of studies, no information on confounding but they discussed the subgroup analysis and impact of Chinese studies.
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes, Subgroup analysis to try to explain the large heterogeneity
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Publication bias was evaluated by using funnel plots and

Yao 2023 (gestational diabetes)	Comments
	Egger's test when sufficient studies (n > 10) were available. no publication bias in the included studies
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes

Critical domains according to Shea 2017:

- item 2,9,15 'yes'
- item 4 adequacy of literature search 'partially yes'
- item 7 justification of excluding studies: no
- item 11 , No, the overall pooling of the same studies but for different PFAS compounds into one overall estimate is not correct
- Item 13 consideration of risk of bias when interpreting study results 'no'

Conclusion: critically low - The systematic review has critical limitations (no appropriate pooling of the data, no info on confounding, no consideration of risk of bias when interpreting study results because all considered high quality, no justification of excluding studies).

3.1.4 Appraisal of the SRs on miscarriage

3.1.4.1 Haimbaugh 2024[27]

Haimbaugh 2024[27]	Comments
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes • **Population:** humans (no children or infants) in community (no occupational exposure) community samples and those seeking assistive reproductive technologies (ARTs) • **Exposure:** any PFASs • **Comparator** lowest exposed compared to higher exposed (continuous, lowest tertile vs. highest) • **Outcomes:** fertility, preterm birth/gestational age at birth, miscarriage, menopause/menstruation, ovarian health, sperm health, and fetal growth • **Timeframe:** 2017-2022 • **Studies:** peer reviewed published reports

Haimbaugh 2024[27]	Comments
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Not applicable because in this field there are only observational studies in humans- No explanation/ scientific justification – excluded studies on any non-human model, infants, or children, occupational exposure or exposure through pollution of drinking water Excluded reviews, meta-analyses, abstracts
4. Did the review authors use a comprehensive literature search strategy?	Partial yes • Consulted databases (PubMed, Embase,Web of Science, and Health and Environmental Research Online (HERO).), search strategy are mentioned in table 1. Full-strategy do not include the numbers of hits. • no consultation of trial/study registries, no consultation of experts, no grey literature listed.
5. Did the review authors perform study selection in duplicate?	Yes. discrepancies between the 2 reviewers was discussed with third author
6. Did the review authors perform data extraction in duplicate?	Yes (one reviewer via a common template, and checked by second reviewer)
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No list available (general prisma with numbers of ref and reason) Excluded medium or high risk of bias (12 studies)
8. Did the review authors describe the included studies in adequate detail?	Yes (see Table 1 data, but no info on adjustments)
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	2 independent reviewers used NOS: Reports scoring medium or very high were not included in further analysis. Any studies receiving a 0 in the “assessment of outcome” domain were not included
10. Did the review authors report on the sources of funding for the studies included in the review?	No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	No meta-analysis was conducted
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Not applicable
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Yes

Haimbaugh 2024[27]	Comments
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Not applicable.
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes

Critical domains according to Shea 2017:

- Item 2 (no prior protocol)
- Item 4: partly yes on comprehensive literature search
- item 7 (justification for excluding individual studies is 'no')
- Item 9,13 : risk of bias assessment including only those with high quality
- item 11 and 15 not applicable

Conclusion: low – critical limitation is that there is no transparency in inclusion process (no list of excluded studies and partly yes for comprehensive search, which is especially important because they only included only three studies, no protocol).

3.1.4.2 Liu et al 2024[28]

Liu et al 2024[28]	Comments
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes • **Population:** pregnant women • **Exposure/ Comparator: EDC exposure** PFASs, PAEs, phenol/paraben, and organochlorine) were observed in serum, plasma, whole blood, urine, and cord blood • **Outcomes:** preterm birth, small for gestational age, low body weight, miscarriage – effect estimates and 95% CI • **Timeframe:** before 2023 • **Studies:** cohort and case-control

Liu et al 2024[28]	Comments
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Not applicable because in this field there are only observational studies in humans- No explanation/ scientific justification – animal studies, review and letters were excluded as well as studies without risk estimates
4. Did the review authors use a comprehensive literature search strategy?	Partial yes • Consulted databases (web of science and Pubmed), search strategy are mentioned in supplement. Full-strategy do not include the numbers of hits. • no consultation of trial/study registries, no consultation of experts, no grey literature listed.
5. Did the review authors perform study selection in duplicate?	Yes. discrepancies between the 2 reviewers was discussed with third author
6. Did the review authors perform data extraction in duplicate?	Yes (two authors independently extracted)
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No list available (general prisma with numbers of ref and reason)
8. Did the review authors describe the included studies in adequate detail?	Yes (see Table 1 data on the included exposure contrast, adjustments of the odds ratio,…). No info on exposure range
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes (Newcastle-Ottawa scale- NOS). All rated high quality (score 7-9).
10. Did the review authors report on the sources of funding for the studies included in the review?	No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Partly yes : In the forest plots and summary statistics for individual PFAS they combine different exposure measures (categorical highest vs. lowest, or continuous per unit increase). Weights are from random-effect models. The exact meaning of the pooled OR is unclear, and must be seen as a qualitative signal of an association. When they combine all the individual PFAS results in an overall PFAS summary effect (the same population is available in every individual PFAS within-study correlation). A random effects model assumes independence across effect sizes, which is not the case. sensitivity analyses, study-by-study exclusion to see the effect on the overall estimate

Liu et al 2024[28]	Comments
	limitations:" *we did not study the mixed effect of EDCs for adverse pregnancy outcomes due to the methodological limitations of the meta-analysis."* Each study had several adjusted covariates When evaluating health outcomes associated with multiple PFAS measured in the same individuals, the key methodological challenge is correlated exposures and shared biological endpoints.
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	All included studies were considered high quality research (NOS score between 7-9)
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Partly - All included studies were considered high quality research. Part in discussion on selection bias, and reason why not accounting for parity.
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Partly: they reported considerable heterogeneity for PFOS and miscarriage The heterogeneity mostly related to Asia and developing countries because of the differences in climate, habits, dietary habits, and degree of economic development
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes (Egger test and funnel plot). They consider there is no publication bias
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes

Critical domains according to Shea 2017:

- Item 2 (no prior protocol)
- Item 4: partly yes
- item 7 (justification for excluding individual studies is 'no')
- item 11 is answered 'partial yes', but biased way of reporting the overall PFAS effect
- item 13: partly
- items, 9 and 15 are answered 'yes'

Conclusion: low (critical limitation: no appropriate statistical method to combine effect measures of separate PFAS, and the reporting on it is not sufficient; other considerations: no protocol, no list of excluded studies).

3.1.5 Appraisal of SRs on prematurity

3.1.5.1 Yang 2022[29]

Yang et al. 2022[29]	Comments
1. Research question and inclusion criteria include components of PICO/PECO	Yes Population: general pregnant women without restrictions on regions and race. 2) Exposure/Intervention: maternal and/or cord blood were collected for PFASs assessment. 3) Controls: participants exposed to lower PFASs levels from the same or referent population. 4) Outcome: articles reporting PTB, LBW, SGA, and miscarriage as outcomes. 5) Studies: cohort, case-control, or cross-sectional studies exploring associations between PFASs exposure and aforementioned birth outcomes and reporting estimated effects with corresponding confidence intervals (CI).
2. Explicit statement on protocol prior to conduct of review	No
3. Explain selection study design (RCT and/or observational)	Not applicable because in this field there are only observational studies in humans-
4. Comprehensive literature search strategy	Partly Yes Embase, PubMed, Web of Science; search date: 21 March 2021 Exact search string in supplement no consultation of trial/study registries, no consultation of experts, no grey literature listed
5. Study selection in duplicate	Not reported
6. Data extraction in duplicate	Yes
7. List of excluded studies	No
8. Details included studies	Partly 14 studies on prematurity: 12 cohort studies, 1 nested case-control, and 1 cross-sectional study with a total of 21 935 participants . Four studies were conducted in China, 5 in Europe, and 5 in the Americas. One study used cord blood and the other studies used maternal blood for the PFAS exposure assessment. A total of 20 PFASs were measured, 4 of which were associated with sufficient data and used for subsequent analyses (PFOS, PFOA, PFHxS, PFNA). Some relevant elements are missing, particularly how the OR was obtained in each individual study, how prematurity was defined, and the methods for confounding adjustment.
9. Satisfactory technique to assess Risk of Bias included studies	Yes "*The quality of eligible studies was assessed by two investigators independently using Newcastle Ottawa Scale (NOS) and the consistent result was obtained by a third reviewer. The selected studies were divided into three categories of high, moderate, and low quality, with*

Yang et al. 2022[29]	Comments
	scores of 7–9, 4–6, and 0–3, respectively". All included studies were rated high quality (7-9)
10. Source of funding included studies	No
11. Appropriate methods for statistical combination of results (meta-analysis)	Partly "*When studies investigated the associations of PFASs exposure and birth outcomes using the first quartile of PFASs concentrations as a reference, the estimate with the largest effect was selected.*" "*If the studies reported crude and adjusted ORs at the same time, the adjusted one was chosen*" "*estimated effect (odds ratio (OR), relative risk or hazard ratio) and their 95% CI, and covariates."* Therefore, the exact meaning of the pooled OR is unclear, and must be seen as a qualitative signal of an association. Taking the largest effect may be appropriate as linearity is not guaranteed. "*The I^2 statistics was used to evaluate heterogeneity between included studies. If there was statistical significance heterogeneity (I^2 > 50%), random-effects model was performed to combine estimates; otherwise, fixed-effects model was used. Stratified analyses by region, sampling time, and sample type were conducted to investigate the influence of potential modifiers on the pooled effects when more than 3 studies were included. In addition, sensitivity analyses were performed to examine the robustness of our results and Egger's test was used to evaluate publication bias. All statistical analysis was done by STATA software*."
12. Assess potential impact of risk of bias individual studies on the results of meta-analysis	All the 14 included studies were rated as high-quality on the Newcastle Ottawa Scale (NOS)
13. Account for risk of bias individual studies when interpreting/discussing results of the review	Yes - Mentioned possible bias due to timing of PFAS exposure measurement.
14. Satisfactory explanation for heterogeneity observed	Yes There was significant heterogeneity (I^2 > 50%) between included studies in some groups (PFOS, I^2 = 63.4%; PFOA, I^2 = 58.8%; PFHxS, I^2 = 55.9%). Sampling time (p= 0.010) and sample type (p=0.009) could explain part of the heterogeneity between the effect sizes of PFOA.
15. Adequate investigation of publication bias	Yes
16. Report potential sources of conflict of interest including funding	Yes No competing interest declared

Critical domains according to Shea 2017

- Item 2 (no prior protocol)
- Item 4: partly yes
- item 7 (justification for excluding individual studies is 'no')

- item 11 is answered 'partial yes'
- 9, 13 and 15 are answered 'yes'

Conclusion: Moderate quality - Limitations but not critical (no protocol and no table of excluded studies are provided). However, this SR included more studies than any other. Individual study ORs are not necessarily corresponding to the highest quartile (vs first quartile) but to the quartile with the strongest association. In a way, that approach accounts for the possible non linearity of the association. But it makes it difficult to interpret the pooled OR, except as a qualitative signal of an association.

3.1.6 Appraisal of SRs on foetal growth retardation

3.1.6.1 Wright 2023[30]

Wright 2023[30]	Comments
1. Research question and inclusion criteria include components of PICO/PECO	Yes, PECO in the Supplements
2. Explicit statement on protocol prior to conduct of review	Yes- A systematic review protocol used to guide the development of five IRIS PFAS assessments (including PFNA) was used here after being released for public comment in 2019 and updated in 2021 (US EPA, 2021).
3. Explain selection study design (RCT and/or observational)	Not applicable because in this field there are only observational studies in humans- The meta-analysis inclusion criteria included epidemiological studies which reported beta coefficients (βs), 95% confidence intervals (CIs), standard errors and/or p-values relating mean BWT changes (in grams (g) or kilograms (kg)) in PFNA exposure biomarkers in the overall population or stratum-specific data available for both sexes.
4. Comprehensive literature search strategy	Yes To identify manuscripts examining PFNA exposures and health effects published prior to July 2022, including: PubMed (National Library of Medicine); Web of Science (Thomson Reuters); Toxline (National Library of Medicine); TSCATS (Toxic Substances Control Act Test Submissions). The literature search queries had no date or language restrictions. In addition, relevant literature not found through database searching was identified by: • Review of studies cited in any PFNA PECO-relevant studies and published journal reviews; finalized or draft U.S. state, U.S. federal, and international assessments (e.g., the Agency for Toxic Substances and Disease Registry [ATSDR] assessment released publicly in 2021). • Review of studies submitted to federal regulatory agencies brought to our attention. • Identification of studies during screening for other PFAS.

Wright 2023[30]	Comments
	• Other grey literature (i.e., primary studies not indexed in typical databases, such as technical reports from government agencies or scientific research groups; unpublished laboratory studies conducted by industry; or working reports/white papers from research groups or committees) brought to our attention.
5. Study selection in duplicate	Yes - The literature was screened by two independent reviewers with a process for conflict resolution, first at the title and abstract level and subsequently at the full-text level, using structured forms in DistillerSR
6. Data extraction in duplicate	Yes
7. List of excluded studies	No
8. Details included studies	Yes
9. Satisfactory technique to assess Risk of Bias included studies	Yes - For each study, at least two independent reviewers evaluated each domain (Participant Selection, Exposure Measurement, Outcome Ascertainment, Confounding, Analysis, Selective Reporting, and Study Sensitivity) and determined a consensus rating specific to each domain and the overall confidence level. Ratings for each domain were either Good, Adequate, Deficient, or Critically Deficient, while overall confidence ratings included high, medium, low, or uninformative.
10. Source of funding included studies	No
11. Appropriate methods for statistical combination of results (meta-analysis)	Yes • We rescaled studies that used either log10 or log2 to natural logarithmic (ln) units (i.e., loge). We also converted results that were presented in inter-quartile ranges or units of standard deviation changes into a ln-unit change. To increase the number of available studies, we also converted the studies reporting results in the natural scale (i.e., per ng/mL) into ln units (i.e., per ln(ng/mL)) using a percentile-based re-expression method. • The meta-analysis was based on a random effects model following the assumption that each study produced an estimate of a study-specific true effect that varies across studies • We employed stratified analyses to evaluate whether the pooled effect estimate varied by study confidence or by the timing of maternal serum sampling. Earlier pregnancy included studies reporting samples from pre-conception (0 days), the first trimester (0 days to13 weeks and 6 days) or a combination of the first and second trimesters (0 days to 27 weeks and 6 days); mid-to late-pregnancy studies exclusively sampled in the second trimester (14 weeks and 0 days to 27 weeks and 6 days), a combination of the second and third trimester (14 weeks and 0 days to birth), or the third trimester only (28 weeks and 0 days to birth); post-pregnancy studies sampled at or after birth

Wright 2023[30]	Comments
	• To further examine the impact of biomarker sample timing beyond categorical groupings, we conducted a meta-regression based on continuous gestational age at sampling using measures of central tendency for each study
12. Assess potential impact of risk of bias individual studies on the results of meta-analysis	Yes - Sensitivity analysis per level of study quality was carried out
13. Account for risk of bias individual studies when interpreting/discussing results of the review	Yes
14. Satisfactory explanation for heterogeneity observed	Yes
15. Adequate investigation of publication bias	Yes - Funnel plot
16. Report potential sources of conflict of interest including funding	Yes - No conflict of interest reported

Critical domains according to Shea 2017

- Item 2 (protocol): yes
- Item 4: yes
- item 7 (justification for excluding individual studies is ‘no’)
- item 11 is answered yes’
- 9, 13 and 15 are answered ‘yes’

Conclusion: High quality review despite the lack of a table with excluded studies on full-text. No critical limitations

3.1.6.2 *Wright 2025*[31]

Wright 2025[31]	Comments
1. Research question and inclusion criteria include components of PICO/PECO	Yes - The study clearly defines PECO criteria (population: mother–child pairs; exposure: PFOS biomarkers; outcome: birth weight), explicitly described in methods and supplement.
2. Explicit statement on protocol prior to conduct of review	No explicit PROSPERO registration or protocol publication reported; supplement states protocol but no accessible registration.
3. Explain selection study design (RCT and/or observational)	Not applicable because in this field there are only observational studies in humans- Inclusion of epidemiological studies justified, but limited explicit rationale for excluding other designs beyond PECO framework.
4. Comprehensive literature search strategy	Yes - Multiple databases (Medline, Web of Science, Toxline, TSCATS Toxic Substances Control Act Test Submissions), citation chaining, no language restriction, detailed search strategy provided. no explicit expert consultation
5. Study selection in duplicate	Yes - Screening performed by two independent reviewers with conflict resolution process described.
6. Data extraction in duplicate	Partial Yes - Dual review implied but not clearly stated for extraction specifically (clear for screening, less explicit for extraction).
7. List of excluded studies	Partly yes - Exclusions described (duplicates, missing data, uninformative studies), but no full explicit list of excluded studies with reasons.
8. Details included studies	Yes - Detailed characteristics extracted (design, timing, matrix, confounders, etc.), presented in supplementary tables.
9. Satisfactory technique to assess Risk of Bias included studies	Yes - Uses US EPA/IRIS-based tool with domains (confounding, selection, exposure, outcome, etc.), assessed by two reviewers.
10. Source of funding included studies	No
11. Appropriate methods for statistical combination of results (meta-analysis)	Yes - Random-effects models, heterogeneity assessment (I^2, Q), subgroup analyses, sensitivity analyses appropriately conducted.
12. Assess potential impact of risk of bias individual studies on the results of meta-analysis	Yes - Stratified analyses by study confidence; discussion acknowledges impact of study quality on results.
13. Account for risk of bias individual studies when interpreting/discussing results of the review	Yes - Discussion explicitly considers study quality and limitations.
14. Satisfactory explanation for heterogeneity observed	Yes - Extensive heterogeneity analyses including subgroup analyses and meta-regression.

Wright 2025[31]	Comments
15. Adequate investigation of publication bias	Yes - Funnel plots, Egger's test, and trim-and-fill analysis conducted.
16. Report potential sources of conflict of interest including funding	Partial Yes - Authors affiliated with US EPA; funding/conflict discussed but limited explicit statement in main text.

Critical domains according to Shea 2017

- Item 2 (protocol): no
- Item 4: yes
- item 7 (justification for excluding individual studies is 'partly yes')
- item 11 is answered yes'
- 9, 13 and 15 are answered 'yes'

Conclusion: High quality review, despite no protocol registration, no reporting of funding sources of included studies and partial transparency on excluded studies. No critical limitations.

3.1.6.3 Fu et al. 2025[32]

Fu et al. 2025[32]	Comments
1. Research question and inclusion criteria include components of PICO/PECO	Yes - The search strategy was constructed around the Population, Exposure, Outcome, and Study design (PEOS) framework. Population (P): Pregnant women exposed to perfluorinated compounds. Exposure (E): Presence or exposure to one or more perfluorinated compounds detected in body fluids (such as serum or plasma). Outcome (O): Birth outcomes determined through clinical assessments, registration data, or medical records based on the International Classification of Diseases (ICD). Study Design (S): All cross-sectional or cohort studies meeting the criteria set for this review
2. Explicit statement on protocol prior to conduct of review	No
3. Explain selection study design (RCT and/or observational)	Not applicable because in this field there are only observational studies in humans : cross-sectional or cohort studies
4. Comprehensive literature search strategy	Partly yes - Systematic search of PubMed, Web of Science, and Embase for studies published before March 2024. Search terms in supplement

Fu et al. 2025[32]	Comments
	In addition, we also searched the references of existing relevant articles. These studies only contain Chinese or English articles. no consultation of trial/study registries, no consultation of experts, no grey literature listed
5. Study selection in duplicate	Yes - Subsequently, two researchers reviewed and assessed the eligibility of the identified articles.
6. Data extraction in duplicate	Yes - Three investigators worked independently on literature quality assessment and data extraction, and the differences were settled through discussion
7. List of excluded studies	No - This is a limitation, as low-quality studies were excluded.
8. Details included studies	Yes in Supplementary Table 1
9. Satisfactory technique to assess Risk of Bias included studies	Yes - The cross-sectional researches were evaluated by the Agency for Healthcare Research and Quality (AHRQ) method. Newcastle-Ottawa Scale (NOS) was used to evaluate cohort studies. All were considered high quality
10. Source of funding included studies	No
11. Appropriate methods for statistical combination of results (meta-analysis)	Yes - The concentrations of all PFAS were calculated as log10 conversion. Q test and I2 were used to test for study heterogeneity. The analysis was performed using the fixed-effects model when there was no significant heterogeneity (I2<50 % or p-value >0.05). Otherwise, a random-effects model was used. To assess the influence of different blood collection times, we employed a three-tiered approach, with subgroups consisting of samples collected during earlier in pregnancy, mid-to-late pregnancy, and after delivery. Earlier pregnancy studies included reports from pre-pregnancy (0 day), the first three months of pregnancy (0 day–13 weeks and 6 days), or the combination of the first and second trimesters (0 day–27 weeks and 6 days); mid-to-late pregnancy studies were conducted solely during the second trimester (14 weeks and 0 days to 27 weeks and 6 days), the combination of the second and third trimesters (14 weeks and 0 days to term), or solely during the third trimester (28 weeks and 0 days to term) Sensitivity analysis consisted of excluding each study one by one, influence of bloodcollection time and region
12. Assess potential impact of risk of bias individual studies on the results of meta-analysis	All considered high quality
13. Account for risk of bias individual studies when interpreting/discussing results of the review	Yes - Sensitivity analyses discussion

Fu et al. 2025[32]	Comments
14. Satisfactory explanation for heterogeneity observed	Yes - PFOS and PFOA showed considerable heterogeneity. We used stratified analysis to study the reasons for the high heterogeneity of PFOS and PFOA, and we performed hierarchical analysis of exposure types and exposure areas. In the results of hierarchical analysis of PFOS and PFOA, different blood collection times and exposure area may be the source of high heterogeneity.
15. Adequate investigation of publication bias	Yes - No publication bias detected
16. Report potential sources of conflict of interest including funding	Yes - No conflict reported. This work was supported by the National Natural Science Foundation of China (grantnumber 21976050).

Critical domains according to Shea 2017

- Item 2 (protocol): no
- Item 4: partly yes
- item 7 (justification for excluding individual studies is 'No')
- item 11 is answered yes'
- 9 yes
- 13 and 15 are answered 'yes'

Conclusion: Moderate quality, mainly because the table with excluded studies is missing and impact of study quality on results was not tested. No critical limitations

3.1.6.4 Ru 2024[33]

Ru 2024[33]	Comments
1. Research question and inclusion criteria include components of PICO/PECO	Yes - PECO in supplements
2. Explicit statement on protocol prior to conduct of review	Yes - This systematic review was conducted in accordance with US EPA's PFAS systematic review protocol based on methods detailed in the Office of Research and Development (ORD) Staff Handbook for Developing Integrated Risk Information System (IRIS) Assessments.

Ru 2024[33]	Comments
3. Explain selection study design (RCT and/or observational)	Not applicable because in this field there are only observational studies in humans -This meta-analysis included epidemiological studies which reported regression coefficients (ie, 'betas' or βs) for the association between mean BW changes and PFHxS exposure concentrations. Included studies were also required to report 95% CIs or other measures of variance such as an SE or a p value.
4. Comprehensive literature search strategy	Yes - PubMed (National Library of Medicine), Web of Science (Thomson Reuters), Toxline (National Library of Medicine) and TSCATS (Toxic Substances Control Act Test Submissions). grey literature (see supplement) Up to April 2023
5. Study selection in duplicate	Yes - Results were screened by two independent reviewers with a process for conflict resolution at two stages. First, at the title and abstract level, and subsequently at the full-text evel, using structured forms in DistillerSR
6. Data extraction in duplicate	Yes - Ru included any epidemiological study reporting a regression coefficient relating PFHxS to birthweight and then invested substantial effort in: -rescaling exposure units, -re-expressing coefficients, -combining sex-specific results, -converting some metrics into a common scale.
7. List of excluded studies	No
8. Details included studies	Yes
9. Satisfactory technique to assess Risk of Bias included studies	Yes - Critical appraisal of studies was performed using the US EPA's IRIS approach for study evaluation as detailed in the US EPA PFAS protocol. At least two independent reviewers rated each study based on the potential risk of bias and study sensitivity using the following domains: Participant Selection, Exposure Measurement, Outcome Ascertainment, Confounding, Analysis, Selective Reporting and Study Sensitivity
10. Source of funding included studies	No
11. Appropriate methods for statistical combination of results (meta-analysis)	Yes - The meta-analysis was performed using random effect models, estimated through the restricted maximum likelihood method, with inverse-variance weighting. Two types of heterogeneity measures, Cochran's Q test statistics and p value, and Higgin's and Thompson's I^2, were calculated.

Ru 2024[33]	Comments
12. Assess potential impact of risk of bias individual studies on the results of meta-analysis	Yes - Stratified meta-analyses were also carried out for high and medium-confidence studies combined, contrasted with low confidence studies (i.e, a two-strata approach).
13. Account for risk of bias individual studies when interpreting/discussing results of the review	Yes
14. Satisfactory explanation for heterogeneity observed	Partial
15. Adequate investigation of publication bias	Yes - Publication bias was evaluated visually using enhanced funnel plot asymmetry and the Egger's regression test
16. Report potential sources of conflict of interest including funding	Yes - No competing interest declared

Critical domains according to Shea 2017:

- item 2, 'yes'
- item 4 adequacy of literature search 'yes'
- item 7 justification of excluding studies: no
- item 11: yes
- item 9, 13, 15 'yes'

Conclusion: High quality, despite the missing table on excluded studies. No critical limitations

3.1.7 Appraisal of SRs on congenital abnormalities

3.1.7.1 Bernardo 2025[34]

Bernardo 2025[34]	Comments
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes • **Population:** pregnant women and neonates/children • **Exposure:** prenatal exposure phthalates, bisphenols, perfluorinated compounds (PFAS), and organochlorines • **Comparator:** unexposed or minimally exposed populations • **Outcomes:**. surgical congenital malformations

Bernardo 2025[34]	Comments
	• **Timeframe:** from 2010 to 2025 • **Studies:** observational studies (cohorts, case-controls, cross-sectional)
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	This systematic review was registered prospectively in PROSPERO (CRD420251158778).
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Not applicable because in this field there are only observational studies in humans - full list of inclusion and exclusion criteria publications in English or Spanish (2010—2025); and sample size ≥30 participants
4. Did the review authors use a comprehensive literature search strategy?	Yes • PubMed, Embase, Web of Science, • Search string in appendix • five systematic reviews included in this synthesis (identified to cross-check primary studies and provide contextual discussion) • Grey literature check • no consultation of trial/study registries, no consultation of experts,
5. Did the review authors perform study selection in duplicate?	Yes, Two reviewers independently performed primary screening of titles/abstracts and full-text review using standardized forms
6. Did the review authors perform data extraction in duplicate?	Yes
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No list of references
8. Did the review authors describe the included studies in adequate detail?	No table, in the Supplementary Material not in sufficient detail
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes NOS but strange they rated SRs with AMSTAR because SRs not in the inclusion criteria
10. Did the review authors report on the sources of funding for the studies included in the review?	No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	No, combined all EDCs - Pooled OR 1.39 (95 % CI: 1.09—1.76; I^2 = 42.1 %; p = 0.008; 95 % PI: 0.98—1.97) based on 6 studies
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Not specifically on RoB. Subgroup analyses were conducted by malformation type, ED class, study quality, and exposure timing. Sensitivity analyses excluded low-quality studies.

Bernardo 2025[34]	Comments
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Yes , they used the OHAT reporting with GRADE
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Overall evidence quality was evaluated using the GRADE methodology
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Publication bias was evaluated using funnel plots and Egger's test when ≥10 studies were available
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes, there was no dedicated funding

Critical domains according to Shea 2017:

- item 2,9,15 'yes'
- item 4 adequacy of literature search 'yes'
- item 7 justification of excluding studies: no
- item 11 , No, pooling of all EDCs
- Item 13 consideration of risk of bias when interpreting study results 'yes'

Conclusion: low - The systematic review has critical limitation (no appropriate pooling of the data) as well as some non-critical weaknesses (no justification of excluding studies, no sufficient details on included primary studies for PFAS, nor individual risk estimates and including source of funding).

3.1.7.2 Elhassan 2024[35]

Elhassan 2024[35]	Comments
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Partly Yes • **Population:** pregnant women and neonates/children • **Exposure:** all kinds of maternal exposure measures for EDCs • **Comparator: ?** • **Outcomes:**. incidence of CHD • **Timeframe:** June 2024 • **Studies:** no restriction in specific study design

Elhassan 2024[35]	Comments
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No protocol
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Not applicable because in this field there are only observational studies in humans excluded review articles, conference abstracts, single-arm studies, and foreign language studies Inclusion: studies that reported adjusted odds ratio (a.O.R.) or crude odds ratio (c.O.R) or provided data to calculate them
4. Did the review authors use a comprehensive literature search strategy?	Partly Yes • PubMed, Scopus,Web of Science, and Cochrane Library • Search string Supplementary Table S2 • no Grey literature check • no consultation of trial/study registries, no consultation of experts,
5. Did the review authors perform study selection in duplicate?	No
6. Did the review authors perform data extraction in duplicate?	No, pre-designed extraction sheet
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No list of references, only flow chart
8. Did the review authors describe the included studies in adequate detail?	Table 1, no details on risk estimate and adjustment
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes NOS: three were of good quality and two were of moderate quality.
10. Did the review authors report on the sources of funding for the studies included in the review?	No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Combined all EDCs, but also provided for PFAS (but as a group, not per individual PFAS) They combined random ORs In Ou 2021 this was the OR for total PFOS In Li 2024 this was the OR for PFDA (highest)
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Subgroup analyses were conducted by malformation type, EDc class, and exposure assessment methods, but not on quality

Elhassan 2024[35]	Comments
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Yes
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes, substantial heterogeneity was observed between the retrieved studies in the majority of endpoints
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Publication bias was evaluated using funnel plots and Egger's test when ≥10 studies were available Only 2 studies for PFAS
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes, there was no dedicated funding

Critical domains according to Shea 2017:

- item 2: no protocol
- item 4 adequacy of literature search ‘partly‘yes’
- item 7 justification of excluding studies: no
- item 11 , No, pooling of all EDCs and the two studies of PFAS
- item,9,13, 15 ‘yes’

Conclusion: critically low - The systematic review has critical limitation (no appropriate pooling of the data) as well as some non-critical weaknesses (no protocol, no justification of excluding studies, no sufficient details on included primary studies for PFAS, nor individual risk estimates and including source of funding).

3.1.8 Appraisal of SRs on vaccine response

3.1.8.1 Crawford 2023[36]

Crawford 2023[36]	Explanation
1. Research question and inclusion criteria include components of PICO/PECO	Yes - Explicit PECO (doubling PFAS, loge antibody).
2. Explicit statement on protocol prior to conduct of review	Yes - PROSPERO registered + amendments. CRD42020193155

Crawford 2023[36]	Explanation
3. Explain selection study design (RCT and/or observational)	Not applicable because in this field there are only observational studies in humans .
4. Comprehensive literature search strategy	Partly Yes - Multiple databases + grey literature (reports ATDSR) reference screening. But no detailed search string in supplements No trial registry/expert consultation
5. Study selection in duplicate	Yes - Dual screening.
6. Data extraction in duplicate	Yes - Dual extraction.
7. List of excluded studies	Yes - Exclusions documented.
8. Details included studies	Yes - Detailed study tables.
9. Satisfactory technique to assess Risk of Bias included studies	Yes - Morgan RoB tool (preludes ROBINS-E). almost all studies were considered moderate risk of bias
10. Source of funding included studies	No - Funding not reported.
11. Appropriate methods for statistical combination of results (meta-analysis)	Yes - Multilevel meta-regression; harmonized effects.
12. Assess potential impact of risk of bias individual studies on the results of meta-analysis	Yes - RoB included in sensitivity analyses.
13. Account for risk of bias individual studies when interpreting/discussing results of the review	Yes - RoB discussed in interpretation.
14. Satisfactory explanation for heterogeneity observed	Yes - Meta-regression explored heterogeneity.
15. Adequate investigation of publication bias	Partially yes - Funnel plots used.
16. Report potential sources of conflict of interest including funding	Yes - COI reported.

Critical domains according to Shea 2017:

- item 2 protocol: yes
- item 4 adequacy of literature search ‘partially yes’
- item 7 justification of excluding studies: yes

- item 11: yes
- item,9,13, 15 'yes'

Conclusion: high – no critical limitations

3.1.8.2 Antoniou and Dekant 2024[37]

Antoniou 2024[37]	Explanation
1. Research question and inclusion criteria include components of PICO/PECO	Yes - Clear PECO (children, PFAS, antibody/infections).
2. Explicit statement on protocol prior to conduct of review	Yes - Protocol registered (Open Science Framework).
3. Explain selection study design (RCT and/or observational)	Not applicable because in this field there are only observational studies in humans. There were clear inclusion and exclusion criteria.
4. Comprehensive literature search strategy	No - Only PubMed searched. No grey literature check, references lists, consultation of trial/study registries or experts
5. Study selection in duplicate	Yes - Dual screening.
6. Data extraction in duplicate	Yes - Extraction verified by second reviewer.
7. List of excluded studies	No list of excluded studies. (in supplements general prisma with numbers of ref)
8. Details included studies	Yes - Detailed exposure/outcome description. (see Table 2) info on mean PFAS levels in supplement
9. Satisfactory technique to assess Risk of Bias included studies	Yes - OHAT tool used. Overall score given and all were considered low risk of bias
10. Source of funding included studies	No - Funding not reported.
11. Appropriate methods for statistical combination of results (meta-analysis)	Yes - Random-effects meta-analysis; I^2; pooled OR/% change. Models fully adjusted for confounding variables, as identified and reported within each study were used for the pooled analyses Reexpression to OR "occurrence of infectious diseases per doubling of PFAS exposure" If multiple ORs, the OR with the highest contrast was chosen Multi-level sensitivity analysis to account for interdependence of using the same populations but with different timings of outcome measurement (but data not shown)

Antoniou 2024[37]	Explanation
12. Assess potential impact of risk of bias individual studies on the results of meta-analysis	Not applicable - All considered low risk of bias
13. Account for risk of bias individual studies when interpreting/discussing results of the review	Partly yes - they applied the GRADE methodology. Limited discussion of RoB impact. They mentioned " some studies failed to adequately account for confounding variables or co-exposures, which may have introduced a certain level of bias"
14. Satisfactory explanation for heterogeneity observed	No - I2 is assumed to be low (< 25%), moderate (25–75%), or high (> 75%) Heterogeneity reported in the forest plots and was very high -but not deeply explored, and not considered in the GRADE assessment.
15. Adequate investigation of publication bias	They addressed possibility of publication bias in the limitation of the study. No publication bias assessment.
16. Report potential sources of conflict of interest including funding	Yes - COI reported. 3M sponsoring

Critical domains according to Shea 2017:

- item 2 protocol: yes
- item 4 adequacy of literature search 'no
- item 7 justification of excluding studies: no
- item 11: yes
- item 13 : partly yes
- item,9, 15 'yes'

Conclusion: Low–moderate critical limitation: limited search strategy and other limitations: limited handling heterogeneity or risk of bias, no table of excluded studies

3.1.9 *Appraisal of the SRs on infections in infants*

3.1.9.1 *Lyrou 2025[38]*

Lyrou 2025[38]	Comments
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes • **Population:** pregnant women or women of reproductive age • **Exposure/ Comparator:** prenatal exposure to PFASs (PFOS, PFOA, and so on) • **Outcomes:** Incidence of respiratory infections in infancy and childhood, including pneumonia, RSV infections, bronchitis, and other respiratory tract infections **Primary outcome:** ARI incidence = upper and lower respiratory tract infections, such as pneumonia, bronchitis, RSV infection, the common cold and streptococcal throat infections, as reported in the included studies. • **Timeframe:** between 2015 and feb 2025 • **Studies:** cohort, case-control, and cross-sectional studies in English
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes, registered at PROSPERO
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Not applicable because in this field there are only observational studies in humans - No exclusion criteria,
4. Did the review authors use a comprehensive literature search strategy?	Partially Yes • Consulted databases PubMed/Medline, Scopus and the Cochrane Library. No exact search string but some key words • Reference lists were checked • Figure 1 shows overview of selection process. • Grey literature check • no consultation of trial/study registries, no consultation of experts,
5. Did the review authors perform study selection in duplicate?	Yes: two independent reviewers conducted the literature search and screened the titles and abstracts for eligibility. Any disagreements were resolved through discussion or consultation with a third reviewer
6. Did the review authors perform data extraction in duplicate?	Yes (performed independently by two reviewers using a standardized extraction form)
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No list available (general prisma with numbers of ref)
8. Did the review authors describe the included studies in adequate detail?	Yes (see Table 1 data)

Lyrou 2025[38]	Comments
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes (quality assessment based on the Caldwell framework,) in table 1 there is a listing of the study limitations
10. Did the review authors report on the sources of funding for the studies included in the review?	No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	No meta-analysis
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No meta-analysis
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Yes, they addressed this in the discussion: critical appraisal of included studies
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes, in the limitations they state: included studies exibit heterogeneity in study design, exposure assessment, outcome definition which may contribute to inconsistency
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No quantitative analysis But they state in limitations that publication bias may be present, given the limited number of eligible studies although grey literature was included.
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes

Critical domains according to Shea 2017:

- items 7 'no'
- item 4 partially yes
- item 9 yes
- item 2,13 yes
- Item 11 and 15 not applicable because no quantitative analysis

Conclusion: high to moderate - The systematic review has more than one weakness (no list of excluded studies, nor the source of funding per study, partial yes for the comprehensive literature review), but no critical limitations.

3.1.9.2 Rosen 2025[39]

Rosen 2025[39]	Comments
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes • **Population:** humans regardless of age • **Exposure:** measured in serum or plasma PFASs (PFOS, PFOA, and so on) • **Comparator:** An incremental increase in concentration of a specific PFAS compared with a lower concentration • **Outcomes:** all infectious diseases. • **Timeframe:** between 2015 and feb 2025 • **Studies:** cohort, case-control, and cross-sectional studies in English
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes, registered at PROSPERO Revisions to the published protocol are described in Supplemental Table 1.
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Not applicable because in this field there are only observational studies in humans - exclusion criteria: no externally measured PFAS concentration (water, food,..), PFAS measured as mixture studies on pre-vaccination antibody titers
4. Did the review authors use a comprehensive literature search strategy?	Partially Yes • Consulted databases PubMed and Web of Science. exact search string in supplement? • Reference lists were checked. • No Grey literature check • no consultation of trial/study registries, no consultation of experts,
5. Did the review authors perform study selection in duplicate?	Yes: two independent reviewers conducted the literature search and screened the titles and abstracts for eligibility.
6. Did the review authors perform data extraction in duplicate?	Yes (performed independently by two reviewers using a standardized extraction form)
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No list available (in supplements general prisma with numbers of ref ➔ wrong outcome, wrong exposure)
8. Did the review authors describe the included studies in adequate detail?	Yes (see Table 2 data) info on mean PFAS levels in supplement
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes (ROBINS-E) in table 3 and in supplement, scored independently

Rosen 2025[39]	Comments
10. Did the review authors report on the sources of funding for the studies included in the review?	No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Yes, reexpression such that all logarithmic results were on the natural log scale, and all results on the absolute scale on a per ng/ml difference Separate pooling of disease risk or disease event rate Sensitivity analyses: leave-one-out analysis showed the sign. Findings were not robust and became non-significant with removal of one study
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes, analyses restricted to only studies with low or some RoB reduced the sample to 11 studies. In these restricted analyses most associations that had been sign. no longer were, though PFOSA log scale was still sign. associated with LRTI rate, PFNA (log) with LRTI rate and PFUnDA log with ID rate
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Yes, they applied the GRADE methodology
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Meta-regression: PFOS-all ID risk (log scale) was the only combination that had sufficient studies for which to conduct a meta- regression.
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	did not have sufficient studies (n ≥10) to test for publication bias in most combinations, and thus did not include it in our GRADE scoring.
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes

Critical domains according to Shea 2017:

- item 7 ‘no’
- item 4 ‘partially yes’
- item 2,9, 11,13,15 ‘yes’

Conclusion: high to moderate - The systematic review has more than one weakness (no list of excluded studies, nor the source of funding per study, and partial yes for comprehensive literature review), but no critical limitations.

3.1.10 Appraisal of SR for breastfeeding

3.1.10.1 Hoadley 2023[40]

Hoadley 2023[40]	Comments
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes, table 1 and table 2 • **Population:** Exposure during lactation, no other restrictions (human and animal) • **Exposure:** Exposure to any PFAS through breastfeeding in humans via biomonitoring data, environmental measures, indirect measures Animal based on administered dose, biomonitoring, environmental • **Comparator:** humans exposed to lower levels • **Outcomes:**. Developmental related , immunological endocrine, or other • **Timeframe:** February 2018 • **Studies:** Peer-reviewed studies with original data, and abstracts in English language
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes, registered at PROSPERO [registration number CRD42019130824]
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Not applicable because in this field there are only observational studies in humans-full list of inclusion and exclusion in table 2
4. Did the review authors use a comprehensive literature search strategy?	Partially Yes • PubMed, Scopus, Embase, CAB Abstracts, Global Health, Medline, and ProQuest Environmental • Search string in appendix • No indication reference lists were checked. • No Grey literature check • no consultation of trial/study registries, no consultation of experts,
5. Did the review authors perform study selection in duplicate?	Yes, screened using a 2-step process two reviewers independently evaluated and third resolved any disagreement
6. Did the review authors perform data extraction in duplicate?	Yes
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No list of references
8. Did the review authors describe the included studies in adequate detail?	Yes, No table, but descriptive. in the Supplementary Material the two cohorts

Hoadley 2023[40]	Comments
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes (OHAT) in table 3.
10. Did the review authors report on the sources of funding for the studies included in the review?	No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Since no outcome was measured in more than 2 cross-foster studies and only one human study was carried forward to lines of evidence rating, meta-analysis was not possible They showed output from cross-foster studies in animals (interventional study)
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No meta-analysis was performed
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Yes , they used the OHAT reporting with GRADE
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	They checked publication bias but no details on how..
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes

Critical domains according to Shea 2017:

- item 2,9 ‘yes’
- item 4 adequacy of literature search ‘partially yes’
- item 7 justification of excluding studies: no
- item 11 , no meta-analysis was performed
- Item 13 consideration of risk of bias when interpreting study results yes
- Item 15 publication bias was reported but no details on how this was handled

Conclusion: High to moderate - The systematic review has more than one weakness but no critical limitations (the adequacy of the literature search and justification of excluding studies was not available, no details on publication bias).

3.1.11 Appraisal of SR on occupational exposure

3.1.11.1 Hussey 2025 [41]

Hussey 2025 [41]	Comments
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes, no specific mention of comparator • **Population:** adults (no children, no infants) pregnant women included when the outcome is measured in the pregnant women (and not in offspring) • **Exposure:** measurements of PFOA and/or PFOS in blood • **Comparator:** • **Outcomes:** measurements of serum or plasma lipids, including total cholesterol (TC), low-density lipoprotein (LDL), highdensity lipoprotein (HDL), and triglycerides (TG) • **Timeframe:** August 31 2023 • **Studies:** Peer-reviewed studies with original data, and abstracts in English language
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No registration of protocol
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Not applicable because in this field there are only observational studies in humans Only included studies with beta coefficient They excluded studies that could not be transformed (e.g. OR) in total 31 studies were excluded
4. Did the review authors use a comprehensive literature search strategy?	Partially Yes • PubMed, google scholar • Search terms in supplement • reference lists were checked. • No Grey literature check • no consultation of trial/study registries, no consultation of experts,
5. Did the review authors perform study selection in duplicate?	Yes, two reviewers independently screened and afterwards three reviewers did full text review

Hussey 2025 [41]	Comments
6. Did the review authors perform data extraction in duplicate?	No mention of duplicate
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Yes justification of exclusions and table in supplement A lot of studies were excluded because child studies and because Incomplete or non-transformable data
8. Did the review authors describe the included studies in adequate detail?	Yes, table (mean concentration, adjustment, outcomes, but not detailed which studies they transformed).
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes ROBINS-E see supplement (a lot of the studies were rated high risk of bias (selection bias)
10. Did the review authors report on the sources of funding for the studies included in the review?	No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Meta-analysis performed with transformation into similar scale of PFAS exposure increase per 1 IQR increase
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	All studies had a high risk or moderate risk of bias They performed several subanalysis (study type) and a sensitivity analysis leave one out
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Yes risk of bias is discussed: inconsistent control for factors such as diet and lipid controlling medication use, preferential selection of specific subjects based upon factors such as worker health, prior exposures, or prior job
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	A large discussion on heterogeneity
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes all funnel plots in supplement
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes , funded by Mitsubishi Corporation

Critical domains according to Shea 2017:

- item 2 protocol = no
- item 4 adequacy of literature search ‘partially yes’
- item 7 justification of excluding studies: yes

- item 9, 13, 15 risk of bias 'yes'
- item 11 , meta-analysis including transformation into similar scale

Conclusion: moderate – high. No critical limitations- there is no mention of a study protocol, the adequacy of the literature search. However, the justification of excluding studies was available, and the meta-analysis was done using a transformation into a similar scale per 1-IQR PFAS increase. However a lot of studies were excluded because they could not be transformed. Heterogeneity and risk of bias was addressed.

3.1.11.2 Sassano 2025 [42]

Sassano 2025 [42]	Comments
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes • **Population:** general population and workers in industrial settings • **Exposure:** any PFAS ➔ **some studies did not use PFAS blood measurement, but modelled (or ecological studies)** • **Comparator:** individuals not exposed to PFAS or with the lowest level of exposure (internal as well as external comparator) • **Outcomes:** incidence, prevalence, and mortality of cancers • **Timeframe:** Update April 2025
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	PROSPERO CRD42024560837
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Not applicable because in this field there are only observational studies in humans - Only included studies with measures
4. Did the review authors use a comprehensive literature search strategy?	Yes • Pubmed and Scopus databases • Search terms in supplement • reference lists were checked. • IARC Monogra ATSDR • no consultation of trial/study registries, no consultation of experts,
5. Did the review authors perform study selection in duplicate?	Four researchers independently screened identified records in pairs by title and abstract
6. Did the review authors perform data extraction in duplicate?	yes

Sassano 2025 [42]	Comments
7. Did the review authors provide a list of excluded studies and justify the exclusions?	no
8. Did the review authors describe the included studies in adequate detail?	Yes, table 1 and a table in supplements (mean concentration, adjustment, outcomes,
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes NOS
10. Did the review authors report on the sources of funding for the studies included in the review?	No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	pooled relative risks (RRs): considered OR, SIR, SMR,HR as RR For each study, the most adjusted available estimates. studies reporting estimates of association stratified by intensity of environmental or occupational exposure, we included in the analysis only those relative to the highest level of exposure (categorical?). however large heterogeneity because pooling
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	modelled PFAS levels can lead to misclassification but no further discussion
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Subanalysis NOS score >7, subanalysis cohort studies, leave on out
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	heterogeneity with the I2 statistic- no high heterogeneity reported
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	contour-enhanced funnel plots and Egger's
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes, involved as expert in litigation

Critical domains according to Shea 2017:

- item 2 protocol = no
- item 4 adequacy of literature search 'yes'
- item 7 justification of excluding studies: no

- item 9, 13 , 15 risk of bias 'yes'
- item 11 , meta-analysis was not appropriate

Conclusion: critical limitation as the meta-analysis combined all kinds of estimates (there was too much heterogeneity to pool). Only a limited number of studies used blood concentrations measured in all participants (most other studies used statistical approaches based on actual serum measurements performed on a limited proportion of study participants together with other exposure-related variables (e.g., residence in a contaminated area, type of job)

3.1.11.3 Seyyedsalehi 2024[43]

Seyyedsalehi 2024[43]	Comments
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes • **Population:** general population and workers in industrial settings • **Exposure:** any PFAS ➔ **some studies did not use PFAS blood measurement, but modelled (or ecological studies)** • **Comparator:** individuals not exposed to PFAS or with the lowest level of exposure (internal as well as external comparator) • **Outcomes:** incidence or mortality from all solid and non-solid cancer • **Timeframe:** 23, January 2024
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	PROSPERO CRD42024560837
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Not applicable because in this field there are only observational studies in humans: cohort, case-control, cross-sectional, and ecological human studies of occupational and environmental exposure based on serum level, drinking water, or workplace exposure to PFAS
4. Did the review authors use a comprehensive literature search strategy?	Yes • Pubmed and Scopus databases • Search terms MeSH terms-supplement table 1 • reference lists were checked. • IARC Monograph ATSDR • no consultation of trial/study registries, no consultation of experts,
5. Did the review authors perform study selection in duplicate?	Four researchers independently screened identified records in pairs by title and abstract

Seyyedsalehi 2024[43]	Comments
6. Did the review authors perform data extraction in duplicate?	yes
7. Did the review authors provide a list of excluded studies and justify the exclusions?	no
8. Did the review authors describe the included studies in adequate detail?	Yes, table 1 and a table in supplements (mean concentration, adjustment, outcomes,
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	NOS, but only two categories (<8 low,≥8 high quality)
10. Did the review authors report on the sources of funding for the studies included in the review?	No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	pooled relative risks (RRs): considered OR, SIR, SMR,HR as RR For each study, the most adjusted available estimates (17 of the 24 studies used adjusted models considering confounders). studies reporting estimates of association stratified by intensity of environmental or occupational exposure, we included in the analysis only those relative to the highest level of exposure (categorical?). however large heterogeneity because pooling
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	modelled PFAS levels can lead to misclassification but no further discussion
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Stratified analysis by region, study design, quality, incidence or mortality, exposure, year of publication leave-one-out sensitivity analyses
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	heterogeneity with the I2 statistic- some meta-analyses had very high heterogeneity (80-90-100%)
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	publication bias by creating a funnel plot and applying a regression asymmetry test
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes, involved as expert in litigation

Conclusion: critical limitation as the meta-analysis combined all kinds of estimates (there was too much heterogeneity to pool). For example the combination of different exposure measures (serum level, modelling via serum level, ecological studies/workplace exposure rapportage)

3.1.11.4 Sassano 2025[44]

Sassano 2025[44]	Comments
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes • **Population:** general population and workers in industrial settings • **Exposure:** exposure to any types of PFAS, including both environmental and occupational exposure, as well as exposure assessed through measurement of PFAS serum levels**) – only 4 studies used direct measurements of PFAS and none of them were occupational** • **Comparator:** individuals not exposed to PFAS or with the lowest level of exposure (internal or external comparison) • **Outcomes:** incidence, prevalence, and mortality of cancers • **Timeframe:** January 23, 2024
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	PROSPERO CRD42024560837
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Not applicable because in this field there are only observational studies in humans : cohort, case-control, cross-sectional, or ecological design
4. Did the review authors use a comprehensive literature search strategy?	Yes • Pubmed and Scopus databases • Search terms in supplement • reference lists were checked. • IARC Monogra ATSDR • no consultation of trial/study registries, no consultation of experts,
5. Did the review authors perform study selection in duplicate?	Two researchers independently screened identified records in pairs by title and abstract
6. Did the review authors perform data extraction in duplicate?	yes

Sassano 2025[44]	Comments
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Yes (two studies were excluded as they investigated the association between serum PFAS levels and self-reported past diagnosis of cancer
8. Did the review authors describe the included studies in adequate detail?	Partly - table 1 but no info on confounders
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes NOS (<7, ≥7).
10. Did the review authors report on the sources of funding for the studies included in the review?	No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	pooled relative risks (RRs): considered OR, SIR, SMR,HR - using restricted maximum likelihood method (REML) for serum level PFAS, there was transformation to the natural log-unit scale (but only possible for thyroid cancer) combining data on incidence and mortality may be appropriate for cancers with low survival such as lung cancer only stratified analyses for lung cancer
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Subanalysis NOS score ≥7, subanalysis cohort studies, only for lung cancer. For the others not enough studies
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	modelled PFAS levels can lead to misclassification but no further discussion lack of information on confounders
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	between-study heterogeneity we used the I2 statistic - Statistical heterogeneity was low for most analyses on lung cancer, for thyroid cancer it was high
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	contour-enhanced funnel plots and Egger's tests only for lung cancer. not assess it for other cancer types due to the limited number of included studies
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes, involved as expert in litigation

Conclusion: moderate - no critical limitations. Separate meta-analysis for serum level measured PFAS (only for Thyroid cancer), done using a transformation into a similar scale on natural log increase. Other meta-analysis done combining all kinds of risk estimates, and only for lung cancer stratified analyses available.

3.1.11.5 Seyyedsalehi and Boffeta 2023[45]

Seyyedsalehi and Boffeta 2023[45]	Comments
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Partly Yes • **Population:** general population and workers in industrial settings • **Exposure:** any PFAS ➔ **some studies did not use PFAS blood measurement, but modelled (or ecological studies)** • **Comparator:** no info • **Outcomes:** incidence or mortality from kidney, liver, and testicular cancers • **Timeframe:** July 8, 2023
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Not applicable because in this field there are only observational studies in humans: cohort, case-control, cross-sectional, and ecological human studies of occupational and environmental exposure based on serum level, drinking water, or workplace exposure to PFAS
4. Did the review authors use a comprehensive literature search strategy?	No • Only 1 database Pubmed • Search terms MeSH terms • reference lists were checked. IARC Monograph, ATSDR • no consultation of trial/study registries, no consultation of experts,
5. Did the review authors perform study selection in duplicate?	Two researchers independently screened the list of titles and abstracts
6. Did the review authors perform data extraction in duplicate?	yes
7. Did the review authors provide a list of excluded studies and justify the exclusions?	no
8. Did the review authors describe the included studies in adequate detail?	Yes, table 1 and a table in supplements (mean concentration, adjustment, outcomes,
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	NOS, but only two categories (<8 low,≥8 high quality)
10. Did the review authors report on the sources of funding for the studies included in the review?	No

Seyyedsalehi and Boffeta 2023[45]	Comments
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	pooled relative risks (RRs): considered OR, SIR, SMR,HR as RR *If only results for subgroups were reported, we combined them using a fixed effect meta-analysis. If RR or CI were not reported, we calculated them from the row data if possible* Random effect models were used to account for heterogeneity Stratified analysis by region, study design, quality, incidence or mortality, exposure source, year of publication, PFAS type, leave-one-out sensitivity analyses
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	yes
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	heterogeneous categories of exposure, which might have resulted in non-differential misclassification. The lack of adjustment for potential confounders is a severe drawback of many available studies.
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Heterogeneity (het.) among studies was evaluated by the Q test, based on the variation across studies rather than within studies, and the I2 statistic (the percentage of variance in a metaanalysis that is attributable to study heterogeneity: not many heterogeneity reported
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	we examined publication bias by creating a funnel plot and applying a regression asymmetry test
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes, involved as expert in litigation

Conclusion: critical limitation as the literature search does not seem to be well documented (e.g. only 1 database), the meta-analysis combined all kinds of estimates (there was too much heterogeneity to pool). For example the combination of different exposure measures (serum level, modelling via serum level, ecological studies/workplace exposure rapportage), as well as the combination of mortality and incidence outcomes

3.2 Appraisal of primary studies with the OHAT risk of bias[46]

RoB domain	Question	Scoring possibilities
Selection bias	Did selection of study participants result in appropriate comparison groups?	Definitely low risk of bias Probably low risk of bias Probably high risk of bias Definitely high risk of bias Not reported (NR) is assumed to be equivalent to high risk Regarding confounding bias, although co-exposure to other pollutants (such as heavy metals or pesticides) is always a potential concern, we did not penalize studies if other exposures were not adjusted or controlled for. Only for occupational cohorts or contaminated regions, this might be opportune.
Confounding bias	Did the study design or analysis account for important confounding and modifying variables?	
Attrition/Exclusion bias	Were outcome data complete without attrition or exclusion from analysis?	
Detection bias:	Question 1: Can we be confident in the exposure characterization? (was it measure during a relevant time-window?) Question 2: Can we be confident in the outcome assessment?	
Selective reporting bias	Were all measured outcomes reported?	
Other sources of bias	Were any other potential threats to internal validity?	

3.2.1 Risk of bias of primary studies on preeclampsia

List of important confounding factors: pre-pregnancy BMI, maternal age, smoking, parity, socio economic profiles

	Selection	Confounding	Attrition	Detection Q1	Detection Q2	Selective reporting	Other
Case-control							
Bomarito, 2021[47]	Probably low Cases and controls were sampled from the same source population (LIFECODES); cases randomly selected; controls frequency-matched on gestational age at first visit (±2 weeks)., but The controls are matched by week of gestation, but not explicitly by the inclusion timeframe (however, the study does not show that the temporal distribution of cases and controls is aligned)	Probably low Adjustment on relevant covariates including the gestational age at timing of measurement but not smoking	Probably high the analyzed sample is moderately smaller (71 cases/73 controls) without documentation and detailed reasons	Probably low PFAS measured early (T1) with validated methods, no consideration of renal function (and presence of participants with hypertension at baseline)	Definitely low Validated definition and early versus late preeclampsia addressed Review of the diagnosis with consensus between two physicians	Probably low Although LIFECODES study has been described, there is no protocol for the present substudy	Tertiary centre
Rylander, 2020[48]	Probably high Cases and controls selected from the same database and similar	Probably low Adjustment on relevant covariates (not	Probably high In adjusted analysis, only 233 cases and 468	Definitely low First trimester (timing optimal for outcome); validity of the	Probably low review of medical files; no validation; no categorisation between early and late	Probably low No protocol but agreement between method and results	

	Selection	Confounding	Attrition	Detection Q1	Detection Q2	Selective reporting	Other
	time frame but controls were seleccted among a group of participants with children not small for gestational age. Availability in the biobank of PFAS measurement for participants were quite similar (93% for cases and 95% forcontrols)	on socioeconomic factors)	controls were available for all covariates	technique, no adjustement for renal function	preeclampsia (no mention of quantification of proteinuria		
Zhao, 2023[49]	Probably high Nested case-control within a longitudinal cohort enrolled in 2016, in one centre. Cases and controls drawn from the same setting, controls randomly selected and frequency-matched on age and blood-draw timing. A flow diagram is provided. No recruitment-level participation rates. Control sampling was conditioned on pregnancy outcome rather than drawn from the risk set (controls restricted to healthy full-term pregnancies)	Probably high Covariates such as smoking or timing at measurement are lacking	Probably low Exclusions pre-specified and reported; two cases missing	Probably low Validity of the technique, no adjustement for renal function	Probably low Review of medical files; no central adjudication; blood samples blindly sent to the laboratory; analysis between early/late and mild/severe preeclampsia	Probably low No protocol but agreement between method and results	High blood concentrations of PFOA and PFOS in comparison to the other studies

	Selection	Confounding	Attrition	Detection Q1	Detection Q2	Selective reporting	Other
Tian, 2023[50]	Probably high Inclusion criteria are mentioned but no selection flows and indications on the participants (cases and controls) were selected	Probably low Adjustment on relevant covariates (but some covariates are not accurately described)	Probably high No information on exclusions criterai, no flow of participants	Probably high Samples collected at the end of pregnancy (haemodilution is to be considered and there is a possibility of reverse causation)	Probably low Diagnostics retrieved from medical records and reviewed by two physicians (late versus early preeclampsia was addressed)	Probably low No protocol but agreement between method and results; many PFAS tested	
Cohort							
Begum, 2024[51]	Probably low Ancillary observational study from a RCT conducted in 3 sites across the US: protocol not available but analytic sample (n=459) was a subset chosen on the availability plasma volume. No table comparing cases and controls but coming from a RCT, we assumed that groups are comparable	Probably low Adjustment on relevant covariates (but not on gestational age at measurement-haemodilution more pronounced at 3rd trimester)	Probably high The subgroup was defined by "availability of suitable plasma volume"; a CONSORT/flow from the full VDAART pregnancy population is not provided nor communicated how many were excluded for sample volume (lack of transparency on exclusion bias)	Probably high Samples collected at the end of pregnancy (haemodilution is to be considered and there is a possibility of reverse causation)	Probably high Outcomes were derived from clinical questionnaires/records at the late pregnancy visit. No diagnosis criterai and medical confirmation reported in the article. Another article that used the same database VDAART mentioned that ACOG criteria were used and that the diagnosis was validated by a committee of four board-certified obstetricians but no certainty in the present publication	Probably low Agreement between method and results	Late inclusion excluding participants with early delivery Data from a trial with vitamine D as intervention (potential unknown efefcts)
Birukov, 2021[52]	Probably low	Probably low	Probably low	Definitely low	Probably low	Probably low	

	Selection	Confounding	Attrition	Detection Q1	Detection Q2	Selective reporting	Other
	Population-based source cohort (same district, 42% participation rate); uniform early-pregnancy inclusion. All pregnant women who met the inclusion criteria were informed about the study by project (midwifes,ultrasonographers, and obstetricians in the Obstetricsand Gynaecology Department of Odense UniversityHospital); flowchart provided	Ajustement on relevant variables but gestational age at timing of measurement, socio-economic factors, renal function not included	Flowchart of the 1436 participants available. (reasons for exclusion for the initially analysed sample of 1699 participants; no comparison)	First trimester (timing optimal for outcome); validity of the technique, no adjustement for renal function	National definition; review of hospital files and blood pressure measurements (electronic files and hand-written documents); no categorisation between early and late preeclampsia	No protocol but agreement between method and results	
Wikström, 2019[53]	Probably low Population-based cohort, recruitment in the same antenatal centre between 2007 and 2010. The article does not fully explain why the number of participants analysed (1,773) is lower than the number of participants included (2,582) (reasons for exclusion). Differences exist between control and cases (parity and weight).	Probably low Ajustement on relevant variables but gestational age at timing of measurement not included	Probably low No flowchart provided but all data were collected from a national register with outcomes for all participants available	Definitely low First trimester (timing optimal for outcome); validity of the technique, no adjustement for renal function; no participants with hypertension at baseline	Probably low Based on ICD-10 codes in the registre, no mention of review and confirmation of the diagnosis (no mention of quantification of proteinuria); no mention of early versus late preeclapmsia	Probably low No protocol but agreement between method and results	

	Selection	Confounding	Attrition	Detection Q1	Detection Q2	Selective reporting	Other
Huo, 2020[54]	Probably low Birth cohort study; recruitment in 6 centres from 2013 to 2016; flow chart available; restriction to singleton live births and exclusion of participants with chronic hypertension; no overall participation denominators, restricted to live singleton births, and no included versus excluded comparison	Probably low Adjustment on relevant covariates including the gestational age at timing of measurement but not smoking	Definitely low reasons were documented when subjects were removed from a study, with flow-chart available (all included were analysed); multiple imputation method was applied to handle with missing data on covariates with complete cases analysis available in annex of the study	Definitely low Preconceptional recruitement ; early pregnancy measurement validity of the technique, no adjustement for renal function;	Probably low ACOG criteria used; diagnostic extracted from medical chart without review; no categorisation between early and late preeclampsia	Probably low Study design already described in another publication but no protocol for the present analysis; agreement between method and results	
Borghese, 2020[55]	Definitely low National cohort (recruitement in 10 centres between 2008 and 2011); reasons for exclusion provided (flow chart described); no overall participation denominators; no included versus excluded comparison	Probably low Adjustment on relevant covariates (gestational age at timing of measurement not considered)	Probably low Reasons were documented when subjects were removed from a study (1909 included to 1739 analysed); no comparison between included and excluded	Definitely low Early pregnancy measurement; validity of the technique	Probably low National canadian criteria used; diagnostic extracted from medical chart without review; no categorisation between early and late preeclampsia	Probably low No protocol for the present analysis; agreement between method and results	Low number of participants with multiparity who developped preeclampsia (n=14)
Preston, 2022[56]	Probably low Subset chosen on the availability plasma volume; reasons for exclusion are provided	Probably low Adjusted analysis for preeclampsia did not include	Probably low Reasons were documented when subjects were removed from a study (1909	Definitely low Early pregnancy measurement; validity of the technique	Probably low Diagnostic extracted from medical chart without review; no categorisation between early and late preeclampsia	Probably low No protocol for the present analysis; agreement between method and results	Low number of preeclampsia (n= 56)

	Selection	Confounding	Attrition	Detection Q1	Detection Q2	Selective reporting	Other
		parity and BMI but sensitivity analysis performed with pregnancy physiological/haemodynamic factors and gestational week at blood collection showed a similar result	included to 1739 analysed); no comparison between included and excluded				
Thompson, 2024[57]	Probably low Cohort study (reference to two initially designed studies to investigating the role of the oral, vaginal, and gut microbiome on pregnancy outcomes, among African American women Atlanta and contributions of maternal prenatal chronic stress exposureand environmental toxicant exposure on infant outcomes). Inclusions within two centres between a large time period (2014-2020). Inclusion criteria clear bt	Probably low Adjustment on relevant covariates (gestational age at timing of measurement not considered)	Probably low All participants were analysed for the assessment of association (no excluded; sensitivity analysis removing those with chronic pre-pregnancy hypertension-n=30/413)	Definitely low Early pregnancy measurement sampling preceded outcomes; validity of the technique ; imputation for levels below the level of detection	Probably low Medical-record abstraction using ACOG 2020 criteria. No central expert adjudication; no early versus late-onset preeclampsia analysis	Probably low No protocol available for the present analysis (measurement of PFAS not mentiojed in the two protocols of the initially designed study used for the present cohort study; agreement between method and results	Few cases of preeclampsia (n=36) Population limlited to African-American participants

	Selection	Confounding	Attrition	Detection Q1	Detection Q2	Selective reporting	Other
	no flowchart describing the selected and non selected (participations rates/denominator)						
Cathey, 2026[58]	Probably low Data collected from 7 cohorts studies across US (with data cleaning and harmonization by the ECHO data analysis centre); a flowchat is provided but the comparison between selected and non-selected is not provided; no inclusion criteria among the 7 databases	Probably high Covariates such as BMI or timing at measurement are lacking	Probably low Some PFAS concentrations values were not available for all analysed participants; sensitivity analysis performed)	Probably low Variability of laboratories; various timings of measurements, imputation for levels below the level of detection	Probably high Outcomes extracted from medical files; no early versus late-onset preeclampsia analysis; self-reported outcomes.	Probably low No protocol for the present analysis; agreement between method and results and sensitivity analysis	Statistically -significant results in a subgroup of participants
Huang, 2019[59]	Probably low Cross-sectional analysis of 674 mother-infant pairs delivering at two Shanghai hospitals between 2011 and 2012. Cases and controls come from the same source. Originally 687 recruited, 13 excluded for missing covariates. No recruitment denominators/participation rates are reported	Probably low Adjustment on relevant covariates including the gestational age at timing of measurement but not smoking	Probably low Exclusion of 13 participants based on availability of variable (no analysis of selected-excluded)	Probably high Validation of results in an external laboratory in Denmark, but reverse-causation concerns (inclusion at delivery, after the occurrence of the outcome- umbilical chord)	Probably low Outcomes extracted from medical files(no proteinuria quantification mentioned); no central adjudication of diagnosis; no early versus late-onset preeclampsia analysis; no absolute number of cases (only 2.8% is reported)	Probably low No protocol for the present analysis; agreement between method and results (two types of logistic regression models)	Hypertensive disorder of pregnancy was the outcome analysed. Measurements performed at delivery and on umbilical chord

	Selection	Confounding	Attrition	Detection Q1	Detection Q2	Selective reporting	Other
Stein, 2009[60]	Probably low Community study using data from the C8 Health Project (2005–2006). Outcomes were self-reported via questionnaire for pregnancies occurring within the 5 years prior to blood draw (PFOA analyses were restricted to women residing in the same water district from approximately the start of pregnancy); the denominator of eligible pregnancies is unclear; restriction to white women without diabetes and for whose covariate data were complete	Probably high Adjusted for age, parity, education, smoking, no ajustement for weight and timing of measurement during pregnancy (haemodilution)	Probably high Attrition important (5624 to 1845)	Probably high Analysis of PFAS is correct but timing of measurement after pregnancy (PFAS levels were measured at C8 Project enrollment in 2005–2006, while the pregnancy outcomes pertained to pregnancies that occurred in the preceding five years, exposure); to approximate gestational exposure, the authors analyzed PFOA only for pregnancies in the prior five years among women who stayed in the same contaminated water district from around pregnancy start to enrollment (with a 3-year sensitivity), while PFOS analyses included all recent pregnancies	Probably high Self-reported outcome; no adjudication of the diagnosis	Probably low No protocol for the present analysis; agreement between described method and results	Multiple outcomes studied, data collected in the setting of a juridical action with participant compensation (high exposure setting-high contaminated area)
Starling 2014[61]	Probably low Substudy of MoBa cohort study (case-cohort); invitation to participate when performing ultrasound examination participation rate in	Probably low Adjustement on age, weight, educational level, somoking but not on the	Probably low 6% missing for modeled covariates; mesaure of association perfomred on 466 cases and 510 controls	Probably low Mid-regnancy measurement, sensitivity analyses for renal function	Probably low Medical files data extraction, ACOG-like criteria; no central ajudication; negative predicted value of having preeclampsia was approximately 95%	Probably low No protocol for the present analysis; agreement between method and results	

	Selection	Confounding	Attrition	Detection Q1	Detection Q2	Selective reporting	Other
	MoBa 39%, inclusion from 2003–2007; inclusion of nulliparous participants; 500 cases selected among 549 preeclampsia cases (466 cases and 510 controls after excluding participants with missing data; detailed flow of eligible non-participants not reported (the non-cases are not all validated (NPV ~ 95%)	timing of measurement	(no included-excluded comparison)				

3.2.2 *Risk of bias primary study on gestational diabetes*

List of important confounding factors for gestational diabetes: pre-pregnancy BMI, advanced maternal age, a history of GDM, and certain metabolic or family-history profiles

	Selection	Confounding	Attrition	Detection Q1	Detection Q2	Selective reporting	other
Starling[62]	All recruited from 16 cohorts Same exclusion criteria for cases and controls	Controlled for a lot of potential confounders but not for previous GDM (though diabetes diagnosis outside pregnancy was an exclusion criteria for both, and parity was considered)	imputed missing covariate data	Timing of PFAS measurement Exposure measured during pregnancy Specific sensitivity analysis for measurement before 24 weeks	primary outcome of GDM was defined based on self-report (18%), medical record documentation of GDM diagnosis or insulin use during the index pregnancy (73%), or both (9%).	All measured outcomes were reported	

3.2.3 Risk of bias of primary studies on miscarriage

List of important confounding factors for miscarriage: reproductive history (most important gravidity, parity), maternal age

	Selection	Confounding	Attrition	Detection Q1	Detection Q2	Selective reporting	Other
Case-control							
Jensen 2015[63, 64]		no previous miscarriages taken into consideration in adjusted analysis: controlled for parity	y cases included with PFAS measurements before 12 weeks (56 on a total of 88 miscarriages =>64%)	Measurement before gestational week 12 before the outcome	Diagnosed at hospital		
Liew 2020[65]	In the cohort a random group of cases and controls was chosen	Reproductive history taken into account (but only as binary ➔ parous: yes/no History of miscarriages: yes/no). Analyses stratified nulliparous/parous		Measurement (at mean 8 weeks) before outcome	hospital register		
Mi 2022[66]	All cases and a random sample of controls	No info on previous miscarriages	nested case control but no info on recruitment	Measurement (at 8 weeks) before outcome	Medical record		

	Selection	Confounding	Attrition	Detection Q1	Detection Q2	Selective reporting	Other
Wang 2024[67]	controls are a specific group of pregnant women searching for termination	Adjusted for gravidity (including previous miscarriages), and sensitivity analysis for nulligravid (in appenix)	No info on recruitment proces	PFAS measurement after outcome occurred (but before abortion)	Missed miscarriage		
Liu 2025[68]	Previous pregnancy loss is an exclusion criteria for controls, and an inclusion criteria for cases. Strange because parent cohort is a cohort of women with at least one pregnancy loss (Yang 2022). So they are not from the same cohort?	No adjustment for parity nor stratified analysis (because of the specific inclusion criteria)	No info on recruitment proces	Measurment preconception (before outcome)	Confirmed cases		
Tatsuta 2025[69]	Cases and matched controls (maternal age, parity and prepregn BMI) from the same cohort. Previous miscarriage was an exclusion criteria only in the cases?	Matched on maternal age, pre-pregnancy BMI, and parity. Sensitivity analysis excluding those with history of miscarriage (in both cases and controls)	525 excluded particpants because missing data on stillbirth, abortion, withdrawals 213 with missing data on confounders	Measurement (in first trim) before outcome	identified in medical records		Reported 0 as lower bound.

	Selection	Confounding	Attrition	Detection Q1	Detection Q2	Selective reporting	Other
Grindstad 2026[70]	From a cohort, selection is conditioned on a subsequent pregnancy progressing beyond the gestational weeks where miscarriage is most prevalent. So possible that women with miscarriage and no subsequent pregancy were excluded	Restricted to nulliparous women: women with no previous pregnancy in the control and only a single miscarriage in the cases: this reduced confounding by reproductive history Extra analyses with multiple confounders and sensitivity analyses.	info on inclusion in figure	Measurement after miscarriage	self reported in prior 2 years	Extra analyses with multiple confounders and sensitivity analyses.	
Cheng 2025[71]	Controls were drawn from group wanting abortion (excluding prior history of adverse pregnancy outomes)	Adjusted for gravidity (<4 or ≥4)	exlcusion of participants with no PFAS measurements (41 cases, 10 controls)	Measurment after diagnosis in the cases (outcome); in controls during pregnancy	Confirmed cases at hospital		
Nian 2022[72]	Controls were healthy non-pregnant women with at least 1 live birth	adjusted for gravidity (<4)	58 cases and 120 controls did not have adequate plasma samples and, therefore, were	Cases:Measurement in non pregnant women after the URSA diagnosis	Although not explicitly mentioned but as diagnosed in a reproductive clinic		

	Selection	Confounding	Attrition	Detection Q1	Detection Q2	Selective reporting	Other
			excluded, leaving 464 cases and 440 controls for analysis	in controls non pregnant			
Cohort							
Darrow 2014[73]	Difference in baseline characteristics are accounted for in adjusted analysis	if we assume that self-reported reproductive history is valid and reliable measurement, parity not as a confounder but stratified analysis by gravidity and parity at the time of serum measurement. but there is no indication of controlling for other exposures as this is a high exposure population	Complete data are required by design in a case-control (only those with followup included)	Measurement preconception (1.8y)	self reported miscarriage	not all analyses are shown in the table. nuligravid	
Wikstrom 2021[74]	All live births and a subgroup of miscarriages (Exclusion of recurrent miscarriages only in the cases)	Adjusted for parity but not on previous pregnancies Analyses stratified nulliparous/parous	N=297 women left study before birth, without report of childbirth or miscarriage	Measurement (at mean 10 weeks) and 36 cases had their miscarriage before 10 weeks but no fetal expulsion	clinical files		
Louis 2016[75]		Controlled for: no prior pregnancy, prior pregnany					

	Selection	Confounding	Attrition	Detection Q1	Detection Q2	Selective reporting	Other
	a cohort of 344 singleton pregnancies	but no loss, prior pregnancy and loss No stratified analysis for those with no prior pregnancy.	For 12 women the PFAS values were imputed. N=24 lost to followup	Measurement before pregnancy in whole cohort	Self reported, but guided with pregancy test		
Wang 2021[76]	A cohort of infertile women	No info on previous pregnancies	10% (35/340) women had uncomplete followup but no info	before IVF treatment	Confirmed in hospital		

3.2.4 Risk of bias primary studies on prematurity

List of important confounding factors: maternal age, smoking, parity, prenatal BMI, socio-economic status

	Selection	Confounding	Attrition	Detection Q1	Detection Q2	Selective reporting	other
Hu et al., 2025 [77]							
Liao et al., 2022 [78]							
Shen et al., 2022[79]							
Siwakoti et al., 2023[80]							

Yu et al., 2022[81]							
Zhang et al., 2023[82]							

Domain	Rating	Justification
Hu et al., 2025 [77]		
Selection bias	+	The paper reports a **nested case-control study** with **177 PTB cases and 531 controls matched according to maternal age and infant sex**. That is stronger than a conventional retrospective case-control because exposure, but the analytic sample still depends on case/control selection and sample availability.
Confounding	++	The adjusted models included **maternal age, BMI, education, annual household income, smoking status in the 1st trimester, parity, season of birth, infant sex,** and maternal medical information during pregnancy [such as gestational diabetes mellitus (GDM), gestational hypertension (GH), hyperthyroidism and hypothyroid ism] were recorded from hospital EMR system. GDM was more frequent in non-PTB.
Attrition / exclusion	+	The supplement reports **sensitivity analyses** and the paper describes the final analytic sample. That supports acceptable handling of exclusions, but the available reporting is not detailed enough to conclude there is definitely low risk from missingness or exclusions.
Exposure characterization	++	The study reports that **PFAS were measured in early-pregnancy serum using UHPLC-MS/MS**. That is objective biomarker-based exposure assessment, measured before delivery.
Outcome assessment	++	The paper states that **PTB, gestational weeks, and birth weight were obtained from the electronic medical record system**. Those are clinically recorded outcomes, so outcome misclassification is unlikely to be substantial.
Selective reporting	+	The paper reports **individual analyses, mixture analyses (WQS, QGC, BKMR), subtype analyses, and sex-stratified analyses**. There is no preregistration information.
Other bias	+	The paper used several mixture methods, which is a strength, but the results may still depend somewhat on modeling choices. no clear major additional bias reported, so probably low risk is appropriate.

Domain	Rating	Justification
Liao et al., 2022 [78]		
Selection bias	-	The paper reports a **prospective cohort study** in Guangxi, China, with explicit **inclusion and exclusion criteria** and a final sample of **1,341 pregnant women**. This is a strong design for selection bias, but there were many exclusions before the final sample, including elective cesarean birth, loss to follow-up, insufficient serum, and samples obtained after 12 weeks, so keep it at probably low rather than definitely low.
Confounding	-	The adjusted model included **maternal age, pre-pregnancy BMI, ethnicity, occupation, gravidity, parity, smoking exposure, alcohol use, cosmetic use, living in a newly decorated house, and infant sex**. The paper also states that it did **not collect family economic level or maternal eating structure and habits**, and it could not rule out **other environmental chemical exposures**. That reported limitation supports a probably low rating.
Attrition / exclusion	+	The authors clearly report who was excluded, including **57 withdrawn or failed follow-up**, and provide the final analytic sample. That is transparent and supports probably low risk, but there is not enough detail on whether excluded participants differed systematically to justify ++.
Exposure characterization	++	PFAS were measured in **maternal serum** using **UHPLC-MS/MS**. The authors also state that this is an accepted and mature detection method. This is objective and appropriate exposure measurement.
Outcome assessment	++	The study defines **PTB as delivery before 37 completed weeks**, with gestational information obtained from records. That is a standard clinical outcome definition.
Selective reporting	+	The paper reports **single-pollutant models, restricted cubic splines, WQS, and BKMR**. The reporting includes both positive and inverse associations and discusses limitations. However no registration of protocol is reported.
Other bias	+	The authors explicitly note that **PFAS were measured only once**, and that women were all from **Guangxi**, which may limit generalizability. They argue single measurement may still be acceptable because PFAS half-lives are long, but it remains a limitation

Domain	Rating	Justification
Shen et al., 2022[79]		
Selection bias	+	The paper reports **506 mother-infant pairs** in Hangzhou and states that maternal serum was collected **before delivery**. It is a cohort-style design,
Confounding	+	The paper states that covariates were selected using a **directed acyclic graph**, and models were adjusted for **maternal age, prenatal BMI, education, occupation, smoking, alcohol drinking, ethnicity, delivery mode, and parity**. Residual confounding still possible.
Attrition / exclusion	-	No clear reporting of losses, exclusions after enrollment, or a detailed missing-data flow are reported. The paper notes that **missing data were imputed**, but not enough is shown here to judge attrition/exclusion bias confidently.
Exposure characterization	-	The paper reports **14 PFAS measured in maternal serum**. All 14 target compounds were analyzed on a UPLC tandem electrospray equipped with the Xevo TQ-Striple quadrupole mass spectrometry system (Waters ACQUITY UPLC I-Class, Milford, MA, USA). There was a strong quality assurance and quality control. But collecting exposure close to delivery is less ideal than early-pregnancy sampling for a preterm birth question because temporality is weaker and there is more room for reverse-causation concerns. The authors themselves mention concerns about effective dose and reverse causality.
Outcome assessment	++	The outcomes include **birth weight, Apgar scores, and preterm birth**, all standard birth outcomes.
Selective reporting	+	The paper reports individual and mixture analyses and discusses transparently unexpected inverse results for some congeners. However, there is no protocol/preregistration information.
Other bias	–	The authors explicitly report several limitations: **mixed conclusions**, lack of **maternal and neonatal evaluation biomarkers**, no investigation of **placenta transfer**, and concern that measuring serum **before delivery** may complicate interpretation.

Domain	Rating	Justification
Siwakoti et al., 2023[80]		
Selection bias	+	Nested case-control within a prospective cohort; inclusion criteria clearly defined, but single-center population may limit representativeness
Confounding	-	Models adjusted for several covariates (maternal age, race, insurance, education, BMI, parity), but authors explicitly state lack of data on diet, physical activity, psychosocial factors
Attrition / exclusion	+	Small proportion of missing covariates (<5%); complete-case analysis used; multiple imputation sensitivity analysis performed
Exposure characterization	+	PFAS measured in plasma using validated laboratory methods; samples collected early pregnancy (median ~10 weeks)
Outcome assessment	++	Outcomes (PTB, subtypes, SGA, LGA) obtained from medical records using defined clinical criteria
Selective reporting	+	Results reported for multiple outcomes, including null findings; sensitivity analyses presented
Other bias	-	Authors report limited sample size in subgroup analyses (e.g., fetal sex stratification) and reduced statistical power

Domain	Rating	Justification
Yu et al., 2022[81]		
Selection bias	+	The paper describes a **family-based birth cohort** in which **355 preterm births and 481 controls** were selected for a nested case-control analysis. The analytic design still involves selected cases and controls rather than full-cohort analysis. Some characteristics differ between cases and controls (Table 1 of the paper)
Confounding	+	The paper says potential confounders were selected **a priori using previous literature and a DAG**, with fully adjusted models including **income, parity, alcohol, seafood consumption, neonatal sex, tobacco exposure**, and in some models **gestational diabetes and hypertension**. The paper also notes reliance on questionnaire information for some variables.

Domain	Rating	Justification
Attrition / exclusion	+	In the material I reviewed, I did not see sufficiently detailed reporting of missing data handling or exclusions into the final analysis to assign a low-risk rating confidently.
Exposure characterization	++	A major strength is that the study measured PFAS in **maternal, paternal, and neonatal cord serum**, giving rich and objective exposure characterization.
Outcome assessment	+	Gestational age was estimated by obstetricians according to Naegele's rule, using each participant's self-reported last menstrual period. No echo.
Selective reporting	++	The paper reports individual maternal, paternal, and neonatal analyses, family-level mixture analyses with BKMR, and interaction by seafood consumption. It also discusses contradictory paternal results rather than hiding them. Protocol approved.
Other bias	+	The paper identifies **family seafood consumption** as an effect modifier and relies partly on questionnaire data for this variable. That could introduce measurement error in covariates/modifiers, but the paper discusses this issue and otherwise the analytic approach is transparent.

Domain	Rating	Justification
Zhang et al., 2023[82]		
Selection bias	++	The paper reports a **prospective prebirth cohort** in Project Viva with **1,400 mother-singleton pairs**, and the supplement includes an inclusion diagram. This is a strong design, but the authors explicitly note possible **selection bias** because the analytic sample differed somewhat in SES factors from the original cohort. However, differences were subtle and several SES factors were included as covariates in the models.
Confounding	+	The adjusted models included a very broad set of covariates: **maternal age, education, race/ethnicity, BMI, smoking history, nulliparity, breastfeeding history, paternal education, household income, infertility, planned pregnancy, infant sex, gestational age at recruitment, diet quality, and fish consumption**. Residual confounding is possible.

Domain	Rating	Justification
Attrition / exclusion	++	The paper reports the analytic population and the supplement includes **participant flow** and **single-value imputation analyses** for missingness. "*In the linear and logistic regressions, we used multiple imputation with chained equations (MICE) toimputemissingcovariate values (missingness rates, 0.07%-6.93%*)"
Exposure characterization	++	PFAS were measured in **early pregnancy plasma** by CDC laboratories, with low-detection compounds excluded appropriately and others detected in more than 99% of samples.
Outcome assessment	++	Gestational age was calculated using the date of the last menstrual period and corrected by ultrasonography (16-20 weeks) if the 2 estimates differed by more than 10 days (9%)
Selective reporting	++	The paper reports main analyses, folate-stratified analyses, fish-adjusted sensitivity analyses, and missing-data sensitivity analyses. That is comprehensive and reduces concern about selective reporting. Protocol approved.
Other bias	+	The authors explicitly mention **multiple comparisons** and possible **selection bias**, but they also provide rationale and sensitivity analyses. I therefore judge this as probably low rather than high risk.

3.2.5 *Risk of bias primary studies on congenital abnormalities*

List of important confounding factors for congenital abnormalities: genetic predisposition, maternal age, socio-economic conditions, parity

	Selection	Confounding	Attrition	Detection Q1	Detection Q2	Selective reporting	other
Ou 2021[83]	Matched on maternal age (+-5y), parity From the same hospital cohort In the cases exclusion of family history and other explanations for CHD , but not in the controls ➔By removing genetic cases, force the remaining cases to be enriched for non-genetic causes, including environmental exposures. This makes PFAS look more strongly associated with the outcome than it truly is	Controlled for the matching criteria, but also more detailed the age of the mother (continuous) and infant sex, parity Other co-exposures?	Although some CHD cases in the parent cohort were captured during one year follow up after discharge, none were included in the current study	Exposure was measured after diagnosis just before birth (but it was more confirmation of diagnosis once born)	Diagnosed during pregnancy and confirmation by 2 cardiologists	All measured outcomes were reported	
Li 2024[84]	A multicentre study on influence of heavy metals Matched on residence and gestational weeks	via interview with research assistent Controlled for maternal age, gestational weeks sample, prepregnancy BMI, folic acid, district, parity, fetal sex,	Complete case analysis the matched case-control pairs were broken because	measurment during pregancy (from <24 weeks to > 28 weeks)	diagnosed during pregancy	all outcomes were reported	

	Selection	Confounding	Attrition	Detection Q1	Detection Q2	Selective reporting	other
	In the cases those with other congential anomalies were exlcuded (n=26)	maternal education, gestational diabetes Specific stratified analysis	insufficient blood volume				
Jiao 2025[85]	Cases recruited from paediatric heart center 2021-2023 that underwent surgery (severe cases) excluding cases associated with other malformations or known chromosomal abnormalities Matched (age, sex, race) Controls from outpatient (healthy no known diseases/chromosomal abnormalities)	Age and sex adjusted from the child (no info on the mother)	Complete case analysis	The PFAS measurement was done in children after the diagnosis	diagnosed pediatric heart center	All outcomes reported	
Wu 2025[86]	matched by age (± 2 years) with mothers who delivered non-congenital malformed infants in the same hospital during the same period same exclusion for cases and control: Mothers with consanguineous marriages, a history of genetic diseases, or those who dropped out or withdrew were excluded from the study.	Matched + age at menarche and prior exposure to harmful factors before or during early pregnancy. Variables related to family and reproductive history, unhealthy lifestyle, and environmental exposures were classified as the “harmful factors		Measurment in early pregnancy	diagnosis of CSM was confirmed through a comprehensive evaluation by obstetricians and gynecologists	No details	

3.2.6 *Risk of bias primary studies on ALL*

List of important confounding factors for ALL: Genetic predisposition (family predisposition), maternal age, socio economic, infections (on the causal pathway between exposure and outcome?)

	Selection	Confounding	Attrition	Detection Q1	Detection Q2	Selective reporting	other
Morimoto 2025[87]	Matched on sex, birth year/month and race Would have been better to also match on mother's age? No indication on whether or not there was a history of ALL in the cases and controls?	Controlled for **proxies** of socio-economic and age of neonate blood collection (the characteristics that showed significance in descriptive analysis) Only for the mixture stratified analysis performed because to small sample? No adjustment for maternal smoking.	Of the 137 identified ALL, 122 had neonatal blood available	Exposure was measured before diagnosis	Diagnosed in California Cancer Registry	All measured outcomes were reported	Sensitivity analysis to control for highly correlated PFAS compounds Strong wording though not statistical significant
Jones 2024[88]	matched on sample year, mother's age, gestational age, birth order, and child's sex exclusion of mothers with history of cancer, exclusion of Down syndrome,	Already matched + Adjusted for maternal smoking No socio-economic Other co-exposure?	Complete case analysis	measurment during early pregancy (before outcome)			Sensitivity analysis to control for correlated PFAS compounds (moderate correlations identified)

4 CHARACTERISTICS AND RESULTS OF INCLUDED STUDIES

4.1 Primary studies on preeclampsia

Author, year	Study design,	Study location and period	Sample size (cases/controls)	Outcome definition	Timing PFAS measurement	Method of measurement and serum concentrations	Maternal age, years	Measure of associations with preeclampsia	Adjustment covariates
Starling, 2014[61]	Substudy of a cohort study (case-cohort study)	Norway 2003-2007	976* (466/510) * only nulliparous	Systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg and proteinuria (dipstick ≥ 1) after 20 pregnancy weeks	Between 17-20 weeks	HPLC tandem MS **Median, ng/mL (IQR):** • PFOA : 2.78 (2.14-3.57) • PFNA : 0.54 (0.39-0.74) • PFDA : 0.10 (DL-0.18) • PFUnDA : 0.17 (0.08-0.27) • PFHxS : 0.69 (0.49-0.95) • PFHpS : 0.15 (0.09-0.23) • PFOS : 12.87 (9.69-17.03)	Age (year): percentages (preeclampsia/ control) • 16-24: 17/16 • 25-29: 43/41 • 30-34: 30/33 • 35-44: 10/10	**aHR (95%CI) ; continuous values in log-2 incremental unit :** • PFOA : 0.89 (0.65-1.22) • PFNA : 0.90 (0.70-1.16) • PFDA : 0.88 (0.75-1.04) • PFUnDA : 0.78 (0.66-0.92) • PFHxS : 0.91 (0.72-1.14) • PFHpS : 1.03 (0.86-1.24) • PFOS : 1.13 (0.84-1.52) **aHR (95%CI); (concentration µg/L) – reference = Q1** **PFOA** • Q2 (2.12-2.77): 1.03 (0.70-1.50) • Q3 (2.77-3.56): 0.92 (0.63-1.35) • Q4 (3.56-11.28): 1.01 (0.69-1.48) **PFNA** • Q2 (0.39-0.54): 0.88 (0.60-1.30) • Q3 (0.54-0.74): 1.04 (0.71-1.53) • Q4 (0.74-3.54): 0.88 (0.60-1.29) **PFDA** • ≥ median (0.10-1.74): 0.88 (0.67-1.16) **PFUnDA** • Q2 (0.08-0.17): 0.51 (0.35-0.76) • Q3 (0.17-0.27): 0.60 (0.41-0.88)	Age, BMI, educational level, smoking status

Author, year	Study design,	Study location and period	Sample size (cases/controls)	Outcome definition	Timing PFAS measurement	Method of measurement and serum concentrations	Maternal age, years	Measure of associations with preeclampsia	Adjustment covariates
								• Q4 (0.27-1.01): 0.55 (0.38-0.81) **PFHxS** • Q2 (0.49-0.69): 0.86 (0.59-1.26) • Q3 (0.69-0.95): 1.01 (0.69-1.49) • Q4 (0.95-11.47): 0.93 (0.64-1.36) **PFHpS** • Q2 (0.09-0.15): 1.30 (0.88-1.92) • Q3 (0.15-0.22): 1.01 (0.69-1.48) • Q4 (0.22-1.19): 1.12 (-0.77-1.63) **PFOS** • Q2 (9.67- 12.79): 1.12 (0.76-1.65) • Q3 (12.80-16.91): 0.88 (0.60-1.29) • Q4 (16.91-56.61): 1.09 (0.75-1.58)	
Wikström, 2019[53]	Prospective cohort (outcome identified postnatally from registers)	Sweden 2007-2010	1 773 (64/1709)	Systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg and proteinuria after 20 pregnancy weeks	Median: 10 weeks	LC-tandem-MS **Median, ng/mL (IQR):** • PFOS : 5.39 (3.95-7.61) • PFOA : 1.61 (1.12-2.31) • PFHxS : 1.23 (0.87-1.97) • PFNA : 0.53 (0.39-0.74) • PFDA : 0.26 (0.19-0.35)	Median (IQR): • Preeclampia: 32 (28-35) • Controls: 31 (28-34)	**aOR (95%CI) ; continuous values in log-2 incremental unit :** • PFOS : 1.53 (1.07-2.20) • PFOA : 1.31 (0.93-1.87) • PFHxS : 1.16 (0.86-1.56) • PFNA : 1.38 (1.01-1.89) • PFDA : 1.11 (0.79-1.59) • PFUnDA : 0.89 (0.68-1.17) • PFHpA : 1.02 (0.86-1.21) **aOR (95%CI); highest quartile (reference first quartile):** • PFOS: 2.68 (1.17-6.12)	Parity, age, body weight, smoking status

Author, year	Study design,	Study location and period	Sample size (cases/controls)	Outcome definition	Timing PFAS measurement	Method of measurement and serum concentrations	Maternal age, years	Measure of associations with preeclampsia	Adjustment covariates
						• PFUnDA : 0.23 (0.15-0.33) • PFHpA : 0.02 (< *DL*- 0.05)		• PFOA: 2.40 (0.95-6.06) • PFNA: 1.72 (0.80-3.67) • Non statistically significant results for the other PFAS (numerical data not provided)	
Rylander, 2020[48]	Case-control	Sweden ○ Biobanked serum : 1989 onwards ○ Register data: 1973 onwards	876 (296/580)	ICD-codes 642E, 642F (ICD9), O140, O141, O149 (ICD10)	12-14 weeks	LC-tandem-MS **Median (ng/mL) (min-max)*:** ***Preeclampsia:*** • PFOA: 2.82 (0.55-10.9) • PFOS: 12.9 (2.15-50.0) • PFNA: 0.47 (0.14-2.82) • PFHxS: 0.66 (DL-9.41) ***Controls:*** • PFOA: 2.83 (0.39-9.38) • PFOS: 12.4 (0.52-54.5) • PFNA: 0.46 (0.03-3.51) • PFHxS: 0.62 (DL-4.48) ** Numbers are given for primiparous participants (n=228*	Mean (min-max): • Preeclampia: 30 (15-44) • Controls: 29 (15-42)	**aOR (95%CI); per quartiles (in ng/mL)* – reference = Q1:** **PFOA** • >1.48-2.12: 0.94 (0.56-1.57) • >2.12-3.29: 1.42 (0.87-2.31) • >3.29: 1.13 (0.68-1.87) **PFOS** • >6.66-10.73: 0.81 (0.50-1.32) • >10.73-18.09: 1.23 (0.78-1.93) • >18.09: 0.96 (0.60-1.53) **PFNA** • >0.28-0.40: 1.34 (0.81-2.22) • >0.40-0.60: 1.41 (0.86- 2.32) • >0.60: 1.51 (0.91- 2.50) **PFHxS** • >0.31-0.53: 1.37 (0.82-2.28) • >0.53-0.78: 1.67 (1.02-2.74) • >0.78: 1.38 (0.83-2.30) ** restricting the analysis to either primiparous or nulliparous participants generated non- statistically significant estimates in the adjusted analysis*	Parity, age, BMI in early pregnancy, smoking in early pregnancy

Author, year	Study design,	Study location and period	Sample size (cases/controls)	Outcome definition	Timing PFAS measurement	Method of measurement and serum concentrations	Maternal age, years	Measure of associations with preeclampsia	Adjustment covariates
						cases /273 controls). Data on multiparous participants are available on demand		*except for the third quartile versus reference for PFHxS*	
Huo, 2020[54]	Prospective cohort	China 2013-2016	3 320 (124/3011)	Gestational hypertension + proteuniria (≥ 300mg/24 hours or ≥ 1 by dipstick test in a random urine sample)	Median: 15 weeks (IQR:13-17)	HPLC tandem MS **Median, ng/mL (IQR)[$]:** **Hypertensive disorders*:** • PFOA: 12.30 (9.52-15.02) • PFOS: 9.07 (2.38-14.70) • PFNA: 1.59 (1.22-2.14) • PFHxS: 0.54 (0.43-0.67) **Controls:** • PFOA: 11.85 (9.16-15.30) • PFOS: 9.36 (6.57-13.65) • PFNA: 1.69 (1.20-2.36) • PFHxS: 0.54 (0.42-0.69) ** Results are not provided for the group with preeclampsia specifically*	N (%): • <30: 1 976 (61.4) • 30-34: 942 (29..3) • ≥ 35: 217 (6.7) • Unknown: 85 (2.6)	**aOR (95%CI) ; continuous values of PFAS (ng/mL) in Ln incremental unit :** • PFOA : 0.89 (0.50-1.57) • PFNA : 0.85 (0.54-1.33) • PFDA : 0.95 (0.64-1.41) • PFUnDA : 0.84 (0.56-1.27) • PFOS : 1.24 (0.82-1.90) • PFHxS : 1.05 (0.60-1.83) • PFHpA : 0.74 (0.54-1.02) • PFBS : 0.98 (0.71-1.36) • PFDoA : 0.90 (0.56-1.43)	Age, pre-pregnancy BMI, parity, parental educational levels, gestational age of blood drawn, fetal sex

Author, year	Study design,	Study location and period	Sample size (cases/controls)	Outcome definition	Timing PFAS measurement	Method of measurement and serum concentrations	Maternal age, years	Measure of associations with preeclampsia	Adjustment covariates
						$ All 10 measured PFAS are not shown; results are available on demand			
Borghese, 2020[55]	Longitudinal cohort	Canada 2008-2011	1 739 (176/1563)	Gestational hypertension and: - Proteinuria (dipstick test ≥ 1 OR urine proteuniria ≥ 300 mg/24 hours or ≥ 0.3g/L), **OR** - Related maternal complication (DIC, pulmonary oedema, convulsion - eclapmpsia, elevated liver enzymes and/or low	Mean (range): 11.6 weeks (2-14)	Ultra-high pressure liquid chromatograph, tandem MS **Median, µg/L (IQR):** **Preeclampsia:** • PFOA: 2.0 (1.6, 2.7) • PFOS: 5.1 (4.1, 7.0) • PFHxS: 1.5 (1.0, 2.0) **Controls:** • PFOA: 1.7 (1.1, 2.4) • PFOS: 4.6 (3.2, 6.8) • PFHxS: 1.0 (0.7, 1.6)	Mean (SD): 32 (5.1)	**aOR (95%CI) ; continuous values in log-2 incremental unit* :** • PFOA : 1.36 (0.90-2.08) • PFOS : 1.25 (0.84-1.82) • PFHxS : 1.32 (1.03-1.70) **aOR (95%CI); expressed as tertiles (concentration µg/L)- reference= first tertile:** • **PFOA :** ○ Tertile 2 (0.05-1.3) : 1.62 (0.69-3.74) ○ Tertile 3 (2.2-11.0) : 1.23 (0.50-3.00) • **PFOS :** ○ Tertile 2 (3.8-5.8) : 1.72 (0.77-3.82) ○ Tertile 3 : (5.9-36.0) : 1.55 (0.68-3.49) • **PFHxS :** ○ Tertile 2 (0.78-1.3) : 1.40 (0.54-3.63) ○ Tertile 3 (1.4-40.0) : 3.06 (1.27-7.39) * *when using a restrictive definition of the outcome (gestational hypertension and proteinuria), estimates for all three*	Age, parity, education, smoking exposure, BMI

Author, year	Study design,	Study location and period	Sample size (cases/controls)	Outcome definition	Timing PFAS measurement	Method of measurement and serum concentrations	Maternal age, years	Measure of associations with preeclampsia	Adjustment covariates
				platelets count)				*PFAS were not found to be associated with preeclampsia*	
Bommarito, 2021[47]	Nested case-control	USA 2006-2008	150 (75/75)	New or worsening hypertension (SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg and proteinuria (> 300 mg/24 hours or protein/creatinine ratio >0.20)	Median: 10 weeks	HPLC tandem MS **Median (ng/mL), IQR:** • PFHpA: 0.63 (0.21-0.76) • PFOA: 2.92 (2.12-3.37) • PFNA: 0.85 (0.66-0.99) • PFDA: 0.30 (0.25-0.42) • PFUnDA:0.23 (0.15-0.38) • PFHxS:0.88 (0.53-1.36) • PFOS:8.45 (5.77-10.7) • MeFOSAA:0.17 (0.11-0.27)	Median (IQR): • Preeclampia: 32.6 (27.9-36.2) • Controls: 32.2 (29.4-36.3)	**aOR (95%CI) ; continuous values in IQR-increase* :** • PFHpA: 1.07 (0.63-1.81) • PFOA: 1.13 (0.78-1.63) • PFNA: 1.18 (0.91-1.53) • PFDA: 1.41 (1.00-2.00) • PFUnDA: 1.01 (0.60-1.70) • PFHxS:1.37 (0.94-1.99) • PFOS: 1.30 (0.89-1.89) • MeFOSAA: 0.96 (0.80-1.15) ** when the distinction was made between early (19 cases/73 controls) and late onset (52 cases/73 controls) preeclampsia (cut-off 34 weeks gestation), IQR-increase of PFDA (aOR; 95%CI: 1.64; 1.08-2.47) and PFOS (aOR; 95%CI: 1.60; 1.06-2.43) were associated with higher odds of preeclampsia*	Age, BMI, race, education, health insurance, parity, gestational age at the time of sampling
Birukov, 2021[52]	Cohort	Denmark 2010-2012	1 436 (104/1283) ~~** 49 participants had hypertension without*~~	Gestational hypertension (de novo SBP > 140/90 mmhg after 20 weeks of	8-16 weeks	LC and triple quadropole MS **Median, ng/mL (IQR):** **Preeclampsia:** • PFOA: 1.78 (1.16-2.51)	Mean (SD): 30.3 (4.5)	**aHR (95%CI) ; continuous values per doubling in PFAS concentrations :** • PFOA: 0.97 (0.75-1.24) • PFOS: 1.05 (0.79-1.40) • PFHxS: 1.14 (0.91- 1.42) • PFNA: 1.01 (0.76-1.36)	Age, BMI, parity, smoking exposure

Author, year	Study design,	Study location and period	Sample size (cases/controls)	Outcome definition	Timing PFAS measurement	Method of measurement and serum concentrations	Maternal age, years	Measure of associations with preeclampsia	Adjustment covariates
			~~preeclampsia~~	gestation on ≥ 2 episodes with at least 4 hours between, or significant aggravation of pre-existing hypertension) AND proteinuria (>0.3g/24 hours or ≥ +1 on sterile urine dipstick)		• PFOS: 7.57 (6.07-10.98) • PFHxS: 0.37 (0.28-0.52) • PFNA: 0.64 (0.48-0.87) • PFDA: 0.26 (0.21-0.38) **Controls:** • PFOA: 1.66 (1.10-2.36) • PFOS: 7.52 (5.49-10.20) • PFHxS: 0.35 (0.24-0.50) • PFNA: 0.64 (0.64-0.86) • PFDA: 0.29 (0.22-0.40)		• PFDA: 0.93 (0.71-1.22)	
Stein, 2009[60]	Cross sectional	USA 2005-2006	7 107 (563/6544) PFOA group: 1 485 PFOS group: 5 262	The questionnaire was not specific to pregnancy outcomes (no criteria definition for preeclamp	Not specifically provided (the study used data at the C8 project enrollment and pregnancy outcomes	Automated solid phase extraction combined with reverse phase HPLC Mean PFOA (SD), ng/mL: 48.8 (77.8) Mean PFOS (SD), ng/mL: 15 (8.2)	PFOA group: • 15-19 years: 6.7% • 20-34 years: 82.2% • 35-55 years: 11.1% PFOS group:	**aOR (95%CI);per increase from the 25th to the 75th percentile*:** • PFOA: 1.1 (0.9-1.4) • PFOS: 1.1 (0.9-1.3) **aOR (95%CI) per percentiles*; (reference = percentile 50th):** ≥ 50th percentile: • PFOA: 1.3 (0.9-1.9)	Age, parity, educational level, smoking, PFOS in the analysis of PFOA and PFOA in the analysis of PFOS

Author, year	Study design,	Study location and period	Sample size (cases/controls)	Outcome definition	Timing PFAS measurement	Method of measurement and serum concentrations	Maternal age, years	Measure of associations with preeclampsia	Adjustment covariates
				sia provided: self-reported outcom)	in the 5 year before enrollment)		• 15-19 years: 8.1% • 20-34 years: 83.0% • 35-55 years: 8.9%	• PFOS: 1.3 (1.1-1.7) ** the other presentation of the results according to 75th and 90th percentiles is available on demand* ** The increase represents to a shift from 10.3 ng/mL to 49.8 ng/mL for PFOA and from 9.0 ng/mL to 17.7 ng/mL for PFOS*	
Preston, 2022[56]	Cohort	USA 1999-2002	1 558 Preeclampsia: 56 Gestational hypertension: 106 No hypertensive disorder of	Elevated BP (SBP ≥ 140 mmHg or ≥ 90 mmHg) with proteinuria (dipstick ≥ 1 one at least one occasion) or chronic	Median 9.7 weeks	Solid phase extraction coupled with isotope dilution HPLC tandem MS Median concentrations (IQR), ng/mL, for the whole cohort (N=1 558): • PFOS: 25.6 (18.7-34.7) • PFOA: 5.9 (4.2-7.9)	Mean (SD): Preeclampsia: 30.6 (6.2) Controls*: 31.9 (5.1) ** no hypertension disorder of pregnancy*	**aOR (95%CI); per quartiles (in ng/mL)*$ – reference = Q1:** **PFOS** ○ Q2 (18.8-25.6): 0.99 (0.45-2.19) ○ Q3 (25.7-34.7): 1.16 (0.55-2.48) ○ Q4 (34.8-185): 1.04 (0.48-2.28) **PFOA** ○ Q2 (4.3-5.9): 0.80 (0.36-1.75) ○ Q3 (6.0-7.9): 0.87 (0.39-1.95) ○ Q4 (8.0-36.7): 1.41 (0.68-2.92) **PFHxS** ○ Q2 (1.7-2.5): 1.14 (0.55-2.38)	Age, race/ethnicity, marital status, smoking, education

Author, year	Study design,	Study location and period	Sample size (cases/controls)	Outcome definition	Timing PFAS measurement	Method of measurement and serum concentrations	Maternal age, years	Measure of associations with preeclampsia	Adjustment covariates
			pregnancy: 1396 (56/1375 *) ** group of normotensive participants*	hypertension and proteinuria after 20 weeks of gestation		• PFHxS: 2.5 (1.6-3.8) • PFNA: 0.7 (0.5-0.9) • EtFOSAA: 1.2 (0.7-1.9) • MeFOSAA: 1.9 (1.3-3.2) • PFDA: *DL* (*DL*-0.3)		○ Q3 (2.6-3.8): 1.08 (0.51-2.29) ○ Q4 (3.9-74.5): 0.81 (0.35-1.87) **PFNA** ○ Q2 (0.6-0.7): 1.16 (0.58-2.31) ○ Q3 (0.8-0.9): 0.98 (0.42-2.30) ○ Q4 (1.0-6.0): 1.20 (0.57-2.53) **aOR (95%CI)* *$*; continuous values per doubling:** • PFOS: 1.02 (0.72-1.46) • PFOA: 1.14 (0.77-1.69) • PFHxS: 0.89 (0.70-1.15) • PFNA: 1.20 (0.83-1.73) ** preeclampsia versus no hypertension disorder of pregnancy* *$: Values for EtFOSAA, MeFOSAA and PFDA are available on demand*	
Begum, 2024[51]	Ancillary study of a RCT	USA 2010-2011	459 (24/435)	No definition provided	Third trimester 32-38 gestational weeks)	Solid phase extraction coupled with isotope dilution HPLC tandem MS **Median concentrations (IQR), ng/mL* :** • n-PFOA: 1.30 (0.90-1.80) • n-PFOS: 2.70 (1.95-3.70)	Mean (SD): 27.4 (5.5)	**aOR (95%CI); continuous values in log incremental unit *:** • PFOA: 0.61 (0.27-1.36) • PFOS: 0.57 (0.19-1.71) • PFHxS: 0.75 (0.33-1.67) • PFNA: 0.73 (0.24-2.24) • PFUA: 0.86 (0.28-2.62) • NASEM total PFAS[#]: 0.95 (0.07-2.08)	Age, BMI, blood vitamine D levels, socio-economic factors, site, parity, alcohol use, smoking, race

Author, year	Study design,	Study location and period	Sample size (cases/controls)	Outcome definition	Timing PFAS measurement	Method of measurement and serum concentrations	Maternal age, years	Measure of associations with preeclampsia	Adjustment covariates
						• PFHxS: 0.80 (0.50-1.40) • PFNA: 0.50 (0.40-0.70) • PFUA: 0.10 (0.07-0.20) • NASEM total PFAS[#]: 18.07 (13.07-22.07) ** other PFAS levels (ME-PFOSA-ACOH, PFDEA, SmPFOS, SbPFOA) are available on demand* *#: cumulative sum of (PFOA, n-PFOS and Sm-PFOS, PFHxS, PFNA, PFDEA, PFUA, ME-PFOSA-ACOH)*		*#: cumulative sum of (PFOA, n-PFOS and Sm-PFOS, PFHxS, PFNA, PFDEA, PFUA, ME-PFOSA-ACOH)* ** results for other PFAS (ME-PFOSA-ACOH, PFDEA, SmPFOS, SbPFOA) are available on demand*	
Thompson, 2024[57]	Cohort (exclusively African Americans participants)	USA 2014-2020	513 (36 preeclampsia cases/425 no hypertensive disorder of pregnancy/ 52 gestational	Elevated BP (SBP ≥140 mmHg or DBP ≥90 mmHg) along with either proteinuria (>300mg/24h or protein/creatinine ratio of >0.30) or	14-18 weeks	Solid phase extraction coupled with isotope dilution HPLC tandem MS in negative electrospray ionization mode **Median concentrations (IQR), preeclampsia vs no hypertensive disorder of pregnancy, ng/mL :**	Mean (SD): • Preeclapmsia: 25 (4.7) • No HDP: 25 (4.9)	**aOR (95%CI); continuous values in Ln incremental unit standardised for an IQR increase (n=36 cases and n= 425 controls) :** • PFAS exposure mixture: 0.96 (0.63-1.45) • PFOA: 0.90 (0.64, 1.31) • PFOS: 1.08 (0.77, 1.61) • PFHxS: 0.90 (0.61, 1.34) • PFNA: 1.08 (0.71, 1.70)	Age, education, BMI, early pregnancy, parity, use of alcohol, tobacco and marijuana

Author, year	Study design,	Study location and period	Sample size (cases/controls)	Outcome definition	Timing PFAS measurement	Method of measurement and serum concentrations	Maternal age, years	Measure of associations with preeclampsia	Adjustment covariates
			hypertension)	new onset of one or more indicators of end-organ dysfunction ≥20 weeks gestation (*see legend*)		• PFOA: 0.66 (0.38-1.10) vs 0.71 (0.45-1.06) • PFOS: 2.18 (1.12-3.09) vs 2.20 (1.42-3.32) • PFHxS: 1.19 (0.78-1.73) vs 1.27 (0.87-1.74) • PFNA: 0.36 (0.15-0.56) vs 0.29 (0.17-0.47)			
Cathey, 2026[58]	Cohort, longitudinal prospective	USA 1998-2002, or 2013-2018	2 342 (121/2221)	Outcomes derived from medical files (n = 1449), or self-reported (n= 893). ≥ 2 recordings of a SBP 140–159 mmHg or a DBP 90–109 mmHg on	First trimester: 50.6% Second trimester: 33.3% Third trimester: 6.4% Missing: 9.7%	Technique not provided **Median concentrations (IQR), ng/mL :** • PFOA: 1.179 (0.50-4.90) • PFOS: 3.54 (1.79-21.60) • PFHxS: 1.40 (0.728-2.40) • PFNA: 0.40 (0.211-0.645) • NMFOSAA/MeFOSAA: 0.084 (0.023-1.600)	Age not provided	**aOR (95%CI); continuous values, per IQR increase :** • PFOA: 1.27 (0.73-2.23) • PFOS: 0.99 (0.47-2.12) • PFHxS: 0.78 (0.57-1.06) • PFNA: 1.13 (0.85-1.49) • NMFOSAA/MeFOSAA: 0.65 (0.24-1.76) • PFDA: 1.24 (0.92-1.65) **Subgroup analysis:** aOR (95%CI); per IQR increase in Hispanic participants (N= 353): • PFNA: 1.68 (1.03-2.75) • PFDA: 2.28 (1.26-4.12)	age, race, education, marital status, parity, child sex

Author, year	Study design,	Study location and period	Sample size (cases/controls)	Outcome definition	Timing PFAS measurement	Method of measurement and serum concentrations	Maternal age, years	Measure of associations with preeclampsia	Adjustment covariates
				separate dates, or any recording of a systolic blood pressure ≥160 mmHg or a diastolic blood pressure ≥90 mmHg on a single day AND a platelet count greater than 100,000/µL after 20 completed weeks of pregnancy.		• PFDA: 0.071 (0.059-0.200)		• PFOA: 2.21 (1.00-4.90) aOR (95%CI) of PFHxS; per IQR increase: • non-hispanic white (n=1272):0.64 (0.44-0.94) • non-hispanic black (n= 461): 0.55 (0.32-0.93)	
Zhao, 2023[49]	Nested case-control	China 2016	88/86 Mild preeclampsia: 53	ACOG criteria 2013: SBP ≥140 mm Hg or DBP ≥90 mm	16-20 weeks	HPLC MS **Median concentrations (IQR), ng/mL :**	Mean (SD)*: 29.4 (2.8) 29.2 (2.9)	**aOR (95%CI)- expressed as high versus low serum concentration (PFOS > 7.1 ng/mL; PFOA > 17.6 ng/mL):** • PFOS: 7.7 (3.8-15.7)	Age, parity, BMI

Author, year	Study design,	Study location and period	Sample size (cases/controls)	Outcome definition	Timing PFAS measurement	Method of measurement and serum concentrations	Maternal age, years	Measure of associations with preeclampsia	Adjustment covariates
			Severe preeclampsia: 33	Hg on 2 occasions >4 hours apart after 20 weeks' gestation in a previously normotensive woman and ≥300 mg protein per 24-hour urine collection Protein:creatinine ratio ≥0.3 mg/dL dipstick reading of 1+		**Cases** • PFOA: 19.3 (14.3-27.0) • PFOS: 23.3 (7.7-34.3) **Controls** • PFOA: 16.1 (13.2-21.4) • PFOS: 4.6 (3.6-7.1)	** mean and SD are assumed because not clearly mentioned*	• PFOA: 1.8 (1.0-3.5)	
Huang, 2019[59]	Cross-sectional	China 2011-2012	686	new onset of hypertension (SBP ^{3} 140mmHg or DBP ^{3} 90mmHg) after 20 gestational weeks with	Delivery (umbilical cord)	LC MS **Median concentrations (IQR), ng/mL :** • PFOA: 6.98 (4.95-9.54) • PFOS: 2.38 (1.81-3.23) • PFNA: 0.64 (0.50-0.83)	Mean (SD) : 29.3 (3.8) years	**aOR (95% CI) per tertiles (in ng/mL) – reference = tertile 1** **PFOA** • T2 : 2.23 (0.67-7.44) • T3 : 1.41 (0.38-5.14) • Standardized*: 1.12 (0.68-1.84) **PFOS** • T2 : 0.59(0.19-1.87) • T3 : 0.70 (0.23-2.08) • Standardized*: 0.83 (0.52-1.32)	Age, education level, BMI, parity

Author, year	Study design,	Study location and period	Sample size (cases/controls)	Outcome definition	Timing PFAS measurement	Method of measurement and serum concentrations	Maternal age, years	Measure of associations with preeclampsia	Adjustment covariates
				proteinuria (urine dipstick of at least +).		• PFUA: 0.40 (0.29-0.53) • PFDA: 0.36 (0.23-0.54) • PFHxS: 0.16 (0.132-0.20) • PFDoA: 0.094 (0.069-0.13) • PFBS: 0.047 (0.037-0.061)		**PFBS:** • T2 : 0.89 (0.39-2.44) • T3 : 2.26 (1.02-5.02) • Standardized*: 1.64 (1.09-2.47) *Results for PFUA, PFDA, PFDoA, PFNA and PFHxS are available on demand* **aOR (95% CI) using elastic net regression:** **PFBS** • T2 : 2.09 (0.51-8.53) • T3 : 3.51 (0.94-13.2) • Standardized*: 1.81 (1.03-3.17) ** PFAS concentration was subtracted by mean and divided by its standard deviation*	
Tian, 2023	Case-control	China 2020-2021	251 (82/169)	Onset of SBP (≥ 140 mmHg) or DBP ≥ 90 mmHg after 20 gestational weeks accompanied by proteinuria	1-2 days before delivery	Ultra performance liquid chromatography-tandem electrospray equipped with Xevo TQ-Stripple quadrupole mass spectrometry system **Median concentrations, ng/mL :**	Mean (SD) : 30.5 (3.94) years	**aOR (95%CI); continuous values, per log-10 increase :** • **PFOA:** 5.29 (1.05-26.7)*$ • **PFOS:** 1.01 (0.941-1.09) • **PFHpA:** 0.971 (0.812-0.998) • **PFUnDA:** 1.98 (1.10-1.98)* • **PFHxS:** 0.133 (0.048-0.373) • **4:2 FTS:** 0.282 (0.092-0.863) • **ADONA:** 0.841 (0.794-0.890) • **6:2Cl-PFESA:** 1.02 (1.00-1.48)* $	Age, BMI, education, occupation, smoking, alcohol drinking, ethnicity, menstrual cycle, menarche age, parity

Author, year	Study design,	Study location and period	Sample size (cases/controls)	Outcome definition	Timing PFAS measurement	Method of measurement and serum concentrations	Maternal age, years	Measure of associations with preeclampsia	Adjustment covariates
				(dipstick) and/or maternal organ dysfunction and/or uteroplacental dycfunction		• PFOS: 3.78 • PFOA: 3.63 • 6:2Cl-PFESA: 2.81 • PFUnDA: 1.18 Other analysed PFAS were: FTS, FOSAs, ADONA, PFCAs PFHpA, PFOA, PFNA, PFDA, PFUnDA, PFDoA, PFTrDA, PFTeDA and PFSAs, PFHxS, PFPeS, PFHpS, PFOS, PFNS and PFDS (*graph available on demand*)		** The estimates were not statistically significant among late-onset preeclampsia cases* *$ a statistically significant association was identified when expressed as tertiles of the concentration* *The results for other tested PFAS are available on demand*	

Legend: indicators of end-organ dysfunction : low platelet count < 100 000/µL, serum creatinine >1.1 mg/dL or doubling in the absence of other kidney disease, liver transaminases at least twice the upper limit of normal, pulmonary edema, persistent headache not accounted for by other diagnoses, visual symptoms; ACOG : American college of Obstetricians and Gynecologists; ADONA: 3H-perfluoro-3-[(3-methoxy-propoxy) propanoic acid] , aHR: adjusted hazard ratio; aOR: adjusted odds ratio; BMI: body mass index; BP: blood pressure; 95% CI: 95% confidence interval; 6:2Cl-PFESA: 6:2/8:2 chlorinated polyfluorinated ether sulfonates DBP: diastolic blood pressure; DIC: disseminated intravascular coagulation; DL: detection limit; FOSAs: perfluorooctane sulfonamides ; FTS: fluorotelomer sulfonates ; HDP: hypertensive diseases of pregnancy; HPLC: high performance liquid chromatography; IQR: interquartile range; LC: liquid chromatography;mg/dL: milligram per decilitre; ln: natural logarithm; log: logarithm; mmHg: millimetres of mercury; MS: mass spectrometry; NASEM: National Academy of Sciences, Engineering and Medicine; PFCAS: perfluoroalkyl carboxylic;PFDS: perfluorodecane sulfonic acid; PFHpA: perfluoroheptanoic acid; PFOA: perfluorooctanoic acid; PFDA: perfluorodecanoic acid; PFDoA: perfluorododecanoic acid; PFHpS: perfluoroheptane sulfonic acid ; PFHxS: perfluorohexane sulfonic acid ; PFNA: perfluorononanoic acid; PFNS: perfluorononane sulfonic acid; PFOS: perfluorooctane sulfonic acid; PFPeS: perfluoropentane sulfonic acid; PFTeDA: perfluorotetradecanoic acid; PFTrDA: perfluorotridecanoic acid ; PFSA: perfluoroalkyl sulfonic acids; PFuNDA: perfluoroundecanoic acid; Q: quartile; RCT: randomised controlled trial; ref: reference group; SBP: systolic blood pressure

4.2 Primary studies on miscarriage

Author, year	Study design,	Study location and period	Sample size (cases/controls)	Outcome definition	Timing PFAS measurement	Method of measurement and serum concentrations	Measure of associations with miscarriage	Adjustment covariates
Darrow 2014[73]	Cohort nested in larger cohort	USA (high exposure mid-Ohio River Valley near DuPont) 2005-2006 recruit 2008-2011 followup	1129 women reporting 1438 pregnancies 304 cases/ 1134 controls (births incl. 11 stillbirth)	Miscarriage (before 20 weeks of gestation) (self-reported)	Preconception (average time between serum measurement and conception was 1.8 years)	LC-MS/MS Only PFOA and PFOS **Geometric Mean, ng/mL (IQR):** • PFOA : 33.7 (9–31.9) • PFOS : 16.9 (10.4–21.2) ⇨ HIGH exposure	**aOR (95%CI) continuous per ln (ng/ml)** **PFOA :** 1.01 (0.88–1.16) **PFOA** limited to first pregnancy after enrolment**:** 1.04 (0.89–1.21) **PFOA:** limited to each woman's first pregnancy in nulligravid at enrolment (nulligravid) the OR per log increase in PFOA = **1.47 (1.00-2.14)** **PFOS:** 1.21 (0.94–1.55) **PFOS** limited to first pregnancy after enrolment**: 1.34 (1.02–1.76)** **aOR (95%CI) per quintiles (Q1 as reference)** **PFOA :** **Q2** 0.84 (0.53–1.32) Q3 1.08 (0.69–1.69) Q4 1.08 (0.69–1.68) **Q5** 1.00 (0.63–1.58) **PFOS :** Q2 1.34 (0.84–2.16) Q3 1.40 (0.88–2.25) Q4 1.59 (0.99–2.54) Q5 1.41 (0.88–2.26)	Age category, educational level, smoking status, BMI, self-reported diabetes, time between conception and serum measurement parity not as a confounder but stratified analysis by gravidity and parity at the time of serum measurement
Jensen 2015[63]	Nested case-control And matched controls	Denmark in Odense child	392 with PFAS measurement before 12 weeks	Miscarriage diagnosed at hospital (before 22	Before week 12 of gestation	LC-MS/MS 5 PFAS Median, ng/mL (IQR): • PFHxS 0.29 ng/mL (0.02–7.28)	**aOR (95%CI) ; continuous values by ln logaritm :** • PFHxS: 1.53 (0.99–2.38) • PFOS: 1.16 (0.59–1.29)	age, BMI, **parity** and gestational age at serum sampling

Author, year	Study design,	Study location and period	Sample size (cases/controls)	Outcome definition	Timing PFAS measurement	Method of measurement and serum concentrations	Measure of associations with miscarriage	Adjustment covariates
		cohort (n= 2874) 2010–2012 Recruit	Case-cohort 56/336 Matched case-control 51/204	weeks of gestation)		• PFOA, 1.58 ng/mL (0.31–9.71); • PFOS, 8.10 ng/mL (1.25–26.12) • PFNA, 0.72 ng/mL (0.18–4.40) • PFDA, 0.27 ng/mL (0.07–1.75)	• PFOA: 0.64 (0.36–1.18) • **PFNA: 16.46 (7.39–36.62)** • **PFDA: 2.30 (1.18–4.47)** **aOR (95%CI): categorical values by tertiles (reference =Q1)** **PFNA:** • **Q2 10.88 (4.76–24.84)** • **Q3 16.17 (6.88–38.03)** **PFDA:** • Q2: 1.86 (0.91–3.83) • **Q3: 2.67 (1.31–5.44)** **Case -control with matching on parity and gestational age of serum sampling – only categorical** **PFOA:** Tertile 2: 1.21 (0.53-2.73) Tertile 3: 0.68 (0.28-1.67) **PFOS:** Tertile 2: 1.03 (0.47-2.29) Tertile 3: 1.06 (0.46-2.41) **PFNA:** **Tertile 2 18.97 (5.49–65.58)** **Tertile 3 37.93 (9.90–145.2)** **PFDA:** **Tertile 2: 1.85 (0.77–4.46)** **Tertile 3: 3.71 (1.60–8.60)**	No info on previous miscarriages

Author, year	Study design,	Study location and period	Sample size (cases/controls)	Outcome definition	Timing PFAS measurement	Method of measurement and serum concentrations	Measure of associations with miscarriage	Adjustment covariates
Louis 2016[75]	Prospective cohort LIFE study	USA (Michigan and Texas) 2005–2009	344 singleton pregnancies (for 12 women the PFAS values were imputed) 98/222 (n=24 loss to follow-up)	Self-reported Pregnancy loss (before 21 weeks) (time to miscarriage)	Before pregnancy	HPLC-MS/MS 7 PFAS Median, ng/mL (IQR): • PFOA: 3.3 (2.2, 4.9) • PFOS: 12.2 (8.3, 17.8) • PFNA: 1.2 (0.7, 1.7) • Me-PFOSA-AcOH: 0.3 (0.1, 0.5) • PFDeA: 0.4 (0.2, 0.6)	**Adjusted Hazard ratio continuous (in units of 1 standard deviation)** **PFOA :** 0.93 (0.75, 1.16) **PFOS :** 0.81 (0.65, 1.00) **PFOSA :** 0.74 (0.50, 1.09) **PFNA :** 0.86 (0.70, 1.06) **PFDA** : 0.83 (0.66, 1.04) **Et-PFOSA-AcOH :** 1.04 (0.87, 1.23) **Me-PFOSA-AcOH : 0.79 (0.62, 1.00)** **Adjusted HR categorical (3rd versus 1 tertile)** **PFNA: 0.57 (0.34, 0.94)**	age (continuous), BMI , **prior pregnancy loss** conditional on prior pregnancy history, any alcohol consumption during pregnancy (no/yes), and any cigarette smoking during pregnancy (no/yes) no stratified analysis
Liew 2020[65]	Nested case control	National Danish birth cohort (n=100 413 pregnancies) Recruit 1996–2002	Randomly chosen 220 miscarriage between 12-22w /218 live births	Miscarriage between 12-22 weeks via hospital register	7 PFAS in plasma around 8 weeks gestation	7 PFAS In the 220 cases the median and IQR (ng/ml) PFOA: 3.96 (3.02;5.22) PFOS: 24.55 (19.5;32.25) PFHxS: 1.06 (0.86; 1.36) PFDA: 0.18 (0.14;0.22)	**Adjusted OR per doubling increase of PFAS (log 2 ng/ml)** **PFOA: 1.4 (1.0,1.9)** **PFOS:** 1.2 (0.9,1.8) **PFHxS:** 0.9 (0.7,1.3) **PFHpS:** 1.3 (0.9,1.9) **PFDA:** 1.1 (0.8,1.7) **PFOSA:** 1.1 (0.9,1.3) **PFNA:** 1.0 (0.8,1.3) **Adjusted OR categorical Q4 versus Q1** **PFOA: 2.2 (1.2,3.9)** **PFOS:** 1.4 (0.8,2.4) **PFHxS:** 0.9 (0.5,1.7) **PFHpS: 1.8 (1.0,3.2)** **PFDA:** 1.3 (0.7,2.2) **PFOSA:** 1.3 (0.7,2.3)	Maternal age, **parity**, socio-occupational status, smoking and alcohol intake, gestational week of blood sampling, and **maternal history of miscarriage** **stratified analysis on parity**

Author, year	Study design,	Study location and period	Sample size (cases/controls)	Outcome definition	Timing PFAS measurement	Method of measurement and serum concentrations	Measure of associations with miscarriage	Adjustment covariates
							PFNA: 1.0 (0.6,1.8) Dose-response relationship: monotonic increase in OR per quartile for PFOA and PFHpS **Only significance in parous women** **Adj OR categorical Q4 vs. Q1 for PFOA = 2.4 (1.0-5.8)** • **PFAS mixture WQS:** each IQR increment in the WQS index was associated with a 64% higher odds for miscarriage (95%CI:1.15,2.34)	
Wang 2021[76]	Prospective cohort	Two IVF centres in China 2015-2017 recruit	305 Women undergoing IVF-ET hCG test negative (100cases/105control), clinical pregnancy failure (136/169), and preclinical spontaneous abortion (36/169)	preclinical spontaneous abortion after hCG test positivity	12 PFAS before IVF treatment	HPLC-MS/MS 12 PFAS Presented separately per outcome and per center and per subgroup The cases in Yantai centre with preclinical spontaneous abortion: PFOA: 5.231 (3.444-8.962) PFOS: 7.383 (4.744-9.520)	**Adjusted relative risk log-binomial regression** (high versus low based on median) **PFOA:** 0.99 (0.94-1.05) **PFOS:** 0.95 (0.87-1.04) **PFDA:** 0.67 (0.16-2.73) **PFBA:** 1.46 (0.84-2.51) **PFHxA:** 2.14 (0.82-5.60) **PFHxS:** 1.04 (0.96-1.12) **PFNA:** 0.27 (0.06-1.24) **Categorical: quartiles** **Mixture BKMR model: no joint effects**	age, BMI, type of pathogenesis, stimulation protocol, endometrial thickness on the hCG trigger day, number of transferred embryos, and number of cycles of embryo transfer

Author, year	Study design,	Study location and period	Sample size (cases/controls)	Outcome definition	Timing PFAS measurement	Method of measurement and serum concentrations	Measure of associations with miscarriage	Adjustment covariates
Wikström, 2021[74]	Cohort	SELMA pregnancy cohort Sweden 2007-2010	1 567 pregnant with PFAS serum and followup 1449 live births as controls Cases: 78 Excluded miscariages: Recurrent (n=7), miscarriage 2nd trim (n= 2) Chrom abnormalities (n=4) Missing data (n=2)	Sporadic miscarriage of unknown aetiology in first trimester in clinical files Exclusion: Recurrent ≥3 miscarriages	Median: 10 weeks of gestation	LC-tandem-MS 8 PFAS Is reported separately for cases and controls **Median in 78 cases, ng/mL (IQR):** • PFOS : 6.09 (3.99–8.77) • PFOA : 2.00 (1.44–2.76) • PFHxS : 1.21 (0.83–2.01) • PFNA : 0.59 (0.43–0.91) • PFDA : 0.27 (0.19–0.38) • PFUnDA : 0.23 (0.16–0.32) • PFHpA : 0.02 (0.01–0.04)	**aOR (95%CI) ; continuous values in log-2 incremental unit :** • PFOS : 1.13 (0.82–1.52) • PFOA : **1.48 (1.09–2.01)*** • PFHxS : 0.96 (0.73–1.26) • PFNA : 1.25 (0.93–1.68) • PFDA : 1.10 (0.81–1.53) • PFUnDA : 0.95 (0.74–1.22) • PFHpA : 1.09 (0.93–1.28) **aOR (95%CI); highest quartile (reference first quartile):** • Figure but numerical data not provided ➔ non-significant, though a dose response indication for PFOA and PFNA. **indications of a monotonic dose response association for PFOA** When stratified for parity PFOA in nulliparous (aOR =1.22, 0.79-1.89) **PFOA in parous (aOR=1.60, 1.02-2.52)**	Age, cotine, parity (nulliparous, primipara, multipara)
Mi 2022 – letter to the editor[66]	Nested case – control	prospective cohort in hospital in Beijing recruit 2018-2020	cases (n=41) and random control (n= 47)	Early pregnancy loss was defined as the spontaneous loss between 9–12 weeks of gestation	At 8 weeks gestation	32 PFC compounds The median and IQR is reported separately for cases and controls Median in 41 cases, ng/ml (IQR) PFOA: 5.444(4.836-9.257) PFNA: 0.943 (0.722-1.562)	**aOR categorical data 95% CI** **with the median level as the cut-off point** **PFOA** 0.83 (0.29–2.39) when conc ≥ 5.640 ng/ml **PFOS** 1.34 (0.46–3.86) when conc ≥ 5.244 ng/ml **PFDA 5.00 (1.53–16.33) when conc was ≥0.810 ng/ml**	parity, maternal passive smoking first trimester, vaginal bleeding during pregnancy

Author, year	Study design,	Study location and period	Sample size (cases/controls)	Outcome definition	Timing PFAS measurement	Method of measurement and serum concentrations	Measure of associations with miscarriage	Adjustment covariates
						PFDA: 0.961 (0.586-1.454) PFOS: 5.996 (3.848-9.222)	**PFUda aOR = 3.87, 95% CI: 1.26–11.89 when ≥ 0.539 ng/ml** **Mixture: principal component analysis** indicated the synthesized effects of PFCAs and PFOS substitutes **Dose-response via restricted cubic spline model of the three components: suggest different patterns**	
Wang 2024[67]	Case control	Single centre Shanghai Recruit 2020	Cases with missed miscarriage(n=198) and control were those seeking for termination of pregnancy (n=195)	Diagnosed Early miscarriage before 12 weeks, but no abortion yet => **missed miscarriage**	Pregnancy-Blood sample before abortion	HPLC-MS/MS, 30 PFAS The median and IQR in the 198 cases PFOA: 8.40 (5.70-12.39) PFNA: 0.94 (0.57-1.38) PFDA: 0.75 (0.47-1.24) PFUdA: 0.65 (0.40-1.07) L-PFOS: 4.96 (2.33-8.52)	**aOR (95%CI) per Log10 increase** **13 PFAS showed significant association** **PFOA: 2.99 (1.96-4.68)** **PFNA: 1.43 (1.02-2.03)** **PFDA: 1.47 (1.12-1.95)** **PFUdA: 1.36 (1.04-1.8)** **L-PFOS: 2.13 (1.57-2.93)** **∑3,4,5m PFOS: 2.35(1.62–3.47)** **aOR for Nulligravid:** **PFOA: 3.4 (1.55-7.98)** **PFNA: 3.26 (1.65-7.00)** **PFDA: 3.29 (1.89-6.24)** **L-PFOS: 3.86 (2.12-7.79)** **∑3,4,5m PFOS: 3.88 (1.93-8.57)** **Mixture analyses: BKMR** - risk of miscarriages increased when PFAS mixture reached 75th percentile as compared to 25th percentile. **Dose response** indications for 1m-PFOS and PFOA	Age, **gravidity,** ethnicity, education, income pre-pregnancy BMI, prepregnancy tobacco exposure (incl passive smoking) Sensitivity analysis for nulligravid.

Author, year	Study design,	Study location and period	Sample size (cases/controls)	Outcome definition	Timing PFAS measurement	Method of measurement and serum concentrations	Measure of associations with miscarriage	Adjustment covariates
Liu 2025[68]	Nested case control in larger cohort	Cohort in a reproductive centre (1532 non-pregnant) China Recruit 2019-2022	Cases (348) and frequency matched controls (n=320) from 1532 cohort	spontaneous abortion occurring before 24 weeks of gestation <European Society of Human Reproduction and Embryology)	10 PFAS in serum before pregnancy attempts (preconception exposure)	HPLC-MS/MS 25 PFAS measured but 10 with detection rates >85% Median and IQR (ng/ml) PFBA: 0.33 (0.18, 1.15) PFOA: 2.02 (1.01, 4.35) PFOS: 1.22 (0.70, 2.66) PFNA: 0.38 (0.24, 0.74) PFHxS: 0.26 (0.12, 0.72)	**aOR EWAS model per ln increase** **PFPeA (OR: 1.22, 95 % CI: 1.07–1.41),** **PFPeS (OR: 1.82, 95 % CI: 1.31–2.62),** **PFHxS (OR: 1.34, 95 % CI: 1.19–1.51),** **PFOA (OR: 1.73, 95 % CI: 1.46–2.07),** **PFOS (OR: 1.33, 95 % CI: 1.14–1.56),** **PFNA (OR: 1.73, 95 % CI: 1.40–2.15).** PFBA (OR : 0.93, 95% CI : 0.84-1.03) When stratified analyses per age: no significant association except for PFNA No analysis of dose-response relationship	parity was not adjusted for in models. Age, education, ethnicity, BMI, waist to hip ratio, blood pressure, menstrual cycle length, menstrual volume, period lenght Previous pregnancy loss is an exclusion criteria for controls, and an inclusion criteria for cases
Tatsuta 2025[69]	Nested case control	Japan 2011-2014 recruit	66 cases and 264 matched control in the Japan Environment and Children's Study cohort (n= 24 412 mother)	'late' miscarriage between 12-22 weeks of gestation (identified in medical records)	During first trim pregnancy	LC-MS/MS 28 PFAS Median (ng/ml) – 5-95 percentile Miscarriage (n=66) PFOA: 1.6 (0.59-6.0) PFNA: 1.3 (0.68-3.9) PFDA: 0.46 (0.20-1.2) PFUnA: 1.1 (0.45-2.2) PFOS: 2.7 (1.3-6.6)	**OR (no adjustment because matched controls) 95%CI in log 10** • **PFOA:** 0.087 (0.000-15.548) • **PFNA:** 4.339 (0.033- 576.705) • **PFDA**: 0.777 (0.010 - 62.890) • **PFUnA**: 0.726 (0.020 - 26.944) • **PFOS**: 0.083 (0.000 - 22.060) **Sensitivity analysis (limited to participants with no history of miscarriages): 61 cases/244 controls** **PFOA:** 1.669 (0.054-51.6) **PFNA:** 5.956 (0.003-11462.2) **PFDA:** 38.741 (0.039-38550.6) **PFUnA:** 9.277 (0.043-2008.9)	• maternal age, pre-pregnancy BMI, and **parity** as covariates used in matching controls • exclusion of recurrent miscarriages (only in the cases) • Sensitivity analysis excluding participants with a history of miscarriage

Author, year	Study design,	Study location and period	Sample size (cases/controls)	Outcome definition	Timing PFAS measurement	Method of measurement and serum concentrations	Measure of associations with miscarriage	Adjustment covariates
							PFOS: 1.647 (0.005-578.1) **BKMR adjusted for maternal age, pre-pregnancy BMI, and parity: no effect**	
Grindstad 2026[70]	Nested case control in larger cohort (The Norwegian Mother, Father, and Child Cohort Study (MoBa) which included three cohorts with PFAS measurements	Norway 1999-2008	Among 2525 nulliparous women 253 cases with recent previous miscarriage 2272 controls with no previous pregnancy	Retrospective self-reported miscarriage between 5 and 22 gestational week in the prior two years	18 weeks gestation In the cases: after miscarriage In the controls: in the first pregnancy	LC-MS/MS 19 PFAS, but only 7 above limit of quantification Median in 253 cases: PFOA: 2.72 (2.08 – 3.34) PFOS: 13.27 (9.91 – 16.94) PFNA: 0.45 (0.33 – 0.59) PFDA: 0.15 (0.11 – 0.20)	**Adjusted (age, education, participant status and maternal year of birth) OR per log 2 increase** **PFOA**: 0.80 (0.64 - 1.01) **PFOS**: 0.93 (0.76, 1.14) **PFNA:** 0.89 (0.73 - 1.08) **PFDA:** 0.97 (0.84, 1.10) **PFUnDA:** 1.02 (0.89, 1.16) **PFHxS:** 0.96 (0.84, 1.10) **PFHpS:** 0.92 (0.79, 1.07) **Also categorical with Q1 as reference** **Mixture: quantile based g computation** no effect OR for miscarriage 0.95, 95 % CI: 0.83-1.09) per quintile increase in the mixture	Nulliparous women • Maternal age, educational level, year of birth, participant status, BMI, smoking, alcohol, menstrual cycle, hormone contraceptive
Recurrent miscarriage								
Cheng 2025[71]	Case control	Beijing 2018-2020 recruit	110 cases and 91 controls (matched on age, occupation, and income) Controls are those without	At least two **recurrent spontaneous** miscarriage with same partner in first 20 weeks of pregnancy	Cases : after confirmed URSA Controls : gestational weeks 4-6	UHPLC-MS/MS 15 PFAS Median IQR **URSA (110 cases)** : PFOA : 3.26 (2.32-4.96) PFNA: 0.63 (0.47-0.91) PFDA: 0.37 (0.27- 0.56) PFOS: 3.18 (2.26-487)	**adjusted OR representing URSA risk per ln-unit increase** **PFBA: 12.84 (4.49- 36.70)** **PFDoDA: 1.58 (1.34-1.85)** **PFUnDA:** 0.74 (0.42-1.29) **PFDA:** 1.14 (0.66-1.98) **PFOA:** 1.19 (0.79-1.79)	• age, BMI, menarche age, education level, occupation, annual household income, tobacco exposure, **gravidity**, and regular menstrual cycle

Author, year	Study design,	Study location and period	Sample size (cases/controls)	Outcome definition	Timing PFAS measurement	Method of measurement and serum concentrations	Measure of associations with miscarriage	Adjustment covariates
			previous adverse pregnancy outcomes	as diagnosed in hospital Excluded: Inherited Chromosomal/genetic Anomalies maternal reproductive tract, endocrine abnormalities		**Controls (n=91)** PFOA: 3.07 (2.10-5.21) PFNA: 0.56 (0.40-0.85) PFOS: 2.47 (1.77-4.14)	**PFNA: 1.93 (1.02-3.67)** **PFOS: 1.79 (1.04-3.08)** **Adjusted OR categorical (3rd versus 1 tertile)** **Mixture:** In the multivariate WQS model, mixed PFASs were positively associated with URSA (OR:4.87; 95% CI: 1.30, 3.72; P<0.001),**this seems a mistake contacted authors* as well as some negative associated (OR: 0.36; 95%CI 0.30-0.44) In the QGC model, no statistically significant association was found between a one-third increase in the PFASs mixture and URSA (OR: 2.05; 95% CI: 0.48, 8.67; P=0.328).	gravidity dichotomised as <4 or ≥4)
Nian 2022[72]	Case-control	China (multicentre) 2014-2016 recruit	464 cases and 440 controls for analysis Controls were healthy non-pregnant women with at least 1 livebirth without endocrine disorders	URSA was defined as patients with ≥2 consecutive spontaneous abortion before 20 weeks Excluded: abnormal karyotype partners, abnormal anatomy, positiveautoantibodies,	Cases: non pregnant after definition of URSA Controls: non pregnant	35 PFAS standards In the 464 cases the median and IQR (in ng/ml) 6:2 Cl PFESA: 2.92 (1.41,6.83) PFOA: 7.06 (3.39;14,48) PFOS: 3.96 (2.58, 6.78)	**aOR (95%CI) representing URSA risk per ln increase** **PFOA:** 1.04 (0.88-1.24) **PFOS:** 1.00 (0.81-1.24) **HFPO-DA: 1.29 (1.08-1.52)** **6:2Cl-PFESA: 1.19 (1.00-1.42)** **In suppl/** **PFNA:** 1.16 (0.93-1.46) **PFDA:** 1.08 (0.89 -1.30) **aOR (95%CI) categorical** **6:2 Cl-PFESA : only Q2 vs Q1 (1.73 (1.13, 2.66),** not with Q3 or Q4	woman's age, age at menarche, **gravidity,** BMI, study site, education, and income. Gravidity categorized as <4

Author, year	Study design,	Study location and period	Sample size (cases/controls)	Outcome definition	Timing PFAS measurement	Method of measurement and serum concentrations	Measure of associations with miscarriage	Adjustment covariates
				TORCH infection			**HFPO-DA (Q1 =ref)** **Q2 3.02 (1.87, 4.87)** **Q3 2.52 (1.56, 4.09)** **Q4 3.02 (1.82, 4.99)** **Dose response via restricted cubic spline failed to show a non-linear relationship** **Mixture:, BKMR model, quantile-based g-computation** overall PFAS mixture was not significantly associated with URSA (adjusted OR = 1.11, 95% CI: 0.86, 1.42)	

4.3 Prematurity

4.3.1 Results from systematic reviews

The results are from the systematic review by Yang et al. 2022[29]

PFAS	Systematic review	Included primary studies	Result	Remark
PFOS	***Yang et al. 2022[29]***	Fei et al., 2007 Stein et al., 2009 Hamm et al., 2010 Chen et al., 2012 Whitworth et al., 2012 Darrow et al., 2013 Bach et al., 2016 Manzano-Salgado et al., 2017 Meng et al., 2018 Sagiv et al., 2018 Chu et al., 2020 Huo et al., 2020 Liu et al., 2020 Gardener et al., 2021	1. Overall: OR=1.54 (95% CI: 1.20, 1.98; I^2=63.4%, p=0.001; 14 studies) 2. 1st-2nd trimester: OR=1.45 (95%CI: 1.01, 2.08; I^2=68.3%; 9 studies) 3. 3rd trimester: OR=2.88 (95%CI: 1.15, 7.17; I^2=15.8%; 2 studies)	When studies investigated the associations of PFASs exposure and birth outcomes using the first quartile of PFASs concentrations as a reference, the estimate with the largest effect was selected.
PFOA	***Yang et al. 2022[29]***	Fei et al., 2007 Stein et al., 2009 Hamm et al., 2010 Chen et al., 2012 Whitworth et al., 2012 Darrow et al., 2013 Bach et al., 2016 Manzano-Salgado et al., 2017 Meng et al., 2018 Sagiv et al., 2018 Chu et al., 2020	1. Overall OR = 1.22 (95% CI: 0.95, 1.57; I^2=58.8%, p=0.003; 14 studies) 2. 1st-2nd trimester: OR=1.23 (95%CI: 0.88, 1.72; I^2=61.5%; 9 studies) 3. 3rd trimester: OR=2.25 (95%CI: 1.07, 4.74; 2 studies)	When studies investigated the associations of PFASs exposure and birth outcomes using the first quartile of PFASs concentrations as a reference, the estimate with the largest effect was selected.

PFAS	Systematic review	Included primary studies	Result	Remark
		Huo et al., 2020 Liu et al., 2020 Gardener et al., 2021		
PFHxS	***Yang et al. 2022***[29]	Hamm et al., 2010 Bach et al., 2016 Manzano-Salgado et al., 2017 Meng et al., 2018 Sagiv et al., 2018 Huo et al., 2020 Gardener et al., 2021	1. OR =1.22 (95% CI: 0.89, 1.69; I^2=55.9%, p=0.035; 7 studies)	When studies investigated the associations of PFASs exposure and birth outcomes using the first quartile of PFASs concentrations as a reference, the estimate with the largest effect was selected.
PFNA	***Yang et al. 2022***[29]	Chen et al., 2012 Bach et al., 2016 Manzano-Salgado et al., 2017 Meng et al., 2018 Sagiv et al., 2018 Huo et al., 2020 Gardener et al., 2021	1. OR=0.97 (95%CI: 0.84, 1.13; I^2=44.6%, p=0.094, 7 studies)	When studies investigated the associations of PFASs exposure and birth outcomes using the first quartile of PFASs concentrations as a reference, the estimate with the largest effect was selected.

4.3.2 Characteristics of recent primary studies

The six identified primary studies published after the search date of the systematic review by Yang et al 2022.[29]

Study name	Year	Country	Design/Confounders	Period	Number of participants in each group	Sample type	Median gestational age when sample was done	PFAS measured	Lab technique	Statistics
Hu et al. [77]	2025	China (Shanghai)	Nested case-control maternal age, BMI, education, annual household income smoking status in the first trimester, parity (1, ≥ 2), season of birth, infant sex. maternal medical information during pregnancy (such GDM, gestational hypertension (GH), hyperthyroidism and hypothyroidism)	**Not clearly reported**	177 PTB cases, 531 controls (total n=708)	Maternal serum	Around **9 weeks** (IQR 7.86–10.0)	PFOA, PFOS, PFNA, PFDA, PFUnDA, 6:2 Cl-PFESA, PFO5DoA	Liquid-liquid extraction + UHPLC-ESI-MS/MS / UHPLC-MS/MS	Conditional logistic regression, restricted cubic spline (RCS), WQS regression, quantile g-computation (QGC), BKMR, subtype analysis, sex-stratified analysis, sensitivity analyses
Liao et al. [78]	2022	China (Guangxi)	Prospective birth cohort maternal age, pre-pregnancy BMI, ethnicity, occupation, gravidity, parity, smoking exposure, alcohol use, cosmetic use, lived in newly decorated house, infants sex	June 2015 – April 2019	122 PTB, 1219 non-PTB (total n=1341)	Maternal serum	Sample obtained before 12 gestational weeks; median not reported	PFDoA, PFUnA, PFDA, PFOS, PFNA, PFOA, PFHxS, PFHpA, PFBS	UPLC-MS/MS (Waters; electrospray ionization negative mode, MRM)	Binary logistic regression, RCS, WQS regression, BKMR
Shen et al. [79]	2022	China (Hangzhou)	Birth cohort Demographic characteristics, including maternal age, prenatal	October 2020 – September 2021	89 PTB, 417 non-PTB (total n=506)	Maternal serum	Before delivery; median/mean sampling GA not reported	14 PFAS homologs including PFOA, PFOS, PFNA,	Solid-phase extraction + UPLC (Acquity UPLC BEH C18); mixture analysis with qgcomp; paper	Spearman correlation, Mann-Whitney U, Kruskal-Wallis, univariate and

Study name	Year	Country	Design/Confounders	Period	Number of participants in each group	Sample type	Median gestational age when sample was done	PFAS measured	Lab technique	Statistics
			BMI, education, occupation, smoking, alcohol drinking, ethnicity, and parity					PFDA, PFUnDA, PFHpA, PFHxS, PFTrDA, PFDoA, PFTeDA, PFDS, PFPeS, PFNS, PFHpS	excerpt does not fully spell out MS detector on the lines reviewed	multivariate linear regression, binary logistic regression, quantile-based g-computation
Siwakoti et al. [80]	2024	USA (Boston, Massachusetts)	Nested case-control within LIFECODES cohort maternal age, race, insurance status, educational status, prepregnancy BMI, and parity	Cohort enrolled 2006–2008	127 preterm cases, 342 controls (total n=469); complete-case repeated-measures dataset: 1485 observations from 448 participants	Maternal plasma	10 weeks at first visit; repeated biomarker visits at 18, 26, 35 weeks	MPAH, PFDA, PFHP, PFHxS, PFNA, PFOA, PFOS, PFOSA, PFUA (PFOSA later excluded from analysis because low detection)	On-line SPE + UHPLC-LC-MS/MS with HESI; CDC-based validated method	Descriptive analyses, Spearman correlations, ICCs, linear mixed-effects models, visit-specific multivariable regression, quantile-based g-computation, weighted analyses with inverse probability weights, stratified analyses
Yu et al. [81]	2022	China (Maoming)	Nested case-control in a family-based birth cohort household annual income, parity, paternal alcohol consumption,	2015–2018	355 preterm cases, 481 term controls (total n=836 families)	Maternal serum, paternal serum, neonatal	Third trimester maternal/paternal blood: mean 32 weeks (range 12–40); cord blood at delivery	PFBA, PFHxA, PFHxS, PFOA, PFOS,	Detailed LC-MS methods in supplement; main paper reports serum PFAS assessment from supplemental liquid	Logistic regression, Spearman rank tests, BKMR, multilevel latent profile analysis (MLPA),

Study name	Year	Country	Design/Confounders	Period	Number of participants in each group	Sample type	Median gestational age when sample was done	PFAS measured	Lab technique	Statistics
			seafood consumption, neonatal sex and environmental tobacco exposure			cord blood		PFNA, PFDA	chromatography–mass spectrometry methods	sensitivity analyses incl. spontaneous PTB and primiparous subgroup
Zhang et al.[82]	2023	USA (eastern Massachusetts)	Prospective prebirth cohort maternal age, maternal and paternal educational level, maternal ethnicity, annual household income, maternal prepregnancy BMI, smoking status, parity, infertility history	April 1999 – November 2002	99 PTB, 1301 non-PTB (total n=1400); folate subpopulation n=898	Maternal plasma	9.6 weeks (IQR 8.7–10.9)	Six PFAS in final analyses: PFOA, PFOS, PFHxS, PFNA, MeFOSAA, EtFOSAA (PFDeA and PFOSA measured but excluded due to low detection)	Online solid-phase extraction + HPLC isotope-dilution tandem mass spectrometry at CDC	Descriptive analyses, Spearman correlations, linear regression, logistic regression, quantile-based g-computation, generalized additive models, multiple imputation (MICE)

BKMR: Bayesian Kernel Machine Regression; CDC: Centers for Disease Control and Prevention; Cl-PFESA: Chlorinated Polyfluoroether Sulfonic Acid; EtFOSAA: N-ethyl perfluorooctane sulfonamidoacetic acid; GA: Gestational Age; HESI: Heated Electrospray Ionization; HPLC: High-Performance Liquid Chromatography; ICC: Intraclass Correlation Coefficient; IQR: Interquartile Range; LC-MS/MS: Liquid Chromatography–Tandem Mass Spectrometry; LIFECODES: Longitudinal Investigation of Fertility and the Environment Study; MLPA: Multilevel Latent Profile Analysis; MPAH: 2-(N-methyl-perfluorooctane sulfonamido) acetic acid; MRM: Multiple Reaction Monitoring; PFAS: Per- and Polyfluoroalkyl Substances; PFBA: Perfluorobutanoic Acid; PFBS: Perfluorobutane Sulfonate; PFDA: Perfluorodecanoic Acid; PFDoA: Perfluorododecanoic Acid; PFHpA: Perfluoroheptanoic Acid; PFHpS: Perfluoroheptane Sulfonate; PFHxA: Perfluorohexanoic Acid; PFHxS: Perfluorohexane Sulfonate; PFNA: Perfluorononanoic Acid; PFNS: Perfluorononane Sulfonate; PFOA: Perfluorooctanoic Acid; PFOS: Perfluorooctane Sulfonate; PFOSA: Perfluorooctane Sulfonamide; PFPeS: Perfluoropentane Sulfonate; PFTeDA: Perfluorotetradecanoic Acid; PFTrDA: Perfluorotridecanoic Acid; PFUA: Perfluoroundecanoic Acid; PTB: Preterm Birth; QGC: Quantile g-Computation; RCS: Restricted Cubic Splines; SPE: Solid-Phase Extraction; UHPLC: Ultra-High-Performance Liquid Chromatography; UPLC: Ultra-Performance Liquid Chromatography; WQS: Weighted Quantile Sum (regression)

4.3.3 Results of primary studies

The results from the 6 primary studies retrieved after the search date in the systematic review by Yang et al. 2022 are presented in the table.

PFAS	N	Study	Median concentration of PFAS	Main results
MPAH	1	**Siwakoti 2023**[80]	0.16 ng/mL (maternal plasma)	**Overall PTB, female offspring:** OR = 1.45 (95% CI 0.98–2.14) per IQR increase; no association in male offspring
PFBA	1	**Yu 2022**[81]	Paternal: 1.25 ng/mL in PTB vs 1.25 in controls; maternal: 1.28 vs 0.70; cord blood: 1.96 vs 1.47	**Paternal serum:** OR = 1.03 (95% CI 0.97–1.10) per 1 ln-ng/mL increase **Maternal serum:** OR = 1.16 (1.09–1.25) per 1 ln-ng/mL increase; **Cord blood:** OR = 1.16 (1.05–1.29) per 1 ln-ng/mL increase **Maternal quartiles:** Q3 vs Q1 OR = 1.66 (1.08–2.56), Q4 vs Q1 OR = 2.70 (1.75–4.18); **Cord blood quartiles:** Q4 vs Q1 OR = 3.28 (2.16–4.98)
PFBS	1	**Liao 2022**[78]	1.26 ng/mL (maternal serum)	**RR=1.21 (0.96-1.53) per log10-ng/ml increase**
PFDA	3	**Hu 2025**[77]	0.93 ng/mL (maternal serum)	**Overall PTB:** Q2 vs Q1 OR = 1.21 (95% CI 0.73–1.99), Q3 vs Q1 OR = 1.77 (1.04–3.01), Q4 vs Q1 OR = 2.79 (1.67–4.65); **sPTB:** Q2 vs Q1 OR = 1.09 (0.59–2.03), Q3 vs Q1 OR = 1.38 (0.72–2.66), Q4 vs Q1 OR = 2.03 (1.16–3.54); **iPTB:** Q2 vs Q1 OR = 1.45 (0.56–3.72), Q3 vs Q1 OR = 2.84 (1.16–6.94), Q4 vs Q1 OR = 3.34 (1.34–8.31)
		Siwakoti 2023[80]	0.29 ng/mL (maternal plasma)	**Placental PTB:** OR = 1.60 (95% CI 1.00–2.56) per IQR increase; **male offspring, placental PTB:** OR = 2.53 (1.25–5.13) per IQR increase
		Yu 2022[81]	Paternal: 0.65 ng/mL in PTB vs 0.73 in controls; maternal: 0.40 vs 0.37; cord blood: 0.10 vs 0.09	**Paternal serum:** OR = 0.83 (95% CI 0.68–1.01) per 1 ln-ng/mL increase; **Maternal serum:** OR = 1.20 (0.95–1.53) per 1 ln-ng/mL increase; **Cord blood:** OR = 1.11 (0.97–1.28) per 1 ln-ng/mL increase; **Family profile "high PFNA and PFDA" vs least exposed:** OR = 2.55 (1.45–4.50)
PFHpA	1	**Liao 2022**[78]	1.41 ng/mL (maternal serum)	RR = 1.34 (1.05–1.71) per 1 log10-unit increase
PFHP	1	**Siwakoti 2023**[80]	0.07 ng/mL (maternal plasma)	**sPTB, above vs below LOD:** OR = 1.77 (95% CI 1.00–3.12)
PFHxA	1	**Yu 2022**[81]	Paternal: 0.03 ng/mL in PTB vs 0.01 in controls; maternal: 0.02 vs 0.02; cord blood: 0.04 vs 0.02	**Paternal serum:** OR = 1.37 (95% CI 1.24–1.51) per 1 ln-ng/mL increase; **Maternal serum:** OR = 0.96 (0.86–1.06) per 1 ln-ng/mL increase; **Cord blood:** OR = 1.46 (1.32–1.62) per 1 ln-ng/mL increase;

PFAS	N	Study	Median concentration of PFAS	Main results
				Paternal quartiles: Q2 vs Q1 OR = 1.63 (1.00–2.66), Q3 vs Q1 OR = 1.50 (1.01–2.22), Q4 vs Q1 OR = 3.19 (2.14–4.78); **Maternal quartiles:** Q2 vs Q1 OR = 0.43 (0.28–0.67), Q3 vs Q1 OR = 0.64 (0.42–0.98), Q4 vs Q1 OR = 0.56 (0.36–0.86); **Cord blood quartiles:** Q2 vs Q1 OR = 3.42 (2.22–5.29), Q3 vs Q1 OR = 5.45 (3.52–8.42), Q4 vs Q1 OR = 4.23 (2.73–6.57)
PFHxS	4	**Liao 2022**[78]	0.10 ng/mL (maternal serum)	RR=0.73 (0.39-1.38) per log10-ng/ml increase
		Siwakoti 2023[80]	0.88 ng/mL (maternal plasma)	PFHxS was not associated with overall or subtype-specific preterm birth
		Yu 2022[81]	Paternal: 0.70 ng/mL in PTB vs 0.82 in controls; maternal: 0.16 vs 0.16; cord blood: 0.06 vs 0.07	**Paternal serum:** OR = 0.75 (95% CI 0.63–0.89) per 1 ln-ng/mL increase; **Maternal serum:** OR = 0.93 (0.80–1.08) per 1 ln-ng/mL increase; **Cord blood:** OR = 1.15 (1.05–1.26) per 1 ln-ng/mL increase
		Zhang 2023[82]	2.4 ng/mL (early-pregnancy plasma)	**Per doubling PFHxS:** in dietary folate Q1 OR = 1.20 (95% CI 0.84–1.69), in dietary folate Q2–Q4 OR = 1.08 (0.85–1.37); in plasma folate Q1 OR = 1.03 (0.67–1.56), in plasma folate Q2–Q4 OR = 0.95 (0.69–1.30)
PFNA	5	**Hu 2025**[77]	1.13 ng/mL (maternal serum)	**Overall PTB:** Q2 vs Q1 OR = 1.22 (95% CI 0.70–2.140), Q3 vs Q1 OR = 1.59 (0.99–2.54), Q4 vs Q1 OR = 2.20 (1.40–3.47); **sPTB:** Q2 vs Q1 OR = 1.37 (0.70–2.59), Q3 vs Q1 OR = 1.45 (0.81–2.61), Q4 vs Q1 OR = 2.03 (1.16–3.54); **iPTB:** Q2 vs Q1 OR = 1.36 (0.49–3.74), Q3 vs Q1 OR = 2.33 (0.95–5.68), Q4 vs Q1 OR = 2.58 (1.00–6.64)
		Liao 2022[78]	0.568 ng/mL (maternal serum)	RR=1.16 (0.69-1.93) per log10-ng/ml increase
		Siwakoti 2023[80]	0.86 ng/mL (maternal plasma)	**Placental PTB:** OR = 1.67 (95% CI 1.06–2.61) per IQR increase; **male offspring, placental PTB:** OR = 4.01 (1.80–8.97) per IQR increase
		Yu 2022[81]	Paternal: 0.44 ng/mL in PTB vs 0.42 in controls; maternal: 0.20 vs 0.12; cord blood: 0.20 vs 0.13	**Paternal serum:** OR = 0.63 (95% CI 0.49–0.82) per 1 ln-ng/mL increase; **maternal serum:** OR = 1.36 (1.01–1.83) per 1 ln-ng/mL increase; **cord blood:** OR = 1.30 (1.09–1.56) per 1 ln-ng/mL increase

PFAS	N	Study	Median concentration of PFAS	Main results
		Zhang 2023[82]	0.6 ng/mL (early-pregnancy plasma)	**Per doubling:** in dietary folate Q1 OR = 1.38 (95% CI 0.85–2.25), in dietary folate Q2–Q4 OR = 1.06 (0.75–1.51); in plasma folate Q1 OR = 1.39 (0.75–2.57), in plasma folate Q2–Q4 OR = 0.87 (0.54–1.41)
PFNS	1	**Shen 2022**[79]	0.050 ng/mL (maternal serum)	**PTB:** OR = 1.59 (95% CI 1.01–2.50) per 1 log-ng/mL increase
PFO5DoA	1	**Hu 2025**[77]	0.27 ng/mL (maternal serum)	**Continuous:** OR = 1.28 (95% CI 1.07–1.52) for overall PTB per unit increase in ln-transformed concentration; **Q2 vs Q1:** OR = 1.17 (0.71–1.92), **Q3 vs Q1:** OR = 1.69 (1.06–2.69), **Q4 vs Q1:** OR = 1.97(1.25–3.09); **sPTB:** Q2 vs Q1 OR = 1.16 (0.63–2.14), Q3 vs Q1 OR = 1.67 (0.93–3.00), Q4 vs Q1 OR = 1.90 (1.07–3.37); **iPTB:** Q2 vs Q1 OR = 0.99 (0.40–2.43), Q3 vs Q1 OR = 1.97 (0.88–4.40), Q4 vs Q1 OR = 1.51 (0.66–3.45)
PFOA	6	**Hu 2025**[77]	7.50 ng/mL (maternal serum)	**Continuous:** OR = 2.080 (95% CI 1.519–2.847) for overall PTB per unit increase in ln-transformed concentration; **sPTB:** OR = 1.96 (1.42–2.71); **iPTB:** OR = 2.51 (1.31–4.80); **overall PTB quartiles:** Q2 vs Q1 OR = 1.25 (0.73–2.14), Q3 vs Q1 OR = 1.39 (0.82–2.36), Q4 vs Q1 OR = 2.80 (1.74–4.50); **sPTB Q4 vs Q1:** 2.85 (1.62–5.03); **iPTB Q4 vs Q1:** 2.61 (1.13–6.06)
		Liao 2022[78]	1.909 ng/mL (maternal serum)	RR=0.76 (0.36-1.58) per log10-ng/mL increase
		Shen 2022[79]	13.6 ng/mL (maternal serum)	**PTB:** OR = 2.17 (95% CI 1.27–3.71) per 1 log-ng/mL increase
		Siwakoti 2023[80]	2.53 ng/mL (maternal plasma)	**Male offspring, placental PTB:** OR = 2.69 (95% CI 1.20–6.01) per IQR increase; **female offspring, placental PTB:** OR = 0.53 (0.29–0.98) per IQR increase
		Yu 2022[81]	Paternal: 2.52 ng/mL in PTB vs 2.66 in controls; maternal: 1.30 vs 0.98; cord blood: 0.65 vs 0.74	**Paternal serum:** OR = 0.91 (95% CI 0.73–1.14) per 1 ln-ng/mL increase; **Maternal serum:** OR = 1.51 (1.27–1.80) per 1 ln-ng/mL increase; **Cord blood:** OR = 1.07 (0.91–1.26) per 1 ln-ng/mL increase
		Zhang 2023[82]	5.6 ng/mL (early-pregnancy plasma)	**Per doubling:** dietary folate Q1 OR = 1.31 (95% CI 0.77–2.24), dietary folate Q2–Q4 OR = 1.01 (0.69–1.48); plasma folate Q1 OR = 1.11 (0.60–2.04), plasma folate Q2–Q4 OR = 1.15 (0.66–2.03)

PFAS	N	Study	Median concentration of PFAS	Main results
PFOS	6	**Hu 2025**[77]	5.79 ng/mL (maternal serum)	**Continuous:** OR = 1.488 (95% CI 1.22–1.81) for overall PTB per unit increase in ln-transformed concentration; **sPTB:** OR = 1.43 (1.13–1.82); **iPTB:** OR = 1.85 (1.15–2.96)
		Liao 2022[78]	0.892 ng/mL (maternal serum)	**Q3 vs Q1:** RR = 1.83 (1.12–3.01); **per 1 log10-unit increase:** RR = 2.25 (1.31–3.87)
		Shen 2022[79]	4.32 ng/mL (maternal serum)	OR=1.52 (0.78-2.97) per 1 log-ng/mL increase
		Siwakoti 2023[80]	7.14 ng/mL (maternal plasma)	No significant PTB or PTB-subtype association (exact figures are not reported in the article, only on a forest plot)
		Yu 2022[81]	Exact PFOS medians not fully visible in retrieved text	**Paternal serum:** OR = 0.44 (95% CI 0.36–0.54) per 1 ln-ng/mL increase; **Maternal serum:** OR = 2.07 (1.70–2.52) per 1 ln-ng/mL increase; **Cord blood:** OR = 0.87 (0.72–1.04) per 1 ln-ng/mL increase
		Zhang 2023[82]	24.8 ng/mL (early-pregnancy plasma)	**Per doubling PFOS:** in dietary folate Q1 OR = 1.55 (95% CI 0.92–2.62), in dietary folate Q2–Q4 OR = 1.14 (0.80–1.64); in plasma folate Q1 OR = 1.51 (0.80–2.85), in plasma folate Q2–Q4 OR = 1.16 (0.69–1.95)
PFPeS	1	**Shen 2022**[79]	0.050 ng/mL (maternal serum)	**PTB:** OR = 0.36 (95% CI 0.17–0.74) per 1 log-ng/mL increase
PFUA / PFUnA / PFUnDA	4	**Hu 2025**[77]	0.97 ng/mL (PFUnDA, maternal serum)	**PFUnDA continuous:** OR = 1.700 (95% CI 1.333–2.168) for overall PTB per unit increase in ln-transformed concentration; **sPTB:** OR = 1.600 (1.243–2.060); **iPTB:** OR = 1.751 (1.146–2.677); **overall PTB quartiles:** Q2 vs Q1 OR = 1.225 (0.702–2.139), Q3 vs Q1 OR = 1.590 (0.994–2.542), Q4 vs Q1 OR = 2.205 (1.402–3.469); **sPTB quartiles:** Q2 vs Q1 OR = 1.374 (0.701–2.588), Q3 vs Q1 OR = 1.453 (0.808–2.613), Q4 vs Q1 OR = 2.028 (1.161–3.542); **iPTB quartiles:** Q2 vs Q1 OR = 1.360 (0.495–3.736), Q3 vs Q1 OR = 2.326 (0.953–5.676), Q4 vs Q1 OR = 2.582 (1.004–6.643)
		Liao 2022[78]	0.422 ng/mL (PFUnA, maternal serum)	**Q2 vs Q1:** RR = 0.621 (95% CI 0.395–0.977); **Q3 vs Q1:** RR = 0.616 (0.384–0.986)

PFAS	N	Study	Median concentration of PFAS	Main results
		Shen 2022[79]	1.33 ng/mL (PFUnDA, maternal serum)	OR=0.87 (0.49-1.53) per 1 log-ng/mL increase
		Siwakoti 2023[80]	0.23 ng/mL (PFUA, maternal plasma)	**Placental PTB:** OR = 1.77 (95% CI 1.00–3.12) per IQR increase
PFAS mixture	3	**Liao 2022**[78]	ΣPFAS = 9.300 ng/mL; ΣPFSA = 2.680 ng/mL (maternal serum)	**ΣPFAS Q2 vs Q1:** RR = 1.707 (95% CI 1.052–2.770); **ΣPFSA Q3 vs Q1:** RR = 1.773 (1.068–2.944)
		Yu 2022[81]	Not applicable	**Family-level "high PFNA and PFDA" exposure profile vs least exposed:** OR = 2.55 (95% CI 1.45–4.50)
		Zhang 2023[82]	Not applicable	**Per doubling of PFAS mixture:** in dietary folate Q1 OR = 1.30 (95% CI 0.77–2.22), in dietary folate Q2–Q4 OR = 1.20 (0.84–1.72); in plasma folate Q1 OR = 1.69 (0.88–3.25), in plasma folate Q2–Q4 OR = 0.99 (0.59–1.66)

∑PFCAs=sum of perfluoroalkanoic carboxylic acids (sum of PFHpA, PFOA, PFNA, PFDA, PFUnA, and PFDoA); ∑PFSAs=sum of perfluoroalkane sulphonic acids (PFBS, PFHxS, and PFOS); The sum of PFASs concentrations (∑PFASs) was calculated as a sum of ∑PFCAs and ∑PFSAs

4.4 Foetal growth restriction

4.4.1 Results from systematic reviews

PFAS	*Systematic review*	Included primary studies	Results
PFOS	***Wright 2025***[31]	Apelberg et al., 2007 Ashley-Martin et al., 2017 Bach et al., 2016 Bell et al., 2018 Buck Louis Cai et al., 202 3 Callan et al., 2016 Cao et al., 2018 Chang et al., 2022 Chen et al., 2012 Chen et al., 2021 Chu et al., 2020 Darrow et al., 2013 de Cock et al., 2016	1. Across all 53 studies, a 30 g BW deficit (95%CI: −41.6, −18.9; I^2 = 42.4%, pQ < 0.0001) was seen with each ln-unit PFOS increase 2. There was no substantial difference across level of study quality 3. No examined variable explained heterogeneity in the meta-regression analyses, either in univariable models or in multivariable models adjusted for central tendency of sample timing 4. There was a small non-significant decrement in average change in BW across studies with increasing median PFOS level (β =−1.4 g; 95%CI: −2.9, 0.1) per unit increase. 5. There was no evidence of a gradient of BW deficits across biomarker sample timing (β range: −24 to −39 g per ln-unit increase). Deficits were larger for the 23 late sample (β =−38.9 g; 95%CI: −59.7, −18.2) than the 12 post-partum sample studies (β =−30.6 g; 95%CI: −60.5, −0.6) and the 18 early sampled studies (β=−23.6 g; 95%CI: −38.7, −8.6)

PFAS	*Systematic review*	Included primary studies	Results
		Eick at al., 2020 Espindola Santos et al., 2021 Gao et al., 2019 Gardener et al., 2021 Govarts et al., 2016 Gyllenhammar et al., 2018 Hamm et al., 2010 Hjermitslev et al., 2020 Kashino et al., 2020 Kwon et al., 2016 Lauritzen et al., 2017 Lenters et al., 2016 Lind et al., 2017 Luo et al., 2021 Maisonet et al., 2012 Manzano-Salgado et al., 2017 Meng et al., 2018 Mwapasa et al, 2023 Peterson et al., 2022 Robledo et al., 2015 Sagiv et al., 2018 Sevelsted et al., 2022 Shen et al., 2022 Shi et al., 2017 Shoaff et al., 2018 Siwakoti et al., 2023 Starling et al., 2017 Valvi et al., 2017 Wang et al., 2019 Wang et al., 2023a Wang et al., 2023b Whitworth et al., 2012 Wikström et al., 2020 Workman et al., 2019 Xiao et al., 2020 Xu et al., 2019 Yao et al., 2021 Zhang et al., 2022 Zhang et al., 2024	6. There was some evidence of funnel plot asymmetry which might be indicative of potential publication bias. The Egger's test of symmetry identified that there may have been four unpublished studies showing generally smaller BW deficits. Imputation of four studies on the right side of the funnel plot decreased the overall effect estimates by 10% from −30 g to −27 g Common confounders in most primary studies: maternal age, parity, BMI, pregnancy weight gain, ethnicity, parental education, socioeconomic status, maternal smoking, maternal alcohol intake, gestational age, fetal sex, sampling timing

PFAS	Systematic review	Included primary studies	Results
		Zheng et al., 2024	
PFOA	*Fu 2025*[32]	Apelberg et al., 2007 Bjerregaard-Olesen et al., 2019 Callan et al., 2016 Cao et al., 2018 Chen et al., 2012 Darrow et al., 2013 Fei et al., 2007 Hamm et al., 2010 Hjermitslev et al., 2020 Kashino et al., 2020 Kobayashi et al., 2022 Lee et al., 2016 Li et al., 2017 Manzano-Salgado et al., 2017 Minatoya et al., 2017 Mphatso et al., 2023 Shen et al., 2022 Shi et al., 2017 Starling et al., 2017 Wang et al., 2019 Washino et al., 2009 Wikström et al., 2019	1. A mean decrease of −81.3 g (95 %CI= −126.1, −36.4; I^2=67.2%) for every log_{10} unit ng/ml increase in PFOA exposure, with great heterogeneity across studies (, p<0.0001). 2. This association was not statistically significant in the group of earlier pregnancy[a] (β=-51.3 g; 95%CI: -129.6, 26.9; 7 studies), whereas it was β=-97.9 (95%CI: -181.8, -13.9; 8 studies) and β=-138.1 (95%CI: -255.9, -20.2; 8 studies) for mid-late pregnancy[b] and after delivery, respectively. 3. No test for differences observed across sample timing strata was provided Common confounders in most primary studies: gestational age, maternal age, BMI, race, parity, smoking, alcohol consumption, baby sex

[a] Earlier pregnancy studies included reports from pre-pregnancy (0 day), the first three months of pregnancy (0 day–13 weeks and 6 days), or the combination of the first and second trimesters (0 day–27 weeks and 6 days)

[b] Mild-to-late pregnancy studies were conducted solely during the second trimester (14 weeks and 0 days to 27 weeks and 6 days), the combination of the second and third trimesters (14 weeks and 0 days to term), or solely during the third trimester (28 weeks and 0 days to term)

PFAS	Systematic review	Included primary studies	Results
		Wu et al., 2012 Xu et al., 2019	
PFHxS	Fu et al. 2025[32]	Apelberg et al., 2007 Bjerregaard-Olesen et al., 2019 Callan et al., 2016 Cao et al., 2018 Chen et al., 2012 Darrow et al., 2013 Fei et al., 2007 Hamm et al., 2010 Hjermitslev et al., 2020 Kashino et al., 2020 Kobayashi et al., 2022 Lee et al., 2016 Li et al., 2017 Manzano-Salgado et al., 2017 Minatoya et al., 2017	1. no statistical significant association between maternal PFHxS exposure (for every log10 unit ng/ml increase) and neonatal birth weight (β=4.6; 95 %CI= −10.6, +19.8; I2=29%, p=0.14). 2. In subgroup analyses by timing of exposure, PFHxS remained non-significantly associated with birth weight across all periods. 3. In subgroup analyses by geographic region, there was no significant association between PFHxS exposure and neonatal birth weight in any region. Common confounders in most primary studies: gestational age, maternal age, BMI, race, parity, smoking, alcohol consumption, baby sex
	Ru et al. 2024[33]	Ashley-Martin, 2017 Bach, 2016 Buck Louis, 2018 Callan, 2016 Chang, 2022 Chen, 2021 Gyllenhammar, 2018 Hamm, 2010 Hjermitslev, 2020 Kashino, 2020 Kwon, 2016 Lenters, 2016	1. The meta-analysis of all 27 studies yielded a decrease of −7.9 g (95% CI –15.0 to –0.7; I^2=0%) in BW per each ln ng/mL increase in PFHxS 2. The pooled effect for the 12 high confidence studies (β=−6.8 g; 95% CI: −16.3 to 2.8; I^2=0%) was smaller than the 11 medium confidence studies. There was no statistically significant difference (p=0.82) in effect size among these three strata of study quality 3. The mean BW deficit among 12 studies with early sampling periods based on our classification (e.g., preconception, trimester 1-only, trimesters 1 and 2 and trimesters 1−3) (β=−7.6 g; 95% CI −16.2 to 1.1) showed slightly larger deficits per each PFHxS ln-unit change than the 10 studies with mid-pregnancy to late-pregnancy sampling (eg, trimester 2-only; trimesters 2 and 3; trimester 3-only; trimesters 2, 3 and at delivery) (β=−3.9 g; 95% CI −17.7 to 9.9). The mean BW deficit for five postpartum serum or plasma sample studies (eg, birth and postbirth) studies was even larger (β=−28.3 g; 95% CI −69.3 to 12.7) but considerably more imprecise. Common confounders in most primary studies: maternal age, prepregnancy BMI, educational level, occupation, family income, smoking and alcohol use, parity, fetal sex

PFAS	Systematic review	Included primary studies	Results
		Li, 2017 Lind, 2017 Luo, 2021 Maisonet, 2012 Marks, 2019 Manzano-Salgado, 2017 Meng, 2018 Sagiv, 2017 Shi, 2017 Shoaff, 2018 Starling, 2017 Valvi, 2017 Wikström, 2020 Workman, 2019 Xu, 2019 Yao, 2021	
PFNA	***Wright 2023[30]***	Bach et al., 2016 Buck Louis et al., 2018 Callan et al., 2016 Chang et al., 2022 Chen et al., 2012 Chen et al., 2021 Gyllenhammer et al., 2018 Hjermitslev et al., 2020	1. A mean decrease of −32.9 g (95%CI: −47.0, −18.7; I2=36%) birthweight per each ln PFNA was observed. 2. The twelve high confidence studies yielded a smaller pooled effect estimate (β = −28.0 g; 95%CI: −49.0, −6.9) than the others. 3. The stratum-specific results based on earlier pregnancy sampling periods in 11 studies showed smaller deficits (β = −22.0 g; 95%CI: −40.1, −4.0) compared to other studies.[c] When restricted to high quality studies, β = −14.6 (95% CI: −38.4, 9.2) in earlier samples as compared to β = −59.1 g (95% CI: −91.0, −27.1) in mid-/late samples. The hypothesis test for differences across sample timing strata was not statistically significant (p = 0.14)

[c] Earlier pregnancy included studies reporting samples from pre-conception (0 days), the first trimester (0 days to13 weeks and 6 days) or a combination of the first and second trimesters (0 days to 27 weeks and 6 days)

PFAS	*Systematic review*	Included primary studies	Results
		Kashino et al., 2020 Kwon et al., 2016 Lenters et al., 2016 Li et al., 2017 Lind et al., 2017 Luo et al., 2021 Manzano-Salgado et al., 2017 Meng et al., 2018 Robledo et al., 2015 Sagiv et al., 2018 Shi et al., 2017 Shoaff et al., 2018 Starling et al., 2017 Valvi et al., 2017 Wang et al., 2016 Wikström et al., 2020 Workman et al., 2019 Xu et al., 2019 Yao et al., 2021	Common confounders in most primary studies: maternal age, parity, BMI, pregnancy weight gain, ethnicity, parental education, socioeconomic status, maternal smoking, maternal alcohol intake, gestational age, fetal sex, sampling timing

5 BREASTFEEDING

5.1 Identified primary studies on exposure through breastfeeding

Table 6 – More recent identified primary studies on exposure to PFAS via breastfeeding and health outcomes

Author study	Study details	Conclusion reported
van Beijsterveldt et al 2026[89]	Sophia Pluto study, The Netherlands Cohort of 371 healthy term-born infants • 150 exclusively breast fed • 97 exclusive formula fed • 124 mix Outcome: alterations in adipokine levels and eating behaviour in the first 2 years of life	*PFAS exposure does not compromise breastfeeding's health benefits on metabolic health and insulin sensitivity until age 2 years*
Bing-Chun Lin 2025[90]	73 mother-preterm infant dyads in China 13 PFAS measured in breast milk or formula at 4 weeks postpartum Outcome: gut microbiota of preterm infants	*Our findings suggest that PFAS exposure through feeding (breast milk or formula) may adversely affect the gut microbiota and normal development of preterm infants, potentially posing health risks*
van Beijsterveldt et al 2025[91]	Sophia Pluto birth cohort, the Netherlands 237 healthy term-born infants • 99 exclusively breast fed • 57 exclusive formula fed • 81 mix 5 PFAS in plasma samples collected at age 3 months and 2 years Outcome: anthropometrics, body composition, blood pressure at 3 years	*higher plasma PFAS levels in the 'first 1000 days of life' associate with negative effects on (linear) growth, body composition and bone mineralization at age 3 years, indicate that PFAS have a negative effect on overall growth* *An increase of 1 ng/mL in plasma PFAS level at age 3 months associates with a decrease in linear growth of 0.069 SDS between birth and age 3 year* *In contrast, exclusive breastfeeding for at least three months was positively associated*

Author study	Study details	Conclusion reported
van Beijsterveldt 2024[92]	372 healthy term-born infants • 150 exclusively breast fed • 97 exclusive formula fed • 125 mix 5 PFAS at age 3 months Outcome: adiposity in the first 2 years of life	*Higher plasma PFAS levels at age 3 months were associated with rapid fat mass percentage gain during the first 6 months of life.*
Zhang 2026[93]	longitudinal study enrolled 114 mother-infant pairs, longitudinally collected human milk and infant fecal samples at 0.5, 1, and 3 months postpartum outcome: Infant neurodevelopment assessed via questionnaires	*Findings establish gut microbiota as a mechanistic link between lactational PFAS exposure and neurodevelopmental delays, identifying the microbiota as a potential therapeutic target.*
Laue 2022[94]	119 infants from the New Hampshire Birth Cohort Exposure: PFOS and PFOA in breast milk at 6 weeks postpartum Mean PFOS 30 ng/l Mean PFOA 22 ng/l Outcome: microbiome in infant stool at 6weeks and 1y	*We found associations of exposure with bacterial diversity and the relative abundance of biologically meaningful bacterial species (especially for PFOS)*
Desalegn 2021[95]	Case cohort in Norwegian Human Milk Study (2606 mother-infant pairs, of which 1326 mother-son and 641 with exposure info) 26 cases of congenital cryptorchidism Exposure: PFAS and other EDCs in breast milk Outcome: self-reported cryptorchidism by mothers	*There were no associations for individual PFASs with any of the cryptorchidism definitions.*
Iszatt 2019[96]	Norwegian Birth cohort (NoMIC) in Ostfold hospital 267 mother-child pairs PFOA and PFOS (among other pollutants) measured in breast milk Median 126.7 ng/l PFOS in breast milk Median 57.6 ng/l PFOA Outcome: gut microbiota of infants sampled 1 month after birth	*Our results suggest that environmental toxicants in breast milk, notably PBDE-28, PFOA, PFOS, and dioxin-like PCB-167, influence infant gut microbial composition and function. These novel findings must be interpreted with caution, and should be replicated in independent populations*

Author study	Study details	Conclusion reported
Lenters 2019[97]	Norwegian Birth cohort of 2606 mother-child pairs PFOA and PFOS (among other pollutants) measured in breast milk and via PK model estimation of postnatal exposure median 117 ng/L PFOS in breast milk Outcome: ADHD diagnosis in nationwide register	*PFOS was associated with increased risk of ADHD, (OR) = 1.77, 95% (CI): 1.16, 2.72) per interquartile range increase in ln-transformed concentrations, with suggestion of sex-specific effects*

5.2 Guidance

Table 7– Overview of available international guidance on breastfeeding

Author	Recommendation/guidance
Australian Government Department of Health and Aged Care *PFAS Guidance Statement (2024)*[98]	*The significant health benefits of breast feeding are well established and outweigh any potential health risks to an infant or child from the possibility of any PFAS being transferred through breast milk.* *PFAS have been detected in human breast milk and breast feeding may contribute to an infant's exposure. enHealth does not recommend that mothers living in or around sites contaminated with PFAS cease breastfeeding.*
American Academy of Pediatrics, 2024[99]	*Breastfeeding is recommended for infants, even when it has been learned that drinking water may have been contaminated with one or more PFAS. Although some environmental pollutants, such as PFAS, can pass to the infant through human milk, the advantages of breastfeeding continue to far outweigh any known risks in nearly every circumstance. However, if a family is known to have been chronically exposed to PFAS in highly contaminated drinking water or other known sources, the clinician should have a discussion with them, weighing their preferences and the advisability of breastfeeding*
US Agency for Toxic Substances and Disease Registry (ATSDR) *Clinical Evaluation and Management:* *PFAS Information for Clinicians - 2024*[100]	*Current science suggests the benefits of breastfeeding or providing human milk outweigh potential risks of PFAS.* *The Centers for Disease Control and Prevention and the American Academy of Pediatrics recommend that nursing mothers continue to breastfeed their babies despite the potential presence of environmental contaminants*

Author	Recommendation/guidance
German National Breastfeeding Commission (Stillcommission) PFAS and breastfeeding: Benefit-risk considerations (2021)[101]	*The National Breastfeeding Commission has considered the possible risks of PFAS intake in breastfed children. Due to the proven benefits of breastfeeding, this commission sees no reason to deviate from the existing breastfeeding recommendation based on the current data. A blood test for PFAS in the mother to determine whether breastfeeding should be restricted is not recommended because, given the current level of exposure in Germany, the benefits of breastfeeding outweigh the risks*
USA National Academies Guidance on PFAS Exposure, Testing, and Clinical Follow-Up[102]	*The benefits of breastfeeding are well known and are supported. Clinicians should explain that PFAS can pass through breast milk from a mother to her baby. PFAS may also be present in other foods, such as the water used to reconstitute formula and infant food, and potentially in packaged formula and baby food. It is not yet clear what types and levels of exposure to PFAS are of concern for child health and development.* *Clinicians should offer PFAS testing to patients likely to have a history of elevated exposure. In all discussions of PFAS testing, clinicians should describe the potential benefits and harms of the testing and the potential clinical consequences (such as additional follow-up), related social implications, and limitations of the testing so that patient and clinician can make a shared, informed decision.*
Governement of Canada – Health Canada[103]	*If you're pregnant, breastfeeding or preparing infant formula and are concerned about exposure to PFAS in your drinking water, you may wish to:* *use another source of drinking water, such as bottled water, or* *install a treatment unit certified as meeting NSF/ANSI standards for PFAS removal*
Flanders Department Care Checklist PFAS (update april 2026)[104]	*The benefits of breastfeeding for the child and the mother continue to outweigh the risk of children being exposed to PFAS through breast milk*
The Walloon government (validated by Conseil Scientifique Indépendant PFAS)[105]	*drink water with the lowest possible PFAS levels (if using bottled water, opt for glass bottles) and do not change the duration of breastfeeding.* *Based on current scientific knowledge, the proven benefits of breastfeeding for infants are more substantial and supported by stronger evidence than the potential health effects of exposure to these environmental chemicals via breastfeeding*
Pediatric Environmental Health Speciality Units (PEHSU)[106]	*Even though PFAS has been found in breast milk, it is still important to breastfeed your baby. The advantages of breast milk far outweigh the effects of PFAS in breast milk*

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