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Original Article

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Comprehensive Evaluation of Gestational Diabetes Patients Against Exposure on PFAS and Its Derivatives: An Updated Systematical Review and Meta-Analysis

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Abstract

Background and Aims: Gestational diabetes mellitus (GDM) is characterised by insulin resistance that first manifests during pregnancy. This study aimed to evaluate PFAS exposure as a risk factor for GDM.

Methods: Descriptive Boolean queries were used to search PubMed, Scopus, and Web of Science for articles published between January 2015 to 2023 with "PFAS" OR "per- and polyfluoro alkyl" AND "gestational diabetes" keywords. A total of 10 studies were included.

Results: There were no statistically significant difference between the patient and control groups for PFOS (MD = 0.36, 95% CI = [0.30, 1.02], Z=1.06, P=0.29), PFHxS (MD = −0.02, 95% CI = [−0.11, 0.07], Z=0.39, P=0.69), PFNA (MD = 0.00, 95% CI = [−0.02, 0.04], Z=0.10, P=0.92), PFHpA (MD = 0.01, 95% CI = [−0.00, 0.02], Z=1.63, P=0.10) and PFDA (MD = 0.00, 95% CI = [−0.03, 0.03], Z=0.15, P=0.88). A statistically significant difference was observed between the patient and control groups for PFOA (MD = 1.79, 95% CI = [0.99, 2.58], Z=4.42, P<0.001) and PFUnDA (MD = 0.10, 95% CI = [0.01, 0.19], Z=2.23, P=0.03).

Conclusion: Our meta-analysis has shown a strong correlation between PFUnDA and PFOA levels in connection with GDM. A total of 10 randomised controlled trials (RCTs) were assessed to investigate the relationship between GDM and PFAS. Consistent with previous research, the presence of long-chain chemicals such as PFUnDA and PFOA may disrupt the normal functioning of β cells, leading to the development of GDM. These results can enhance future research on the relationship between GDM and hazardous exposures.

Keywords Gestational diabetes mellitus · Meta-analysis · Polyfluoro alkyls · Environmental exposure · Endocrin disruptor · accumulation

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INTRODUCTION

Gestational diabetes mellitus (GDM), which is different from type 1 and type 2 diabetes, is defined as insulin resistance that first occurs during pregnancy (Association, 2018; Ugwudike & Kwok, 2023). GDM is the most prevalent complication of pregnancy, with an increased prevalence over the past decade (Wang et al., 2022). Various criteria parameters have been used by many institutions at different times for the diagnosis of GDM. However, the cutoff value is accepted as 7.8 mmol/L for blood sugar level 1 h after the glucose challenge test, which is still used for GDM screening today (Gao et al., 2019). Insulin therapy or diet modifications are helpful for the treatment, and it does not persist after giving birth (Etminan-Bakhsh et al., 2020). Most studies suggest that it is an endocrine disorder, and probably placental hormones cause insulin resistance besides increased fat deposits, but the cause is still unclear (Etminan-Bakhsh et al., 2020; Ugwudike & Kwok, 2023). Although its prevalence varies due to different diagnostic criteria, in the last meta-analysis conducted in 2021 by Saeedi et al., GDM prevalence was reported as 14.7% according to the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria (Mazumder et al., 2022; Saeedi et al., 2021). According to the International Diabetes Federation (IDF), 16.7% (nearly 21.1 million live births) of women had suffered from hyperglycaemia during pregnancy in 2021 (IDF). Previous history of GDM is a major risk factor, in addition to the other risk factors, including overweight or obesity, maternal age over 35 years, family history of diabetes or insulin resistance, hypothyroidism, sleep-disordered breathing, previous macrosomic baby, polycystic ovary syndrome, and certain high-risk ethnicities (Etminan-Bakhsh et al., 2020; Ugwudike & Kwok, 2023). There are both maternal and foetal complications in the short and long term, including an increased risk of diabetes and cardiovascular disease in the mother, as well as an increased risk of preterm labour, polyhydramnios, and hypertension in the foetus (Etminan-Bakhsh et al., 2020; Plows et al., 2018).

The incidence of metabolic diseases such as diabetes and obesity is increasing day by day. Although nutritional status and genetic factors seem to be effective in general, it is estimated that environmental pollutants also play an important role in this (Casals-Casas & Desvergne, 2011; Wan et al., 2014). There has been interest in recent studies that look at how chemicals in the environment might affect the cause and progression of GDM. This is because it has significant health effects on mothers and their babies. The underlying mechanism of GDM is poorly understood, but there are studies that point out that per- and polyfluoroalkyl substances (PFAS) modulate the glucose metabolism, and elevated prenatal levels trigger GDM (Yu et al., 2021).

PFAS are persistent environmental pollutants with a synthetic organic chemical structure that is structurally similar to fatty acids and has an endocrine-disrupting effect (Birru et al., 2021; Margolis & Sant, 2021; Wang et al., 2022). PFAS are short- or long-chain alkyl compounds consisting of F's linked to a C atom. (Buck et al., 2011). The use of PFAS dates back to the 1950s (Calafat et al., 2007; Inoue et al., 2004). It has become an important environmental problem because it is found everywhere, including in groundwater, and is persistent in both humans and wildlife (Armitage et al., 2006; Johnson et al., 2022; O'Rourke et al., 2022; Zhang et al., 2022). Because they are used in numerous industries as textiles, food packaging materials, cosmetic products, waterproof fabrics, and foam extinguishing agents, they are contaminated with food, water, and air that results in human exposure (Birru et al., 2021b; Margolis & Sant, 2021; J. Wang et al., 2022). Furthermore, due to its long serum half-lives varying from 2.3 to 8.5 years, it is biologically persistent in the human body (Wang et al., 2022). Perfluorooctanoic acid (PFOA), perfluorooctane sulphonate (PFOS), perfluorohexane sulphonate (PFHxS), perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), and perfluoroundecanoic acid (PFUnDA) are the most frequently studied forms (Wang et al., 2022). To eradicate the most prevalent PFAS, primarily PFOS and PFOA, legislative measures have been implemented in numerous countries. Nevertheless, despite the cessation of production, these chemicals continue to persist and accumulate in the environment due to their inherent stability (Birru et al., 2021).

The cause of the endocrine disruption of homeostasis in the body starts from foetal development (Gore et al., 2015). Studies have shown that PFAS negatively affects the development of the foetus due to its endocrine disrupting properties (Deji et al., 2021). According to studies conducted in recent years, PFOS, one of the PFAS types, is observed to cause hepatotoxicity, endocrine disrupting effects, and carcinogenicity (Li et al., 2018; Margolis & Sant, 2021; Sant et al., 2019). With the Stockholm Convention, the use of PFOA and PFOS was restricted in 2009, and the use of these substances was banned in 2019; however, the effects of these substances on the body still continue (Wang et al., 2009; Xu et al., 2022). Few studies have investigated the association between PFAS exposure and GDM progression (Jensen et al., 2018; Liu et al., 2019; Matilla-Santander et al., 2017; Rahman et al., 2019; G. D. Shapiro et al., 2016; Valvi et al., 2017; Wang et al., 2018; Xu et al., 2022; Xu et al., 2020; Yu et al., 2021; Zhang et al., 2015; Zhang et al., 2023). However, while some of these studies showed positive results (Jensen et al., 2018; Liu et al., 2019; Rahman et al., 2019; Wang

et al., 2018; Xu et al., 2022; Xu et al., 2020; Yu et al., 2021; Zhang et al., 2015; Zhang et al., 2023) with GDM for some types of PFAS, no association (Jensen et al., 2018; Xin Liu et al., 2019; Xu et al., 2020; Zhang et al., 2023) was found with some types. PFAS species have been associated with increased insulin resistance along with the formation of oxidative stress (Kim et al., 2016). Increased insulin resistance and obesity; it has been associated with GDM in pregnant women (Birru et al., 2021). However, the effect of PFAS on the progression of GDM has not been clarified. Birru et al. speculated that the maternal thyroid changes with PFAS exposure, which regulates glucose homeostasis. The theory posits that alterations in thyroid homeostasis, characterised by elevated TSH levels and reduced T3-T4 levels, disrupt glucose metabolism. Furthermore, it has been postulated that PFAS may also disrupt maternal and foetal glucose homeostasis during pregnancy, exerting a direct toxic effect on the maternal liver and/or pancreas (Birru et al., 2021). Xu et al. conducted a case-control cohort study with 171 GDM patients and quantified 15 PFAS serum concentrations and 15 PFAS detected in over 70% maternal serum samples. While some of the compounds (PFOA, PFOS, PFUnDA, PFDoA, and 6:2Cl-PFESA) have been linked to disturbances in glucose homeostasis and an elevated risk of GDM, others (4:2FTS, 6:2FTS, PFHxS, and ADONA) have been associated with a negative correlation (Xu et al., 2022).

The available evidence increasingly indicates a potential association between PFAS and GDM. A meta-analysis was therefore performed to review existing epidemiological studies and to provide a systematic and comprehensive evaluation of the impact of exposure to PFAS on the risk of GDM. The research question of our study is, "Is exposure to PFAS and its derivatives a risk factor for GDM?"

MATERIALS AND METHODS

Search Strategy and Study Protocol

This systematic review was reported on the basis of the updated Preferred Reporting Items for Meta-Analyses (PRISMA) statement. The 2020 PRISMA statement is an evidence-based set of items for reporting meta-analyses (Page et al., 2021). It has been registered with PROSPERO (International Prospective Register of Systematic reviews with the following ID; 455622).

A search for PFAS was conducted in the PubMed, Web of Science and Scopus databases from January 2015 to 2023 for randomised controlled trials (RCTs). The keywords used were "PFAS" OR "per- and polyfluoro alkyl" AND "gestational diabetes". ((PFAS[Title/Abstract]) OR (per-polyfluoro alkyl[Title/Abstract])) AND (gestational diabetes[Title/Abstract]) is the screening formulation for literature research. All the retrospective randomised clinical trials were accepted for the study.

Inclusion and Exclusion Criteria

Types of studies. All clinical studies were evaluated related to PFAS exposure and gestational diabetes. Studies without a control group were eliminated. Furthermore, we excluded studies that did not discuss the level of PFAS and its impact on blood. Studies were excluded if they were observational, crossover, immediate-mal, conference abstracts or letters. Additionally, studies with a sample size of fewer than thirty patients were excluded. The studies lacking data were disregarded. Only studies written in English were considered.

Types of participants. GDM was identified by reviewing the OGTT test findings in the medical records. The diagnosis of gestational diabetes was based on 24-28 weeks of gestation. A 75-g oral glucose tolerance test (OGTT) was conducted in the morning following an overnight fast. At fasting and throughout the first and second hours, the plasma glucose levels were assessed. At least one of the following aberrant readings was required for the diagnosis of GDM: fasting glucose ≥5.1 mmol/L, 1-hour glucose ≥10.0 mmol/L, or 2-hour glucose ≥8.5 mmol/L. There are no restrictions on the research subjects' age, race, health, length of time, or level of intensity (Liu et al., 2019; Xu et al., 2022).

Types of control groups. Those without gestational diabetes, that is, those whose blood values were not above the values stated above, were considered as controls.

Study Selection and Data Extraction

Based on the search strategy, a single author (BSM) conducted the inquiries. Based on the inclusion and exclusion criteria, two researchers (OS and BSM) evaluated the papers for eligibility after examining the references' titles and abstracts. We subsequently obtained the full texts of the relevant papers to make the final choice.

Three authors (SY, OS, BSM) independently extracted data from each study using a predesigned form. The study design, patient characteristics, sample size, diagnostic criteria, interventions, treatment sessions, clinical end findings, follow-up length, and adverse events were among the data that were extracted. We would eliminate the research if we could not get data access by getting in touch with the authors. We resolved the conflicts by revisiting the original documents and consulting with the third author (KK).

All initial searches yielded a total of 118 studies (PUBMED 27, Web of Science 16, Scopus 75), of which 75 were retained after screening and removing duplicates and 16 were excluded based on their titles and abstracts. The eligibility of 27 full-text

studies was then assessed. In the end, 10 eligible RCTs were included in the systematic review. Figure 1 depicts a flowchart of the study selection procedure.

Description of the Included Studies

In 10 studies, the International Association of Diabetes and Pregnancy Study Groups, Carpenter-Coustan criteria, and the World Health Organization's 1999 criteria were used to diagnose all GDM patients. The sample sizes of the included articles ranged from 204 to 2747 people. Table1 presents the main characteristics of the included studies.

Statistical Analysis

The mean, standard deviation, median, IQR, min, max, mean difference (MD), and 95% confidence intervals (CI) were used to display the summary data. We estimated the total MD with 95% CI from systematic reviews and meta-analyses of continuous data (PFOS, PFOA, PFHxS, PFNA, PFHpA, PFDA, and PFUnDA); the Higgins I^2 test and chi-square test were used to assess heterogeneity. The fixed-effects model was used when I2 ≤ 50%, P ≥ 0.10; in other cases, the random-effects model was employed, and heterogeneity was examined by subgroup analysis. All results were presented with a forest plot and funnel plot. We favoured 95% CIs between studies and considered p-values < 0.05 statistically significant. We prepared our meta-analysis in accordance with the PRISMA standards. The Review Manager software (Review Manager, version 5.4.1 for Windows; the Nordic Cochrane Centre, Copenhagen, Denmark) was used to conduct the meta-analysis.

RESULTS

Literature Search Results. A total of 118 studies were identified during the initial search. After scanning the title and abstracts, 27 studies were included. Finally, ten articles involving 7691 female participants (Female: mean age: 30.5 years; range, 28 to 38 years) met our inclusion criteria after scanning full texts in the last eight years. The flow diagram of the study is shown in Figure 1.

Basic Characteristics of Eligible Studies. The defining features of all the included studies are given in Table 1. All studies were published between January 2015 and 2023. The sample size of the studies ranged from 204 to 2747 participants.

Comparison of PFOS Levels Between the GDM and Control

The forest plot for the PFOS exposure was monitored in Figure 2A. The random-effects model was employed to account for the heterogeneity of the data (Tau^2 = 0.79; Chi^2 = 81.79, df=8; P < 0.001, I^2 = 90%). There was no statistically significant difference between the patient and control groups for PFOS (MD = 0.36, 95% CI = [0.30, 1.02], Z=1.06, P=0.29). The funnel plot for PFOS was also exhibited in Figure 3A.

Comparison of PFOA Levels Between the GDM and Control

The forest and funnel graphs are plotted in Figures 2B and 3B, respectively. The random-effects model was employed to account for the heterogeneity of the data; (Tau^2 = 1.35; Chi^2 = 727.92, df=8; P < 0.001, I^2 = 99%). There was a statistically

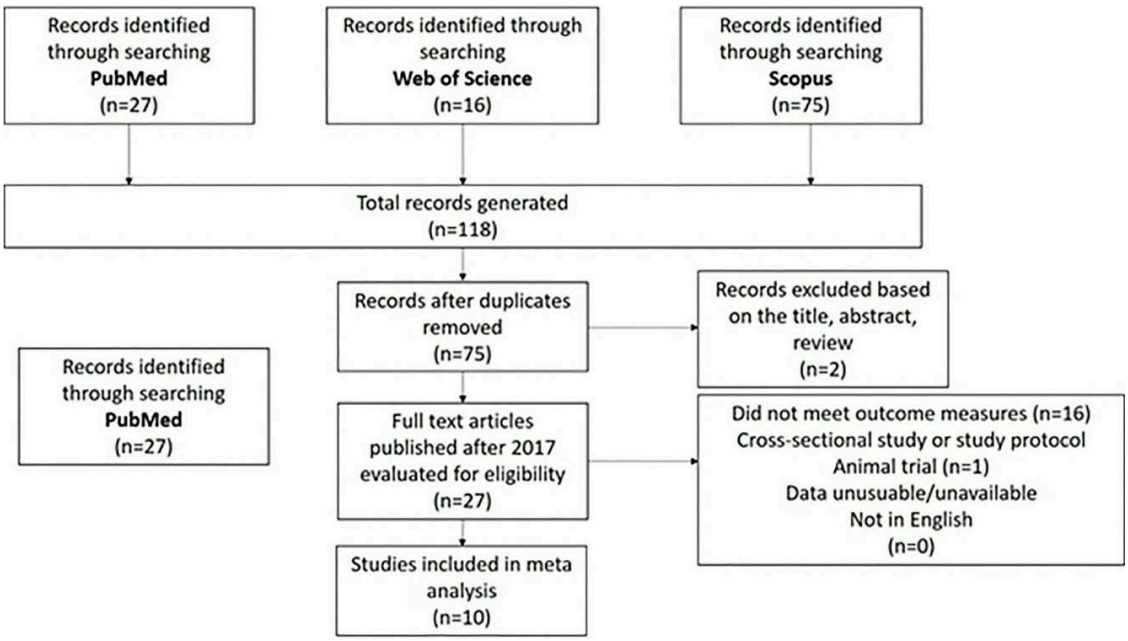

Figure 1. Flow chart of the database search

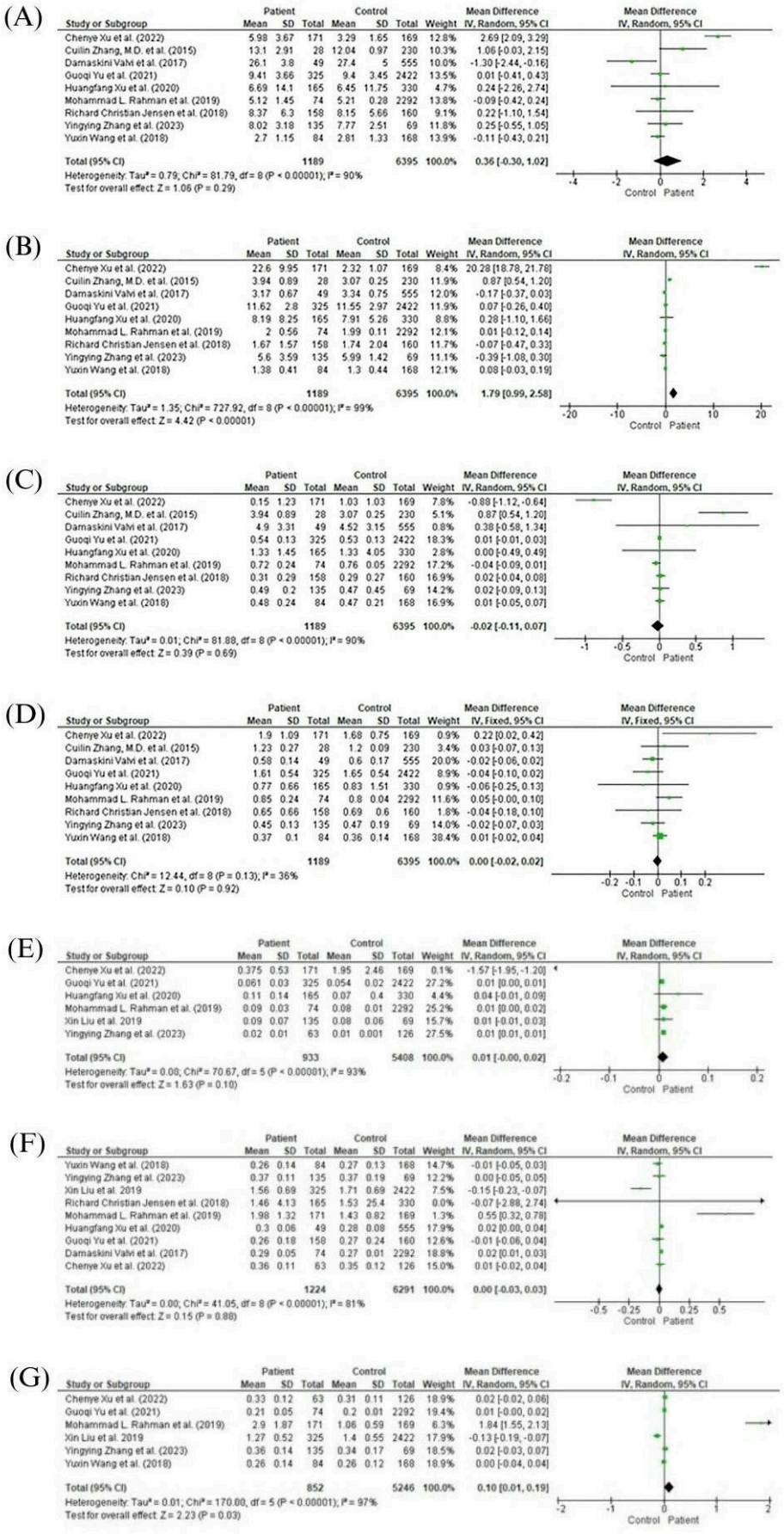

Figure 2. A forest plot in the meta-analysis comparing PFOS (A), PFOA (B), PFHxS (C), PFNA (D), PFHpA (E), PFDA (F), and PFUnDA (G) between the patient and control groups

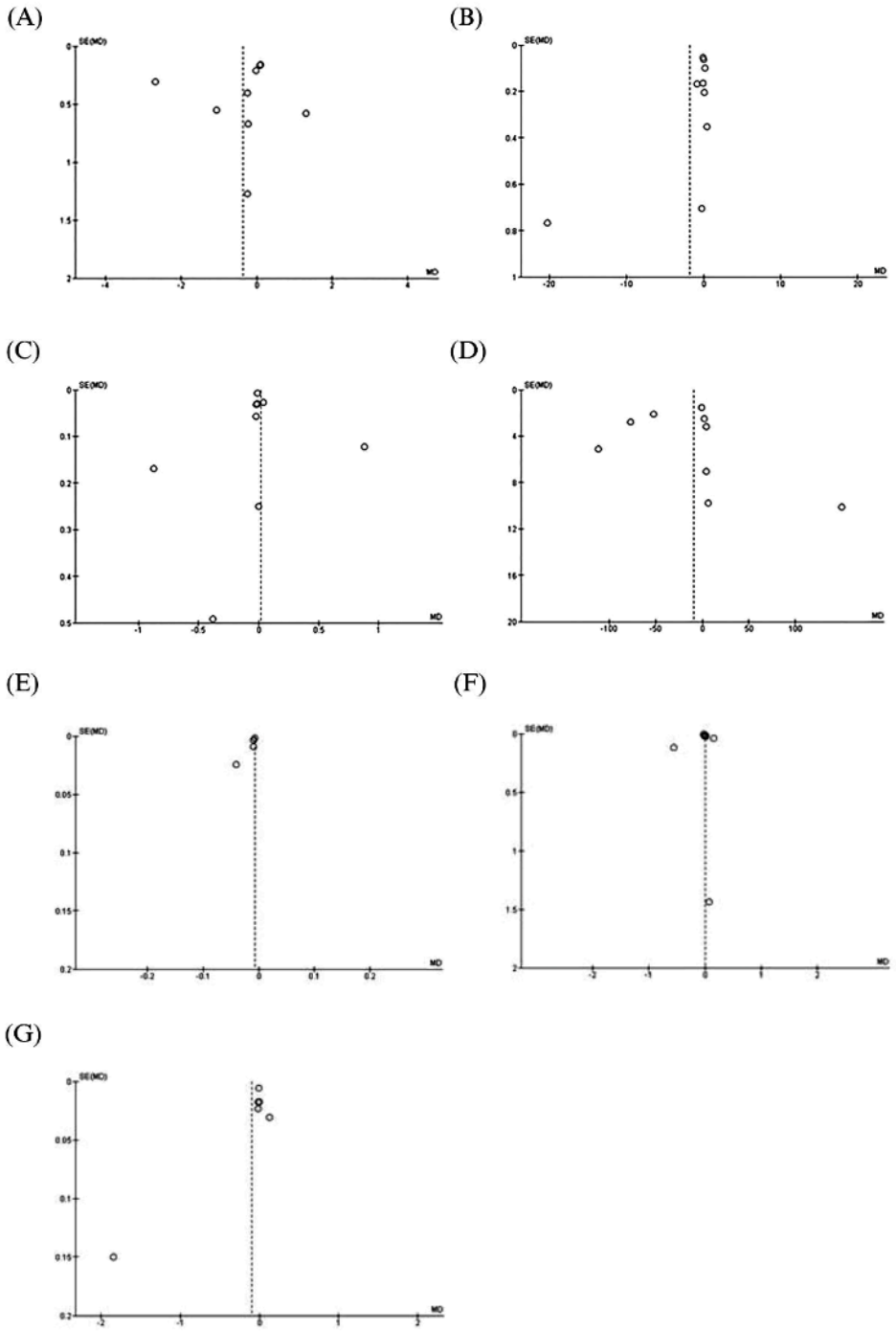

Figure 3. A funnel plot in the meta-analysis for PFOS (A), PFOA (B), PFHxS (C), PFNA (D), PFHpA (E), PFDA (F), and PFUnDA (G)
X-axis: Mean difference (MD); Y axis: Standard Error of the MD

significant difference between the patient and control groups for PFOA (MD = 1.79, 95% CI = [0.99, 2.58], Z=4.42, P<0.001).

Comparison of PFHxS Levels Between the GDM and Control

PFHsS levels were evaluated via the forest plot (Figure 2C) and funnel plot (Figure 3C). The random-effects model was employed to account for the heterogeneity of the data; (Tau^2 = 0.01; Chi^2 = 81.88, df=8; P < 0.001, I^2 = 90%). There was no statistically significant difference between the patient and control groups for PFHxS (MD = −0.02, 95% CI = [−0.11, 0.07], Z=0.39, P=0.69).

Comparison of PFNA Levels Between the GDM and Control

PFNA levels were compared for GDM patients vs controls. According to the data obtained from the previous studies, a forest graph (Figure 2D) and funnel diagram (Figure 3D) were

plotted for the PFNA levels. The fixed-effects model was used due to the lack of heterogeneity in the data (Tau^2 = 0.00; Chi^2 = 12.44, df=8; P = 0.13, I^2 = 36%). There was no statistically significant difference between the patient and control groups for PFNA (MD = 0.00, 95% CI = [−0.02, 0.04], Z=0.10, P=0.92).

Comparison of PFHpA Levels Between the GDM and Control

Forest plot and funnel plot were monitored in Figure 2E and Figure 3E for the PFHpA levels between GDM patients and controls. The random-effects model was employed in order to account for the heterogeneity of the data (Tau^2 = 0.00; Chi^2 = 70.67, df=5; P < 0.001, I^2 = 93%). There was no statistically significant difference between the patient and control groups for PFHpA (MD = 0.01, 95% CI = [−0.00, 0.02], Z=1.63, P=0.10).

Comparison of PFDA Levels Between the GDM and Control

The PFDA levels of the published articles were evaluated via a forest plot (Figure 2F) and a funnel plot (Figure 3F). The random-effects model was employed to account for the heterogeneity of the data; (Tau^2 = 0.00; Chi^2 = 41.05, df=8; P < 0.001, I^2 = 81%). There was no statistically significant difference between the patient and control groups for PFDA (MD = 0.00, 95% CI = [−0.03, 0.03], Z=0.15, P=0.88).

Comparison of PFUnDA Levels Between the GDM and Control

Comparison of PFUnDA levels was used via Forest plot (Figure 2G) and funnel plot Figure 3G). The random-effects model was employed to account for the heterogeneity of the data; (Tau^2 = 0.01; Chi^2 = 170.00, df=5; P < 0.001, I^2 = 97%). There was a statistically significant difference between the patient and control groups for PFUnDA (MD = 0.10, 95% CI = [0.01, 0.19], Z=2.23, P=0.03).

Publication Bias

Publication bias was assessed with funnel plots. Publication bias was evaluated separately for PFOS, PFOA, PFHxS, PFNA, PFHpA, PFDA, and PFUnDA. The funnel plots were symmetric, and no clear publication bias was detected (Figure 3).

DISCUSSION

According to the research in 1988, diabetes has been diagnosed in 4% of pregnant women all over the US. It is estimated that 88% of them were GDM patients (Engelgau et al., 1995). It is observed that the risk of GDM increases with time (Ferrara, 2007). GDM has similarities with diabetes type 2 and is one of the most encountered complications for pregnancy (Johns et al., 2018). In the mechanism, insulin sensitivity is reduced due to the pregnancy period and insulin synthesis is elevated in β cells of the pancreas. Due to that reason, glucose clearance is ascended related to high insulin level which causes hyperglycaemia (Catalano et al., 1993; Johns et al., 2018). Several environmental factors also triggered this situation. It is thought that environmental and genetic effects could be remarkable in the aetiology of GDM. As environmental affects; chronical exposure on endocrine disruptors is accepted as one of the main reasons for the increasing incidence of GDM (Bellavia et al., 2019).

PFAS act as endocrine disruptors and have been associated with GDM in many studies (Kassotis et al., 2020; Long et al., 2013; C. Xu et al., 2022). PFAS are C-F bonded synthetic chemicals that are used as surface-active compounds (Das et al., 2017). They have strong and stable C-F bonds, which are hardly degraded in the environment. Because they easily accumulate in nature for a long time and permeate the food chain and water resources (Giesy & Kannan, 2002). PFAS may lead to hepatoxicity, immunotoxicity, neurotoxicity, reproductive toxicity, nephrotoxicity and pulmonary toxicity (Cui et al., 2009). In our meta-analysis, PFOS, PFOA, PFUnDA, PFHpA, PFNA, PFDA, and PFHxS were evaluated. Only exposure to PFOA and PFUnDA compounds was found to be significantly related to GDM. In a previous meta-analysis study conducted on GDM and PFAS (PFOS, PFOA, PFHxS, PFNA), only PFOA gave statistically significant results. The authors stated that this situation is mostly caused by different cut-off values determined in Asian countries for OGTT, which raise the positive diagnosis and change the whole statistical analysis (Wang et al., 2022). In another meta-analysis study conducted between GDM and PFAS, only PFBS and PFDoA among the PFAS gave statistically significant results (Yan et al., 2022). In our meta-analysis study, unlike previous meta-analysis studies on the same subject, the relationship of the more frequently used PFAS (PFOS, PFOA, PFHxS, PFNA, PFHpA, PFDA, and PFUnDA) with GDM was evaluated. Similar to earlier research, our study found a significant association between PFOA and GDM. In addition, unlike other meta-analysis studies, we also found a significant link between GDM and a different long-chain PFAS, PFUnDA.

In nature, one could easily run across PFOA species due to the long chain and nondegradable features of these chemicals (Frömel & Knepper, 2010). In 2019, PFOA usage was forbidden. Despite this prohibition, PFOA continues to accumulate in nature and affect the human body. Elimination of PFOA may last for 3.5-3.8 years. This period may last 5.1 and 7.9 years for PFOS and PFHxS, respectively (Olsen et al., 2007). A high concentration of PFOA exposure may change the elimination rate of metabolism.

Table 1. Eligible studies on PFAS exposure and gestational diabetes

Study	Country	Sample Size	Interventions	Gestational Diabetes	Measurement Times	Outcomes
Liu et al. 2019	China	439	Non-GDM: Non-gestational diabetes GDM: gestational diabetes mellitus	Healthy pregnant women without a previous history or a family history of diabetes were recruited during the first trimester of pregnancy at their initial prenatal care visit. GDM cases were diagnosed at 24–28 weeks of gestation and individually matched in a 1:2 ratio to controls.	6-7 (month)	1 m-PFOS, 3 m-PFOS, 4 m-PFOS, 5 m-PFOS, 6 m-PFOS, PFOS(C8), L-PFOS, 6 m-PFOA, L-PFOA, PFHxS(C6), PFNA(C9), PFHpA, PFDA, PFUnDA
Mohammad L. Rahman et al. 2019	USA	2292	Overall Cohort GDM Cases: gestational diabetes	OGTT tests were performed at a mean (± standard deviation) gestational age of 27.5 (± 4.3) weeks. GDM was diagnosed by medical record review of the OGTT test results.	16–22/week 24–29/week 30–33/week 34–37/week and 38–41/week	PFOS, PFOA, PFHxS, PFNA, PFHpA, PFDA, PFUnDA
Jensen et al. 2018	Denmark	318	High GDM risk: High gestational diabetes risk Low GDM risk: Low gestational diabetes risk	We analysed 604 Faroese pregnant women and their offspring born in 1997–2000.		PFOS, PFOA, PFHxS, PFNA, PFDA
Valvi et al. 2017	Faroe islands	604	GDM – no: Non-gestational diabetes GDM – yes: gestational diabetes	The GDM diagnosis was extracted from the medical records. Following standard clinical guidelines, women with elevated fasting blood glucose concentrations and/or those considered at elevated risk for GDM based on their age, pre-pregnancy BMI, family history of diabetes, GDM in previous pregnancy, previous stillbirth, macrosomia in previous delivery and polyhydramnios were identified at 24–28 weeks of gestation and given a 2-h oral glucose tolerance test (OGTT) (13% of the analysis population) to establish a possible GDM diagnosis. Maternal serum was obtained at gestational week 34.		PFOS, PFOA, PFHxS, PFNA, PFDA
Xu et al. 2022	China	340	GDM: gestational diabetes mellitus Non- GDM: Non-gestational diabetes	According to the Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria, GDM was diagnosed from a 75 g oral glucose tolerance (OGTT) test between 24 and 28 gestational weeks.	This case–control study was conducted at the Women's Hospital of the School of Medicine of Zhejiang University in Hangzhou, China between October 2020 and September 2021.	PFOS, PFOA, PFHxS, PFNA, PFHpA, PFDA, PFUnDA
Xu et al. 2020	China	495	GDM cases: gestational diabetes Controls	A nested case–control study was conducted in a prospective cohort of 2,460 women enrolled between July 1, 2017, and 31 January 2019 At the Obstetrics and Gynaecology Hospital, affiliated with Fudan University. Healthy pregnant women were all recruited at the time of their first prenatal examination and screened for GDM over 24–28 gestational weeks.		PFOS, PFOA, PFHxS, PFNA, PFHpA, PFDA

Study	Country	Sample Size	Interventions	Gestational Diabetes	Measurement Times	Outcomes
Yu et al. 2021	China	2747	Non-GDM GDM	SBC recruited women in early pregnancy from six participating hospitals in Shanghai, China during 2013–2016. GDM was diagnosed based on a 75-g oral glucose tolerance test (OGTT) between 24 and 28 gestational weeks according to the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria: the glucose concentration met any of the following 3 thresholds: a) fast plasma glucose (FPG) ≥ 5.1 mmol/L; b) 1-h plasma glucose ≥ 10.0 mmol/L; or c) 2-h plasma glucose ≥ 8.5 mmol/L. In brief, eligible women were those who were at least 20 years old, registered Shanghai resident or married to a Shanghai resident; planned to seek prenatal care and give birth at the collaborative hospitals; were willing to sign a consent form and have regular follow-up visits in the following 2 years.		PFOS, PFOA, PFHxS, PFNA, PFHpA, PFDA, PFUnDA
Zhang et al. 2023	China	204	Non-GDM GDM	Research cohort and specimen collection. A case–control study was conducted between July 2011 and November 2012 at the Women's Hospital School of Medicine, Zhejiang University, China. All participants were recruited at their first prenatal visit during the first trimester. Eligible pregnant women were screened for GDM at 24–28 weeks of gestation.		PFOS, PFOA, PFHxS, PFNA, PFHpA, PFDA, PFUnDA
Wang et al. 2018	China	252	Non-GDM GDM	84 GDM subjects were recruited from pregnant women diagnosed with GDM from January to March 2013 at the Haidian Maternal & Child Health Hospital in Beijing, China. All subjects returned to the hospital for the six-week postpartum checkup and the levels of fasting blood glucose were measured and recorded.		PFOS, 1 m-PFOS, 3 m-PFOS, 5 m-PFOS, 6 m-PFOS, PFOA, PFHxS, PFNA, PFDA, PFUnDA
Zhang, M.D. et al. 2015	ABD	258	Non-GDM GDM	Specifically, the cohort was recruited in 16 counties in Michigan and Texas during the years 2005–2009 upon discontinuing contraception for the purpose of becoming pregnant and were followed daily until an hCG-positive pregnancy test and then through the first 8 weeks of pregnancy. Subsequently, the women were followed monthly until delivery.		PFOS, PFOA, PFNA

It is reported that PFOA exposure may elevate serum insulin, leptin and body mass index in rats due to the elimination disorders (Hines et al., 2009). Furthermore, Yamaguchi et al. claimed that PFOA and PFOS may change the elimination rate of metabolism, which causes significant alteration in liver enzymes (Yamaguchi et al., 2013). According to 15 years of cross-sectional research, PFOA and PFOS may cause dyslipidemia, which may elevate the risk of diabetes (Fenton et al., 2021; Lin et al., 2019). Diabetes is mostly diagnosed due to a disorder in pancreatic function. It was observed that PFOA exposure increases the pancreatic lesions. However, there is no certain evidence about the diabetic effect of PFOA (Biegel et al., 2001). *In vitro* studies have elucidated that PFOS and PFOA exposure may be responsible for adipose transportation, insulin sensitivity, liver disorders, and activation of PPAR (a metabolic receptor) (Francis et al., 2003; Zhang et al., 2013). In addition, there are several scientific reports, such as our paper, which claim the relationship between high concentrations of PFOA exposure and the increasing incidence of gestational diabetes (Shapiro et al., 2016; Wang et al., 2022). Although many PFOA and PFOS compounds were restricted, their endocrine disruptor effects are continuing. It is also found that the affinity of PFUnDA is much higher on the L-FABP protein, which is a fatty acid bonding protein in the liver (Zhang et al., 2013). These studies confirm our findings about PFOA and PFUnDA concentration that is significantly altered in patients suffering from gestational diabetes.

Early childhood exposure to PFOS and PFOA may cause obesity in older ages. Furthermore, disorders in β cell functions may also be observed (Domazet et al., 2016). After the prohibition of PFOS and PFOA, long-chain-chained perfluoroalkyl (like PFUnDA) have been used worldwide. In a model organism study on zebrafish, it is exhibited that PFOA and PFUnDA may accelerate the metabolic elimination of thyroid hormone, which causes malformation in larvae (Kim et al., 2021). Based on the study by Birru et al. (Birru et al., 2021), it is thought that an imbalance in the thyroid hormone may disrupt glucose homeostasis. All this information reveals that PFUnDA could disrupt the function of the thyroid hormone, which causes a disorder in glucose homeostasis. Because gestational diabetes may trigger this reason. Another study was carried out in rats via exposure to PFOS, PFHxS, PFNA and PFDA. It has been reported that the urine elimination PFAS were decreased in long-chain compounds. Therefore, long-chain alkyls are more highly accumulated in the body than short-chain alkyls. Higher concentrations may have a higher effect on the body (Kudo et al., 2001). This finding may explain our findings about PFUnDA.

In our study, we could not find a statistically significant correlation between gestational diabetes and PFOS, PFHpA, PFHxS, PFNA, and PFDA exposure. Matilda et al. published a study that also confirmed our findings. They did not observe a significant relationship between PFOS and PFHxS and gestational diabetes (Ebel et al., 2023; G. D. Shapiro et al., 2016). The study on *the Cyprinus carpio* fish species produced results that support our results. The study mentions that one of the biotransformation products of PFOA is PFHpA and that PFOA plays a direct role in the formation of the PFHpA metabolite. It was also mentioned that PFOA in the liver showed a negative correlation with PFHpA (Petre et al., 2023). Based on this information, the liver is an important organ in the development of gestational diabetes and explains why PFHpA did not give significant results in our study. In another study, it has been reported that there is no relationship between thyroid hormone and PFNA accumulation in the human body (Preston et al., 2020). As our study suggests, PFNA concentration cannot directly trigger gestational diabetes. In the meta-analysis study conducted with PFA types, no significant relationship was found between PFDA and gestational diabetes, as in our study (Gao et al., 2021).

CONCLUSION

Gestational diabetes is a very common disease during pregnancy. Several studies were performed to assess the risk factors that may trigger GDM. Per- and polyfluoro alkyls were one of the most studied compounds that were suspected to elevate GDM during the pregnancy. According to our meta-analysis, we found a significant relationship between PFuNDA and PFOA concentration in GDM. 10 different RCTs were evaluated, and we found no direct relationship between GDM and other per- and polyfluoro alkyls. This phenomenon can probably be explained by the difference in the chemical structures of these compounds. The chemical structure of a compound is an important feature that affects its fate in the body. In particular, the tendency of long-chain compounds to accumulate in the body and the slowing down of their elimination rate cause them to interact more with the organism. In addition, their existing undesirable effects lead to unwanted health problems in this long-term interaction. Long-chain PFAS compounds such as PFuNDA and PFOA may accumulate in the body and probably cause disorder in β cell functions which induce the GDM. With the increasing number of studies showing the negative health effects of such compounds, the need to protect public health is the basis for the views of regulatory authorities about banning these compounds. Although PFOA has been banned in this direction, its negative health effects continue due to its accumulation. It is important to take steps towards banning it after more detailed studies are

conducted within PFuNDA and its negative health effects are proven, because even if it is banned today, its negative health effects will continue for a long time.

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