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Correlation of perfluoroalkyl and polyfluoroalkyl substance levels during pregnancy with gestational diabetes mellitus: a systematic review and meta-analysis

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Abstract

Background Perfluoroalkyl and polyfluoroalkyl substances (PFAS) are a major class of contaminants in recent years. Pregnant women are more susceptible to the influence of these compounds, which could heighten the risk of developing gestational diabetes mellitus (GDM). This study aims to conduct an updated systematic review and meta-analysis to determine the correlation between PFAS exposure during pregnancy and the risk of developing GDM and delve into their dose-response relationship.

Methods Pubmed, EMBASE, Web of Science, and Cochrane Library databases were searched. Data were statistically analyzed using Stata 15.0. Fixed-effects (FEM) or random-effects (REM) models were used to combine STD mean difference (SMD) or odds ratio (OR) and 95% confidence intervals (CIs) according to heterogeneity. Dose-response meta-analyses were performed when applicable.

Results A total of 12 papers were included in this study. Meta-analysis results indicated significantly higher levels of PFOA, PFBS, and PFUnDA in GDM patients compared to healthy pregnant women. Pregnant women exposed to high levels of PFOA and PFBS had a significantly increased risk of developing GDM, with ORs of 1.513 and 1.436, respectively. Dose-response analyses indicated that for each 1 ng/ml increase in PFOA and PFBS exposure, the risk of GDM increased by 0.3% and 11.7%, respectively. In contrast, no significant associations were observed between high exposure to other PFAS compounds, such as PFNA, PFHxS, and PFOS, and the development of GDM. Subgroup analyses suggested that PFOA, PFBS, and PFOS levels were higher in GDM patients from China compared to those from Western countries. The differences in PFOA and PFOS levels between GDM and normal pregnant women were more pronounced during late pregnancy.

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Conclusion Exposure to PFOA, PFBS, and PFUnDA during pregnancy is associated with an increased risk of GDM. Given the elevated risk, particularly in the Chinese population, it is crucial to reduce exposure to these substances, especially from the preconception period onward.

Keywords Per- and polyfluoroalkyl substances, Pregnancy, Gestational diabetes mellitus, Dose-response relationship

Introduction

Perfluoroalkyl and polyfluoroalkyl substances (PFAS) are a family of organic pollutants characterized by stable physicochemical attributes and hydrophobic and oleophobic properties, which can be categorized into straight and branched PFAS isomers by the presence or absence of branching in the carbon chain structure. Among them, the most studied substances are perfluorooctanoic acid (PFOA), perfluorooctanesulfonic acid (PFOS), perfluorohexanesulfonic acid (PFHxS), and perfluorooctanesulfonic acid (PFNA). PFAS are introduced into the environment through various industrial and consumer products, such as packaging materials and manufacturing processes, contributing to widespread contamination. These substances accumulate in plants and enter the food chain, posing a significant threat to human health and ecosystems [1]. Studies indicate that certain PFAS compounds degrade slowly in the environment and can persist in humans for over a decade, leading to potential toxicity in multiple organs, including the liver, kidneys, nervous system, and reproductive system, thus representing a serious public health concern [2, 3]. Pregnant women are particularly vulnerable to the effects of PFAS exposure. The unique physiological changes that occur during pregnancy may increase susceptibility to these compounds, potentially elevating the risk of developing glucose metabolism disorders, such as gestational diabetes mellitus (GDM).

GDM is a metabolic disorder that is diagnosed for the first time during pregnancy and accounts for approximately 80% of all cases of hyperglycemia in pregnancy [4–6]. Galectin-3, a β-galactoside-binding lectin, has been implicated in regulating inflammation and insulin resistance, which are key pathways in the pathogenesis of GDM [7]. Research suggests that PFAS exposure may contribute to the development of GDM, and it has been hypothesized that PFAS may affect hormone synthesis, placental implantation, and placental transport function through its action on the placenta, which in turn affects the development of several pregnancy complications such as GDM [8]. PFAS may also impact energy metabolism by disrupting the hormonal balance of the hypothalamic-pituitary-adrenal (HPA) axis. Most studies have reported a connection between PFAS and a higher risk of developing GDM [9–13]. However, a few studies have found no such link [14–16]. For example, a cohort study conducted in Spain indicated that PFAS exposure was significantly and positively correlated with the risk of developing impaired glucose tolerance but did not necessarily increase the risk of GDM [17].

To date, epidemiologic research on the association between PFAS exposure during pregnancy and its effects on glucose homeostasis and GDM remains limited. This gap in comprehensive studies highlights the importance of our research. A review in 2020 was the first to analyze the correlation between PFAS exposure and GDM risk in pregnant women and indicated a significant association between PFOA exposure and an increased risk of GDM [18]. However, this review included only nine studies and focused on a limited number of PFAS isoforms. In recent years, a growing body of studies has expanded this research, incorporating additional PFAS isoforms and considering both prenatal and preconception exposure. Thus, the present study aims to conduct an updated meta-analysis and systematic review, synthesizing the latest evidence on PFAS exposure and GDM risk while exploring potential dose-response relationships.

Materials and methods

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to explore the correlation between the dependent variable (PFAS) and the independent variable (GDM). This study was registered on the PROSPERO website (ID: CRD42023477293).

Literature search

Four databases (Pubmed, EMBASE, Web of Science, and Cochrane Library) were searched in this study from their establishment to October 16, 2023, for all studies exploring the correlation between PFAS and GDM. The search formula is detailed in the Appendix.

Back-to-back searches were conducted by two investigators. Additionally, manual searches were conducted to identify any relevant articles not captured by the database queries. All articles retrieved from advanced database searches were imported into Endnote X9 for management.

Literature screening

Inclusion criteria

Literature exploring the correlation between PFAS exposure during pregnancy and the development of GDM, or the effect of PFAS exposure on the risk of developing GDM; exposure substances were PFAS, including but not limited to PFOA, PFNA, PFOS, PFDA, and PFHxS;

observation results were GDM, including ORs with 95% CIs for the association between PFAS exposure and GDM risk, or PFAS levels in pregnant women with and without GDM; there was no restriction on the type of literature, although only studies published in English were considered.

Exclusion criteria

(1) Studies without full-text availability or those lacking essential statistical data, such as OR, HR, and 95% CI;
(2) Animal studies (e.g., pharmacologic or pharmacokinetic studies);
(3) Non-thesis literature such as case reports, letters, abstracts, as well as conference papers, reviews, and meta-analyses;
(4) Repeatedly published literature;
(5) Non-English literature.

Data extraction

Data was independently extracted by two investigators from studies that met the inclusion/exclusion criteria. The following information was collected: first author, year of publication, study site, study type, sample size, sampling gestational weeks, type of PFAS, duration of exposure, effect estimates (OR and 95% CI), chemical analysis methods, and covariates.

Quality assessment

The quality of the included literature was independently assessed by both investigators using the Newcastle Ottawa Scale (NOS) [19], including eight items across three domains: selection, exposure/outcome, and comparability. Each item was rated with a maximum of 1 point in the selection and exposure/outcome domains and 2 points in the comparability domain [20]. Based on NOS scores, we categorized the studies into three categories: high quality (≥7 points), moderate quality (4–6 points), and low quality (<4 points) [21].

Table 1 Dose ranges of substance exposure

PFASs	Study	Minimum exposure (ng/mL)	Maximum exposure (ng/mL)
PFOA	Huangfang Xu 2020	2.81	52.29
	Nuria Matilla-Santander 2017	0.28	31.64
	Lu Zang 2023	7.94	14.4
PFOS	Huangfang Xu 2020	1.38	86
	Nuria Matilla-Santander 2017	0.28	38.58
	Lu Zang 2023	4.15	9.5
PFBS	Huangfang Xu 2020	0	3.94
	Lu Zang 2023	0.01	0.04

Statistical analysis

Qualitative meta-analysis was performed when more than two data groups met the inclusion criteria. Both unadjusted and adjusted data were extracted from the original studies. Specifically, unadjusted data were pooled for univariate analysis, while adjusted data were pooled for multivariate analysis.

During meta-analysis, fixed-effects (FEM) and random-effects (REM) models were used to combine standardized mean differences (SMD), OR, and 95% CI. OR was used to estimate risk for all studies, while SMD was employed to synthesize continuous data. Statistical heterogeneity between studies was measured using I^2. An I^2 value ≤ 50% indicated low heterogeneity, and the FEM was employed for analysis. If I^2 >50%, indicating high heterogeneity, the REM was used [22]. In cases of high heterogeneity, sensitivity analysis or meta-regression was conducted to explore potential sources of heterogeneity.

Publication bias was assessed using Egger's linear regression asymmetry test [23]. All statistical analyses were conducted using Stata software version 15.0 (StataCorp, College Station, TX, USA). A p-value of < 0.05 was considered statistically significant for all analyses, except for the Egger test, where a p-value > 0.05 was indicative of no publication bias.

Subgroup analyses were performed when sufficient data were available. The studies were stratified based on the following factors: study location (China or other countries), year of publication (before 2020 or 2020 and beyond), timing of exposure (preconception, early pregnancy, or late pregnancy), and methods of chemical analysis (HPLC or UPLC).

The dose-response relationship between PFAS exposure and the risk of GDM was analyzed when sufficient data were available. The generalized least squares method (GLSM) was used to calculate the OR and its 95% CI for the risk of developing GDM with different doses of PFAS. For each 1 ng/mL increase in PFAS exposure, the 95% CI was calculated using a dose-response approach [24]. Dose-response analysis was conducted using data from three studies—Xu 2022 [10], Zang 2023 [11], and Matilla-Santander 2017 [17]—that provided original dose-group data (Table 1). Studies lacking dose-specific information were excluded from this analysis. To assess potential non-linear relationships between PFAS exposure and GDM risk, we employed restricted cubic splines (RCS) with four knots located at the 5th, 35th, 65th, and 95th percentiles [25]. Non-linearity was evaluated by comparing the model fit of the RCS model to a linear model using likelihood ratio tests. The results indicated that the linear model provided an adequate fit for the data, as the non-linear terms were not statistically significant (p > 0.05). Therefore, we adopted the linear assumption for the dose-response analysis. The GLSM assumes a

linear or log-linear relationship between PFAS exposure and GDM risk and that the variance-covariance matrix of effect estimates is correctly specified, accounting for correlations between dose levels within each study. To ensure the robustness of our findings, we conducted sensitivity analyses by excluding studies with extreme dose ranges or high heterogeneity. These sensitivity analyses confirmed that the results were consistent and not unduly influenced by any individual study.

Results

Results of literature search and screening

A total of 88 relevant articles were retrieved from the four databases. After excluding 10 duplicates, 17 articles were removed based on title and abstract screening for the following reasons: 12 were irrelevant to the research topic, 3 were reviews or meta-analyses, 1 was an animal study, and 1 was a mechanism study. Upon further reading of the full text, four articles were excluded for the following reasons: 1 was irrelevant to the research topic, and 3 were meta-analyses. Of the remaining 20 articles, 3 were excluded due to incomplete statistical data, and 5 were excluded as they only included abstract and irrelevant exposures or/and results. A total of 12 articles were finally included in the study (Fig. 1).

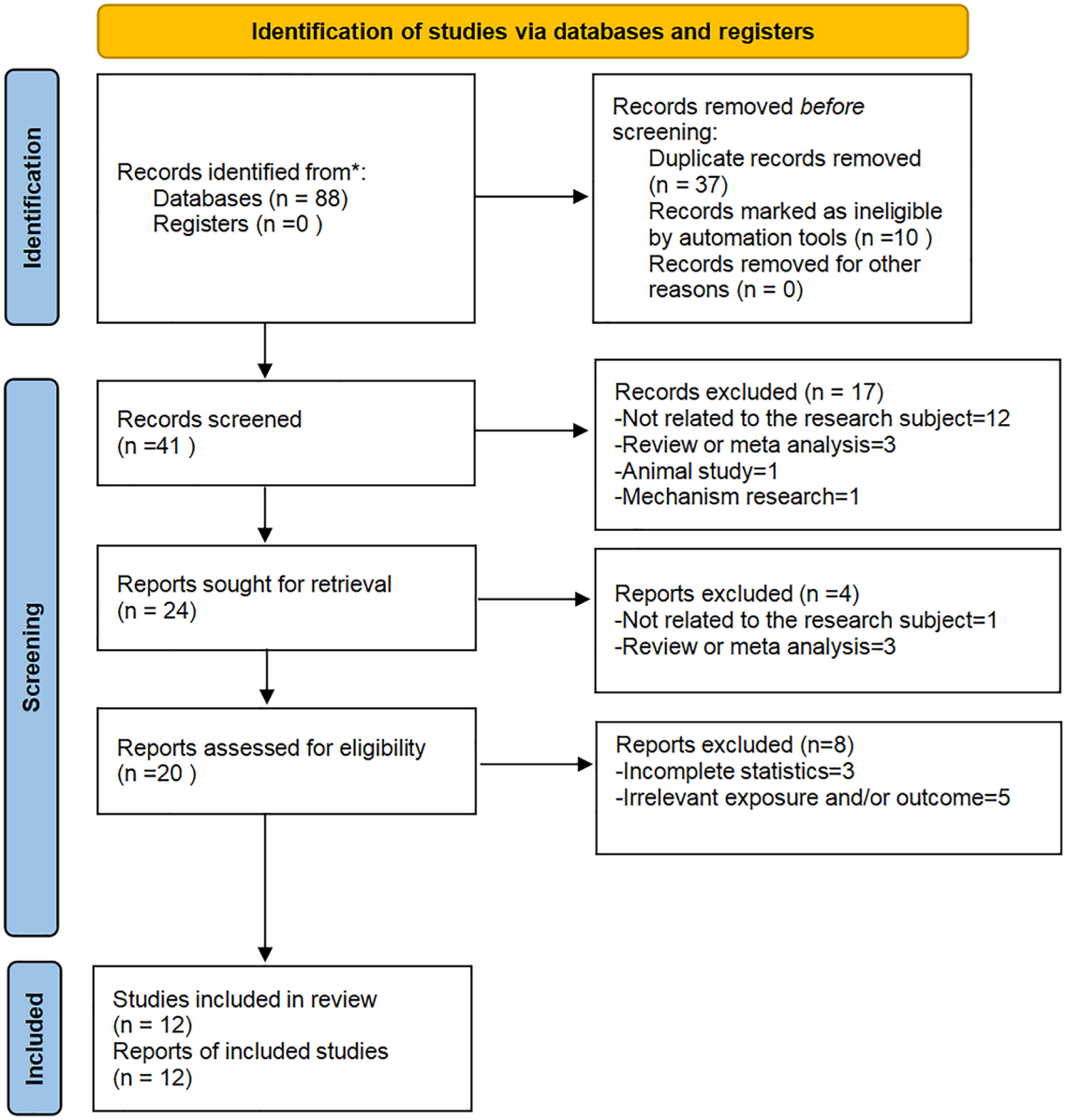

Fig. 1 PRISMA flow diagram of the retrieved eligible articles

Literature characteristics and quality assessment

Table 2 summarizes the characteristics of all articles included in the analysis. The 12 included articles were observational studies, of which 6 were cohort studies [9, 12, 14, 15, 17, 26] and 6 were case-control studies [10, 11, 13, 16, 27, 28]. Most of the studies were conducted in China [10–13, 16, 27, 28], followed by the United States [9, 26]; some studies were conducted in Canada [14], Spain [17], and Denmark [15]. Of the 12 studies, 6 were published between 2015 and 2020, and the other 6 were published between 2020 and 2023. One article [9] was sampled during preconception, 6 [10, 11, 17, 26–28] in early pregnancy, 2 [13, 15] in late pregnancy, and the rest did not mention the specific sampling time. Regarding chemical analysis methods, four studies employed HPLC [9, 12, 15, 17], while six studies utilized UPLC [10, 11, 13, 14, 16, 27]; the remaining studies did not specify the analytical method. All articles involved PFOA and PFOS: 11 involved PFNA, 8 involved PFDA, and 11 involved PFHxS, indicating that the above five substances were the most common substances in PFAS; the remaining substances, such as PFOSA, PFDA, and PFBA, were mentioned in different articles, respectively. As shown in Table 3, the quality of the included 12 eligible articles was assessed: 3 received an NOS score of 8, and 9 received an NOS score of 9, indicating high quality.

Results of meta-analysis

Correlation between PFOA exposure and GDM

A total of 10 studies reported PFOA levels in both GDM patients and normal pregnant women. Given the significant heterogeneity (I^2 = 98.9%), a random-effect model (REM) was employed for the analysis. The pooled SMD was 1.809 (95% CI: 1.106–2.513, $p < 0.001$), indicating that PFOA levels were significantly higher in GDM patients compared to normal pregnant women.

In addition, 8 studies reported the correlation between PFOA exposure levels and the risk of developing GDM. With moderate heterogeneity (I^2 = 51.6%), a random-effect model was again utilized. The results revealed a significant correlation between higher PFOA exposure levels and an increased risk of GDM (OR: 1.513, 95% CI: 1.248–1.833, $p = 0.002$). For each standard deviation increase in PFOA exposure, the risk of developing GDM increased significantly (95% CI:1.071–1.377, $p = 0.002$). Similar results were obtained by univariate and multivariate analyses, as shown in Table 4.

Further dose-response analysis demonstrated a linear relationship between PFOA exposure and GDM risk in the univariate analysis. Specifically, each 1 ng/mL increase in PFOA exposure was associated with a 0.3% increase in the risk of developing GDM (OR:1.003, 95% CI:0.992, 1.015, $p = 0.571$). After adjusting for covariates such as maternal age at delivery, sampling time, number of previous births, educational level, and lipid levels, the risk of developing GDM remained elevated (OR:1.021, 95% CI:0.985, 1.059, $p = 0.257$), as shown in Fig. 2A and B.

Correlation between PFBS exposure and GDM

A total of 5 studies examined PFBS levels in GDM patients and normal pregnant women. Given the substantial heterogeneity (I^2 = 90.3%), REM was employed for the analysis. The pooled SMD was 0.282 (95% CI:0.008–0.557, $p = 0.044$), indicating that PFBS levels were significantly higher in patients with GDM compared to normal pregnant women. Risk analysis of PFBS exposure revealed that pregnant women exposed to high levels of PFBS had a significantly increased risk of developing GDM (OR: 1.436, 95% CI: 1.133–1.820, $p = 0.003$). This association was consistent across both univariate and multivariate analyses, as shown in Table 4.

Moreover, dose-response analysis indicated a linear relationship between PFBS exposure and the risk of developing GDM, following adjustment for covariates. Specifically, for each 1 ng/mL increase in PFBS exposure, the risk of developing GDM increased by 11.7% (OR:1.117, 95% CI:0.988, 1.263, $p = 0.076$), as shown in Fig. 2C.

Correlation between PFUnDA exposure and GDM

Five studies compared the differences in PFUnDA levels between GDM patients and normal pregnant women. Since $I^2 = 99.3\%$, REM was used for analysis. The pooled SMD was 1.207 (95% CI: 0.082–2.331, $p = 0.035$), suggesting that PFUnDA levels were significantly higher in GDM patients than in normal pregnant women. However, the results of risk data analysis indicated that an increase in PFUnDA exposure per standard deviation (SD) was not significantly associated with an increased risk of developing GDM, as shown in Table 4.

Correlation between PFOS exposure and GDM

A total of 10 articles reported PFOS levels in GDM patients compared to normal pregnant women. Due to substantial heterogeneity (I^2 = 98%), REM was applied. Although PFOS levels were found to be higher in GDM patients than in normal pregnant women, the difference was not statistically significant. The pooled SMD was 0.374 (95% CI:-0.123-0.872, $p = 0.14$). Furthermore, the risk analysis showed no significant association between PFOS exposure and the risk of developing GDM, as shown in Table 4.

However, dose-response analysis indicated a linear relationship between PFOS exposure and the risk of developing GDM. Specifically, for each 1 ng/mL increase in PFOS exposure, there was a 0.6% increase in the risk of developing GDM (OR:1.006, 95% CI:0.987, 1.025,

Table 2 Characteristics of literature included in the meta-analysis

First author	Published year	Country	Mean age of participants	Sample size	Study design	Sampling time	PFASs	Method of chemical analysis	Adjusted variables
Cuilin Zhang	2015	US	29.7	258	Cohort	Preconception	PFOA, Et-PFOSA-AcOH, Me-PFOSA-AcOH, PFDeA, PFNA, PFOSA, PFOS	HPLC-MS/MS	age, BMI, race, parity
Yuxin Wang	2018	China	29.5	252	case control	Not mentioned	n-PFOA, PFNA, PFDA, PFUnDA, n-PFOS, PFHxS, 1 m-PFOS, 3 m + 4 m-PFOS, 5 m-PFOS, 6 m-PFOS	UPLC-MS/MS	BMI, gestational weight gain, race, maternal education, parity, maternal drinking during pregnancy, household income
Guoqi Yu	2021	China	29.1	2747	cohort	Not mentioned	PFOA, PFOS, PFNA, PFDA, PFUnDA, PFHxS, PFDoA, PFBS, PFHpA, PFOSA	HPLC-MS/MS	maternal age, BMI, education, smoking, parity, physical activity, economic status
Huangfang Xu	2020	China	29.7	1575	case control	Early pregnancy	PFOA, PFOS, PFBS, PFDA, PFUA, PFNA, PFHpS, PFDoA, PFHxS, PFHpA, PFOSA, PFDS	UPLC-Q/TOF MS	maternal age, sampling time, BMI, parity, serum lipids, educational level
Gabriel D. Shapiro	2016	Canada	33	1259	cohort	Not mentioned	PFOA, PFOS, PFHxS	UPLC-MS-MS	maternal age, BMI, education
Lu Zang	2023	China	31.6	590	case control	Early pregnancy	PFBA, PFPeA, PFHxA, PFHpA, PFOA, PFNA, PFDA, PFUnDA, PFDoDA, PFBS, PFPeS, PFHxS, PFHpS, PFOS, 6:2 Cl-PFESA, 8:2 Cl-PFESA	UPLC-MS-MS	maternal age, pre-pregnancy BMI, education, spontaneous abortion times, pregnancy mode, parity, sampling time, serum lipids
Chenye Xu	2022	China	31.5	340	case control	1–2 days before the delivery	PFHpA, PFOA, PFNA, PFDA, PFUnDA, PFDoA, PFTrDA, PFHxS, PFOS, PFDS, 4:2FTS, ADONA, 6:2FTS, 6:2Cl-PFESA, 8:2Cl-PFESA	UPLC-MS-MS	maternal age, pre-pregnancy BMI, education, occupation, smoking, alcohol drinking, ethnicity, menstrual cycle, menarche age, parity
Nuria Matilla-Santander	2017	Spain	31.9	1240	cohort	13 weeks of gestation	PFOA, PFOS, PFHxS, PFNA	HPLC-MS/MS	country of birth, BMI, previous breastfeeding, parity, sampling time, physical activity, relative Mediterranean Diet Score
Damaskini Valvi	2017	Denmark	29.2	604	cohort	34 weeks of gestation	PFOS, PFOA, PFHxS, PFDA, PFNA	HPLC-MS/MS	maternal age at delivery, pre-pregnancy BMI, parity, education, smoking during pregnancy
Yingying Zhang	2023	China	33.2	204	case control	First-trimester visit	PFBA, PFPeA, PFHxA, PFHpA, PFOA, PFNA, PFDA, PFDoA, PFTrA, PFTeA, PFBS, PFHxS, PFOS, 6:2 Cl-PFESA, 8:2 Cl-PFESA, PFOSA	UPLC-MS-MS	maternal age, BMI, parity, fetal sex
Xin Liu	2019	China	29.3	189	case control	First-trimester visit	1 m-PFOS, 3 m-PFOS, 4 m-PFOS, 5 m-PFOS, 6 m-PFOS, 6 m-PFOA, L-PFOS, L-PFOA, PFBA, PFPeA, PFHxA, PFHpA, PFOA, PFNA, PFDA, PFUnDA, PFDoDA, PFTrDA, PFBS, PFHxS, PFOS	Not mentioned	maternal age, BMI, parity, fetal sex, serum lipids
Emma V. Preston	2020	US	31.9	1540	cohort	First prenatal visit (median 9.7 weeks gestation)	PFOS, PFOA, PFHxS, PFNA, EtFOSAA, MeFOSAA	Not mentioned	age at enrollment, GCT blood glucose, alternative healthy eating index score, physical activity, pre-pregnancy BMI, education, race, smoking, family history of diabetes, history of breastfeeding, annual household income, prior history of GDM/parity

Table 3 Quality assessment for all the studies included

First author	Published year	Quality indicators			Total quality scores
		Selection	Comparability	Outcome	
Cuilin Zhang	2015	4	2	3	9
Yuxin Wang	2018	4	2	3	9
Guoqi Yu	2021	4	2	3	9
Huangfang Xu	2020	4	2	3	9
Gabriel D. Shapiro	2016	4	2	2	8
Lu Zang	2023	4	2	3	9
Chenye Xu	2022	4	2	3	9
Nuria Matilla-Santander	2017	4	2	3	9
Damaskini Valvi	2017	4	2	2	8
Yingying Zhang	2023	4	2	3	9
Xin Liu	2019	4	2	3	9
Emma V. Preston	2020	4	2	2	8

Table 4 Results of risk data analysis

PFAS		High level exposure		Increased exposure per SD	
		Combined OR (95% CI)	*p*	Combined OR (95% CI)	*p*
PFOA	Univariate	1.319 (0.95, 1.831)	0.098	1.167 (0.991, 1.373)	0.064
	Multivariate	1.625 (1.282, 2.06)	0	1.289 (1.057, 1.571)	0.012
PFBS	Univariate	1.554 (1.088, 2.218)	0.015	/	
	Multivariate	1.349 (0.982, 1.853)	0.065		
PFUnDA	Univariate	/		0.947 (0.732, 1.226)	0.679
	Multivariate			0.935 (0.763, 1.145)	0.516
PFOS	Univariate	0.953 (0.662, 1.373)	0.789	0.945 (0.852, 1.048)	0.285
	Multivariate	1.213 (0.949, 1.549)	0.123	1.001 (0.902, 1.111)	0.987

$p = 0.526$). After adjusting for covariates, the risk of developing GDM increased, as shown in Fig. 2D and E.

Correlation between exposure to other PFAS substances and GDM

The results of continuous data analysis showed slightly decreased dose levels of PFNA, PFHxS, PFHpA, and 8:2 CL-PFESA, and slightly increased dose levels of PFDA, PFDoA, and 6:2 CL-PFESA in patients with GDM compared to normal pregnant women. However, none of these differences reached statistical significance (Table 5). Additionally, the pooled risk data analysis confirmed that exposure to elevated levels of PFNA, PFHxS, and PFDA in pregnant women was not significantly associated with an increased risk of developing GDM.

Subgroup analysis

Subgroup analyses were performed for PFOA, PFBS, and PFOS based on study site, publication year, sampling period, and methods of chemical analysis, as shown in Table 6. The results of these analyses revealed that the combined ORs for PFOA and PFOS in studies conducted in China were significantly higher than those in studies from Western countries. This suggested that the exposure levels of PFOA, PFBS, and PFOS were higher among pregnant women in China, resulting in an elevated risk of developing GDM compared to Western countries. The pooled SMD of PFOA and PFOS was significantly higher than that in the preconception and early pregnancy subgroups exposed to the same substances, indicating that the disparity in exposure levels between GDM patients and normal pregnant women was more pronounced in late pregnancy. Furthermore, the combined OR of PFOA and PFOS in the articles published in the year 2020 and later was significantly greater than that published before 2020. This suggests that the association between higher levels of PFOA and PFOS exposure and the risk of developing GDM may be influenced by the study site and publication time. Finally, no significant differences were found in the pooled SMD values for PFOA and PFOS between studies employing different methods of chemical analysis.

Sensitivity analysis

Sensitivity analyses were performed on the substances with high heterogeneity (PFOA and PFDA). The results indicated that the heterogeneity of PFOA data was derived from the literature by Zhang 2015 [9] and Xu 2022 [13]. After excluding these two articles, the analysis of continuous data yielded consistent results, with a recombined SMD of 0.079 (95% CI:0.01–0.149) using a FEM, and there was no between-study heterogeneity ($I^2 = 17.7\%$, $p = 0.29$). The heterogeneity of PFDA data was derived from the literature [12, 13]. After removing the

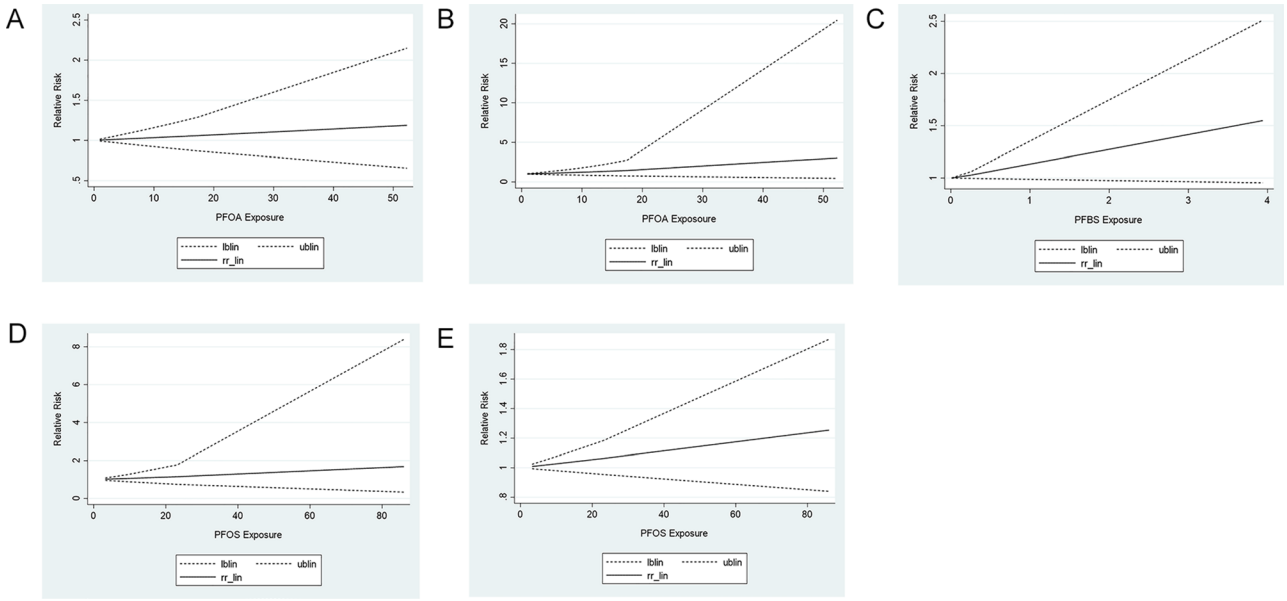

Fig. 2 Dose-response relationship plot between PFAS exposure and GDM. Note: (**A**) PFOA univariate (**B**) PFOA multivariate (**C**) PFBS multivariate (**D**) PFOS univariate (**E**) PFOS multivariate

Table 5 Results of continuity data analysis

PFAS	Combined SMD	95% CI	*p*
PFNA	-0.002	-0.074, 0.069	0.948
PFHxS	-0.111	-0.367, 0.144	0.393
PFHpA	-0.92	-1.861, 0.022	0.055
PFDA	0.056	-0.254, 0.366	0.724
PFDoA	0.028	-0.051, 0.108	0.485
6:2CL-PFESA	2.057	-0.528, 4.642	0.119
8:2CL-PFESA	-0.804	-0.281, 0.113	0.404

two articles, continuous data analysis yielded the same result, with a recombined SMD of 0.029 (95% CI:-0.064-0.121) using a FEM, and there was no between-study heterogeneity ($I^2 = 0\%$, $p = 0.608$).

Publication bias

Publication bias was assessed using Egger's regression test on 10 studies reporting PFOS levels. The results suggested $p = 0.289$, indicating no publication bias.

Discussion

Currently, various studies have produced conflicting results on the relationship between exposure to PFAS and glucose metabolism disorders, leaving their correlation uncertain.

To address this, we conducted a comprehensive analysis to explore the potential association between PFAS exposure and the development of GDM. After literature screening, a total of 12 articles were included, involving 10,798 pregnant women. The pooled analysis of continuous data revealed significantly higher levels of PFOA, PFBS, and PFUnDA in GDM patients compared to normal pregnant women. Additionally, the pooled analysis of risk data demonstrated a significant increase in the risk of developing GDM with higher doses of PFOA and PFBS exposure. Specifically, for each 1 ng/ml increase in PFOA and PFBS exposure, the risk of developing GDM increased by 0.3% and 11.7%, respectively. However, high exposure to other substances such as PFNA, PFHxS, PFHpA, 8:2 CL-PFESA, PFDA, PFDoA, and 6:2 CL-PFESA was not significantly correlated with the development of GDM. Subgroup analyses revealed that the dose levels of PFOA, PFBS, and PFOS were higher in GDM patients in the Chinese literature than in the Western literature, and the risk of GDM in Chinese pregnant women exposed to the above substances may also be greater. Moreover, the difference in PFOA and PFOS levels between GDM patients and normal pregnant women was more pronounced in late pregnancy compared to preconception and early pregnancy. Regardless of the pregnancy stage, exposure to PFOA, PFBS, and PFOS was associated with an increased risk of developing GDM.

The source of heterogeneity for most substances was the literature by Xu 2022 [13]. We found that the sampling time of this study was conducted 1–2 d before labor, while sampling was conducted in early or late pregnancy in the rest of the literature, suggesting that this may be the main cause of heterogeneity.

Previous literature has reported that since 2002, there has been a gradual shift in the production base of PFAS from North America and Europe to China. By 2006, China significantly increased its PFAS production from over 30 tons per year in 2001 to an average of 250–300

Table 6 Results of subgroup analysis

PFAS	Study site		Publication year		Sampling period			Methods of chemical analysis	
	China	Western countries	before 2020	2020 and later	Preconception	Early pregnancy	Late pregnancy	HPLC	UPLC
PFOA									
Combined SMD (95% CI)	2.405 (1.516, 3.294)	0.759 (-0.602, 2.121)	0.535 (-0.166, 1.236)	3.829 (2.617, 5.041)	2.493 (2.045, 2.94)	0.102 (-0.039, 0.243)	16.921 (-16.594, 50.435)	0.045 (-0.06,0.149)	0.045 (-0.135,0.225)
Combined OR (95% CI)	1.954 (1.538, 2.483)	0.952 (0.690, 1.314)	0.862 (0.6, 1.237)	1.889 (1.503, 2.37)	/	1.804 (1.436, 2.265)	1.071 (0.709, 1.617)	/	/
PFOS									
Combined SMD (95% CI)	0.529 (-0.136, 1.193)	0.005 (-0.188, 0.197)	-0.035 (-0.259, 0.19)	0.775 (-0.094, 1.644)	0.142 (-0.251, 0.534)	0.026 (-0.079, 0.132)	1.836 (-2.115, 5.787)	0.004 (-0.107,0.115)	0.015 (-0.089,0.118)
Combined OR (95% CI)	1.253 (0.958, 1.641)	0.976 (0.715, 1.330)	0.887 (0.629, 1.249)	1.281 (0.995, 1.649)	/	1.207 (0.944, 1.543)	1.156 (0.747, 1.789)	/	/
PFBS									
Combined SMD (95% CI)	0.282 (0.008, 0.557)	/	0 (-0.302, 0.302)	0.347 (0.027, 0.667)	/	0.336 (-0.072, 0.744)	/	/	/

tons per year [29]. As the world's largest producer and consumer of PFAS, and with its large population, China faces a heightened risk of PFAS exposure [30]. Studies have shown that PFAS concentrations in drinking water and environmental media in China are significantly higher than in many Western countries, primarily due to intensive industrial activities and pollution [30]. Moreover, global emission inventories indicate that China contributes significantly to global PFAS production and emissions, exacerbating environmental and human exposure levels [29]. Research on PFAS isomer profiles in maternal and cord blood samples has underscored the role of industrial sources and transplacental transfer in increasing PFAS exposure among Chinese populations [31]. Our subgroup analysis also revealed that Chinese patients with GDM had higher levels of PFAS than patients from other regions, suggesting that pregnant women in China may be at an elevated risk of developing GDM due to PFAS exposure. Therefore, it is imperative to prioritize the development of advanced industrial technologies and the restructuring of industrial production processes to mitigate the global production of harmful chemicals, particularly in developing countries and regions. Additionally, the results of our subgroup analysis on chemical analysis methods indicated that the choice of detection method did not significantly influence the overall outcomes of the study.

As Bahreiny [32] noted when examining the relationship between Pro-BNP biomarkers and blood parameters in patients with heart failure, environmental pollutants not only impact metabolic health but may also have profound effects on reproductive health. This aligns with our findings, which suggest that PFAS exposure may elevate the risk of GDM through a similar mechanism. The biological mechanism of the correlation between PFAS and fasting blood glucose (FBG) is still unclear, but some studies have indicated that PPAR receptors are closely related to the regulation of glucose metabolism in vivo [33]. It has been demonstrated that PFAS, 6:2 Cl-PFESA, and 8:2 Cl-PFESA activate PPARα, PPARβ, and PPARγ receptors in mice and humans, and there are structural differences in the affinities of PFAS isoforms and substitutes for the receptors [34–38]. Animal experiments have demonstrated that exposure to PFOS and PFOA can increase blood glucose concentrations and induce insulin resistance in mice by reducing the level of AKT phosphorylation [39–41]. PFNA exposure can alter the expression level of genes related to hepatic glucose metabolism in mice, which can lead to glucose metabolism disorders [42]. Toxicity studies using rat pancreatic β-cells derived from β-insulinoma cells have suggested that PFOA may contribute to pancreatic β-cell toxicity through the induction of oxidative stress and mitochondrial dysfunction [43]. The differences in the

contribution of various PFAS to FBG regulation are likely attributed to variations in the tissue distribution of PFAS isomers and substitutes [44], protein binding capacity [45], PPAR receptor binding capacity [34–38], and the level of influence on the transcription and expression of metabolism-related genes [31, 46]. PFNA, in particular, exhibits intermediate levels of protein binding capacity [47], PPAR receptor binding affinity [48], and transmembrane distribution [38, 49], yet data comparing its ability to disrupt glucose metabolism with that of other PFAS is limited. As evidenced by the dysregulation of nitric oxide (NO) levels in metabolic disorders like polycystic ovary syndrome (PCOS), PFAS exposure may contribute to the development of GDM through mechanisms involving oxidative stress and inflammation [50]. Furthermore, the potential role of antioxidants in mitigating the effects of PFAS exposure is supported by studies demonstrating that melatonin supplementation can reduce oxidative stress and inflammation in diabetic patients [51]. Therefore, our study confirms that PFNA does not fully account for the key component of the combined effect, highlighting the need for further research to better understand the mechanisms through which PFAS and its key components disrupt glucose metabolism.

The results of our study align with those of previous meta-analyses [18], which also identified a positive correlation between high PFOA exposure and an increased risk of developing GDM. In contrast, no significant association was found between high exposure to PFNA, PFHxS, or PFOS and the risk of developing GDM. However, the study only included 9 articles up to 2020 and analyzed only 4 substances, PFOA, PFOS, PFHxS, and PFNA. Moreover, previous studies [52, 53] indicated that high exposure to PAE, PCB, PBDE, and PFAS all significantly increased the risk of developing GDM. However, these studies did not further explore the relationship between exposure to various types of PFAS and the risk of GDM. The present study expanded the scope compared to earlier meta-analyses by including more recent literature, a larger sample size, and a more comprehensive examination of the correlation between various PFAS exposures and GDM based on a broader dataset. Additionally, we performed an analysis of the dose-response relationship between PFAS exposure and the risk of GDM.

Despite the strengths of our study, several limitations should be acknowledged. First, the heterogeneity among studies is evident, possibly due to variations in sampling time, leading to some level of inconsistency in the meta-analysis results, warranting careful interpretation. Second, the majority of the studies included in this analysis were conducted in China, which may limit the generalizability of the findings and impact the comprehensiveness of the results. Additionally, participants in the included studies were predominantly recruited from research institutions, introducing the possibility of selection bias. Furthermore, due to the absence or incompleteness of raw data in some studies, we were unable to impute the missing data and consequently had to exclude these studies from the analysis. This limitation prevented us from incorporating these studies into the meta-analysis, thereby reducing the sample size and limiting the statistical power of the analysis. Although all the included studies were of high quality, these factors should be considered when interpreting the results. Future research with more diverse populations and larger sample sizes is needed to address these gaps. Additionally, previous research by Bahreiny [54] has explored the potential impact of thyroid-related diseases on reproductive health, which provides new ideas for our future research. Specifically, it raises the possibility that environmental pollutants such as PFAS may first disrupt thyroid function and subsequently affect reproductive health, warranting further investigation.

Conclusions

Exposure to PFOA, PFBS, and PFUnDA during pregnancy is associated with a significant increase in the risk of developing GDM. The findings of Bahreiny [55] regarding the relationship between environmental pollutants and adverse reproductive outcomes underscore the importance of public health interventions aimed at mitigating the effects of environmental pollutants, particularly air pollution, on both metabolic and reproductive health. Therefore, it is crucial to monitor PFAS exposure in the environment, regulate PFAS pollution, minimize their production and use, and promote strategies to prevent exposure in women from the preconception period. These measures are essential to reducing the incidence of GDM and safeguarding the health of both mothers and infants.

Supplementary Information

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Supplementary Material 1

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Not applicable.

Author contributions
Dongying Wang, Ting Su, and Sining Luo wrote the original draft text. Meiqi Zhan, Xin Lai, and Jinglin Lin carried out the review and editing of the writing. Dongying Wang, Hongyu Tan, and Xin Lai were responsible for the study's conceptualization. Dongying Wang, Hongyu Tan, and Xin Lai developed the methodology. Dongying Wang, Meiqi Zhan, and Sining Luo conducted the formal analysis and investigation. No one was involved in funding acquisition and resources procurement. Jinglin Lin supervised the study. All authors reviewed previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

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Not applicable.

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Competing interests
The authors declare no competing interests.

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References

1. Nannaware M, Mayilswamy N, Kandasubramanian B. PFAS: exploration of neurotoxicity and environmental impact. Environ Sci Pollut Res Int. 2024;31(9):12815–31.
2. ATSDR. Toxicological profile for perfluoroalkyls [internet]. ATSDR 2021:p. 993.
3. Fenton SE, Ducatman A, Boobis A, DeWitt JC, Lau C, Ng C, Smith JS, Roberts SM. Per- and polyfluoroalkyl substance toxicity and human health review: current state of knowledge and strategies for informing future research. Environ Toxicol Chem. 2021;40(3):606–30.
4. Practice Bulletin No. 180 Summary: gestational diabetes mellitus. Obstet Gynecol. 2017;130(1):244–6.
5. Cho NH, Shaw JE, Karuranga S, Huang Y, da Rocha Fernandes JD, Ohlrogge AW, Malanda B. IDF diabetes atlas: global estimates of diabetes prevalence for 2017 and projections for 2045. Diabetes Res Clin Pract. 2018;138:271–81.
6. Management of Diabetes in Pregnancy. Standards of medical care in Diabetes-2022. Diabetes Care. 2022;45(Suppl 1):S232–43.
7. Bahreiny SS, Ahangarpour A, Aghaei M, Mohammadpour Fard R, Jalali Far MA, Sakhavarz T. A closer look at Galectin-3: its association with gestational diabetes mellitus revealed by systematic review and meta-analysis. J Diabetes Metabolic Disorders. 2024;23(2):1621–33.
8. Zhu Y, Zhang C. Prevalence of gestational diabetes and risk of progression to type 2 diabetes: a global perspective. Curr Diab Rep. 2016;16(1):7.
9. Zhang C, Sundaram R, Maisog J, Calafat AM, Barr DB, Buck Louis GM. A prospective study of prepregnancy serum concentrations of perfluorochemicals and the risk of gestational diabetes. Fertil Steril. 2015;103(1):184–9.
10. Xu H, Zhou Q, Zhang J, Chen X, Zhao H, Lu H, Ma B, Wang Z, Wu C, Ying C, et al. Exposure to elevated per- and polyfluoroalkyl substances in early pregnancy is related to increased risk of gestational diabetes mellitus: A nested case-control study in Shanghai, China. Environ Int. 2020;143:105952.
11. Zang L, Liu X, Xie X, Zhou X, Pan Y, Dai J. Exposure to per- and polyfluoroalkyl substances in early pregnancy, risk of gestational diabetes mellitus, potential pathways, and influencing factors in pregnant women: A nested case-control study. Environ Pollut. 2023;326:121504.
12. Yu G, Jin M, Huang Y, Aimuzi R, Zheng T, Nian M, Tian Y, Wang W, Luo Z, Shen L, et al. Environmental exposure to perfluoroalkyl substances in early pregnancy, maternal glucose homeostasis and the risk of gestational diabetes: A prospective cohort study. Environ Int. 2021;156:106621.
13. Xu C, Zhang L, Zhou Q, Ding J, Yin S, Shang X, Tian Y. Exposure to per- and polyfluoroalkyl substances as a risk factor for gestational diabetes mellitus through interference with glucose homeostasis. Sci Total Environ. 2022;838(Pt 4):156561.
14. Shapiro GD, Dodds L, Arbuckle TE, Ashley-Martin J, Ettinger AS, Fisher M, Taback S, Bouchard MF, Monnier P, Dallaire R, et al. Exposure to organophosphorus and organochlorine pesticides, perfluoroalkyl substances, and polychlorinated biphenyls in pregnancy and the association with impaired glucose tolerance and gestational diabetes mellitus: the MIREC study. Environ Res. 2016;147:71–81.
15. Valvi D, Oulhote Y, Weihe P, Dalgård C, Bjerve KS, Steuerwald U, Grandjean P. Gestational diabetes and offspring birth size at elevated environmental pollutant exposures. Environ Int. 2017;107:205–15.
16. Wang Y, Zhang L, Teng Y, Zhang J, Yang L, Li J, Lai J, Zhao Y, Wu Y. Association of serum levels of perfluoroalkyl substances with gestational diabetes mellitus and postpartum blood glucose. J Environ Sci (China). 2018;69:5–11.
17. Matilla-Santander N, Valvi D, Lopez-Espinosa MJ, Manzano-Salgado CB, Ballester F, Ibarluzea J, Santa-Marina L, Schettgen T, Guxens M, Sunyer J, et al. Exposure to perfluoroalkyl substances and metabolic outcomes in pregnant women: evidence from the Spanish INMA birth cohorts. Environ Health Perspect. 2017;125(11):117004.
18. Wang J, Zhang J, Fan Y, Li Z, Tao C, Yan W, Niu R, Huang Y, Xu Q, Wang X, et al. Association between per- and polyfluoroalkyl substances and risk of gestational diabetes mellitus. Int J Hyg Environ Health. 2022;240:113904.
19. Wells GA, Wells G, Shea B, Shea B, O'Connell D, Peterson J, Welch, Losos M, Tugwell P, Ga SW et al. The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-Analyses. In: *2014*; 2014.
20. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol. 2010;25(9):603–5.
21. Rotenstein LS, Ramos MA, Torre M, Segal JB, Peluso MJ, Guille C, Sen S, Mata DA. Prevalence of depression, depressive symptoms, and suicidal ideation among medical students: a systematic review and meta-analysis. JAMA. 2016;316(21):2214–36.
22. DerSimonian R, Laird N. Meta-analysis in clinical trials revisited. Contemp Clin Trials. 2015;45(Pt A):139–45.
23. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315(7109):629–34.
24. Greenland S, Longnecker MP. Methods for trend Estimation from summarized dose-response data, with applications to meta-analysis. Am J Epidemiol. 1992;135(11):1301–9.
25. J FEH: Regression modeling strategies with applications to models logistic regression and survival analysis. *Springer* 2001.
26. Preston EV, Rifas-Shiman SL, Hivert MF, Zota AR, Sagiv SK, Calafat AM, Oken E, James-Todd T. Associations of Per- and polyfluoroalkyl substances (PFAS) with glucose tolerance during pregnancy in project Viva. J Clin Endocrinol Metab. 2020;105(8):e2864–2876.
27. Zhang Y, Chen R, Gao Y, Qu J, Wang Z, Zhao M, Bai X, Jin H. Human serum poly- and perfluoroalkyl substance concentrations and their associations with gestational diabetes mellitus. Environ Pollut. 2023;317:120833.
28. Liu X, Zhang L, Chen L, Li J, Wang Y, Wang J, Meng G, Chi M, Zhao Y, Chen H, et al. Structure-based investigation on the association between perfluoroalkyl acids exposure and both gestational diabetes mellitus and glucose homeostasis in pregnant women. Environ Int. 2019;127:85–93.
29. Wang Z, Cousins IT, Scheringer M, Buck RC, Hungerbühler K. Global emission inventories for C4-C14 perfluoroalkyl carboxylic acid (PFCA) homologues from 1951 to 2030, part I: production and emissions from quantifiable sources. Environ Int. 2014;70:62–75.
30. Liu L, Qu Y, Huang J, Weber R. Per- and polyfluoroalkyl substances (PFASs) in Chinese drinking water: risk assessment and geographical distribution. Environ Sci Europe. 2021;33(1):6.
31. Beesoon S, Webster GM, Shoeib M, Harner T, Benskin JP, Martin JW. Isomer profiles of perfluorochemicals in matched maternal, cord, and house dust samples: manufacturing sources and transplacental transfer. Environ Health Perspect. 2011;119(11):1659–64.
32. Torfi E, Bahreiny SS, Saki N, Khademi R, Sarbazjoda E, Nezhad IA, Aghaei M. Evaluation of Pro-BNP biomarker in heart failure patients and its relationship with complete blood count parameters: A case–control study. Health Sci Rep. 2024;7(9):e70083.
33. Gross B, Pawlak M, Lefebvre P, Staels B. PPARs in obesity-induced T2DM, dyslipidaemia and NAFLD. Nat Rev Endocrinol. 2017;13(1):36–49.

34. Li CH, Ren XM, Ruan T, Cao LY, Xin Y, Guo LH, Jiang G. Chlorinated polyfluorinated ether sulfonates exhibit higher activity toward peroxisome Proliferator-Activated receptors signaling pathways than perfluorooctanesulfonate. Environ Sci Technol. 2018;52(5):3232–9.
35. Vanden Heuvel JP, Thompson JT, Frame SR, Gillies PJ. Differential activation of nuclear receptors by perfluorinated fatty acid analogs and natural fatty acids: a comparison of human, mouse, and rat peroxisome proliferator-activated receptor-alpha, -beta, and -gamma, liver X receptor-beta, and retinoid X receptor-alpha. Toxicol Sci. 2006;92(2):476–89.
36. Zhang L, Ren XM, Wan B, Guo LH. Structure-dependent binding and activation of perfluorinated compounds on human peroxisome proliferator-activated receptor γ. Toxicol Appl Pharmacol. 2014;279(3):275–83.
37. Wolf CJ, Takacs ML, Schmid JE, Lau C, Abbott BD. Activation of mouse and human peroxisome proliferator-activated receptor alpha by perfluoroalkyl acids of different functional groups and chain lengths. Toxicol Sci. 2008;106(1):162–71.
38. Li CH, Ren XM, Cao LY, Qin WP, Guo LH. Investigation of binding and activity of perfluoroalkyl substances to the human peroxisome proliferator-activated receptor B/δ. Environ Sci Process Impacts. 2019;21(11):1908–14.
39. Du G, Sun J, Zhang Y. Perfluorooctanoic acid impaired glucose homeostasis through affecting adipose AKT pathway. Cytotechnology. 2018;70(1):479–87.
40. Yan S, Zhang H, Zheng F, Sheng N, Guo X, Dai J. Perfluorooctanoic acid exposure for 28 days affects glucose homeostasis and induces insulin hypersensitivity in mice. Sci Rep. 2015;5:11029.
41. Qiu T, Chen M, Sun X, Cao J, Feng C, Li D, Wu W, Jiang L, Yao X. Perfluorooctane sulfonate-induced insulin resistance is mediated by protein kinase B pathway. Biochem Biophys Res Commun. 2016;477(4):781–5.
42. Fang X, Gao G, Xue H, Zhang X, Wang H. Exposure of perfluorononanoic acid suppresses the hepatic insulin signal pathway and increases serum glucose in rats. Toxicology. 2012;294(2–3):109–15.
43. Suh KS, Choi EM, Kim YJ, Hong SM, Park SY, Rhee SY, Oh S, Kim SW, Pak YK, Choe W, et al. Perfluorooctanoic acid induces oxidative damage and mitochondrial dysfunction in pancreatic β-cells. Mol Med Rep. 2017;15(6):3871–8.
44. Fang S, Zhao S, Zhang Y, Zhong W, Zhu L. Distribution of perfluoroalkyl substances (PFASs) with isomer analysis among the tissues of aquatic organisms in Taihu lake, China. Environ Pollut. 2014;193:224–32.
45. Zhong W, Zhang L, Cui Y, Chen M, Zhu L. Probing mechanisms for bioaccumulation of perfluoroalkyl acids in carp (Cyprinus carpio): Impacts of protein binding affinities and elimination pathways. Sci Total Environ. 2019;647:992–9.
46. Stylianou M, Björnsdotter MK, Olsson PE, Ericson Jogsten I, Jass J. Distinct transcriptional response of caenorhabditis elegans to different exposure routes of perfluorooctane sulfonic acid. Environ Res. 2019;168:406–13.
47. Liu X, Zhu Y, Liu T, Xue Q, Tian F, Yuan Y, Zhao C. Exploring toxicity of perfluorinated compounds through complex network and pathway modeling. J Biomol Struct Dyn. 2020;38(9):2604–12.
48. Jackson TW, Scheibly CM, Polera ME, Belcher SM. Rapid characterization of human serum albumin binding for Per- and polyfluoroalkyl substances using differential scanning fluorimetry. Environ Sci Technol. 2021;55(18):12291–301.
49. Nouhi S, Ahrens L, Campos Pereira H, Hughes AV, Campana M, Gutfreund P, Palsson GK, Vorobiev A, Hellsing MS. Interactions of perfluoroalkyl substances with a phospholipid bilayer studied by neutron reflectometry. J Colloid Interface Sci. 2018;511:474–81.
50. Bahreiny SS, Ahangarpour A, Harooni E, Amraei M, Aghaei M, Fard RM. Closer look at Circulating nitric oxide levels and their association with polycystic ovary syndrome: A meta-analytical exploration. Int J Reproductive Biomed. 2025;22(12):943–62.
51. Mohammadpour Fard R, Rashno M, Bahreiny SS. Effects of melatonin supplementation on markers of inflammation and oxidative stress in patients with diabetes: A systematic review and meta-analysis of randomized controlled trials. Clin Nutr ESPEN. 2024;63:530–9.
52. Yao X, Geng S, Zhu L, Jiang H, Wen J. Environmental pollutants exposure and gestational diabetes mellitus: evidence from epidemiological and experimental studies. Chemosphere. 2023;332:138866.
53. Yan D, Jiao Y, Yan H, Liu T, Yan H, Yuan J. Endocrine-disrupting chemicals and the risk of gestational diabetes mellitus: a systematic review and meta-analysis. Environ Health. 2022;21(1):53.
54. Bahreiny SS, Ahangarpour A, Rajaei E, Sharifani MS, Aghaei M. Meta-Analytical and Meta-Regression evaluation of subclinical hyperthyroidism's effect on male reproductive health: hormonal and seminal perspectives. Reprod Sci. 2024;31(10):2957–71.
55. Bahreiny SS, Bastani M-N, Dabbagh MR, Ghorbani H, Aghaei M, Zahedian M, Fard RM. Association between ambient particulate matter and semen quality parameters: a systematic review and meta-analysis. Middle East Fertility Soc J. 2024;29(1):2.

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