Endocrine-Disrupting Chemicals and the Risk of Gestational Diabetes Mellitus: A Systematic Review and Meta-Analysis

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Research

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Abstract

Objective

To conduct a comprehensive systematic review and meta-analysis to estimate the relationship between EDCs, including polychlorinated biphenyls (PCBs), poly-brominated diphenyl ethers (PBDEs), phthalates (PAEs), and per- and polyfluoroalkyl substances (PFAS) exposure and risk of gestational diabetes mellitus (GDM).

Methods

Relevant literatures were identified by searching Embase, Pubmed, and Web of Science through November 2021. The cohort and case-control studies reporting effect size with 95% confidence intervals (CIs) of EDCs exposure and GDM were selected. The heterogeneity among the included studies were quantified by I^2 statistic. Publication bias was evaluated through the Begg's and Egger's tests.

Results

Twenty-five articles with a total of 23,796 participants were finally identified. The results indicated that exposure to PCBs have a significant impact on the incidence of GDM (OR = 1.14; 95% CI = 1.00-1.31; n = 8). For PBDEs exposure, a positive association was observed for the risk of GDM (OR = 1.32; 95% CI = 1.15-1.53; n = 4). Similarly, for PAEs and PFASs exposure, they were also positively associated with the risk of GDM, with summary ORs were 1.10 (95% CI = 1.03-1.16; n = 7 for PAEs) and 1.09 (95% CI = 1.02-1.16; n = 11 for PFASs), respectively. When only included the cohort studies, the summary OR between PCBs exposure and the risk of GDM was 0.99 (95% CI = 0.91-1.09; n = 5). While, for PBDEs, PAEs, and PFASs exposure, the summary ORs from cohort studies were 1.12 (95% CI = 1.00-1.26; n = 2), 1.08 (95% CI = 1.02-1.15; n = 5), and 1.06 (95% CI = 1.00-1.12; n = 8), respectively. The Begg's and Egger's tests didn't show publication bias and the sensitivity analyses didn't change the results in the present meta-analysis.

Conclusion

These results support the notion that EDCs exposure increases the risk of GDM. Further large-sample epidemiologic researches and mechanistic studies are needed to verify the potential relationship and biological mechanisms. These results are of public health significance since daily EDCs exposure have been expected to increase the risk of GDM development.

Introduction

Gestational diabetes mellitus (GDM) is one of the most common complications of pregnancy [1], which is diagnosed in the second or third trimester during pregnancy that was not clearly overt diabetes before gestation. In the past years, the incidence of GDM has increased markedly. On the basis of the 9th edition of the International Diabetes Federation diabetes atlas 2019, there were 20.4 million women globally suffered from hyperglycemia during pregnancy, about 83.6% of them were diagnosed with GDM[2]. Evidences indicated that GDM is associated with dramatic adverse health effects in mothers and their offspring, including birth complications, preeclampsia, and type 2 diabetes mellitus (T2DM) later in life[3, 4]. Maternal characteristics such as advanced age, ethnicity, high-carbohydrate diets, pre-pregnancy obesity, and family history of T2DM have been proved to be associated with the increased risk of GDM[5, 6]. However, the exact reasons behind the GDM are still unknown, as over 50% of GDM patients do not have these classic determinants, suggesting the potential role of environmental factors[7].

Endocrine-disrupting chemicals (EDCs) are a special type of exogenous chemicals that can interfere with a lot of normal endocrine signals[8]. They are structurally similar to some endogenous hormones that can disturb the synthesis, secretion, or elimination of natural hormones, which may lead to hormonal disruption, including obesity, diabetes, and developmental dysfunctions, etc[8]. EDCs are widely existed in food packaging, medical equipment, personal care products, fabrics and upholstery, water, ambient air, detergents, and many industrial products[8]. During the last few decades, the use of EDCs has increased significantly. Humans are frequently exposed to various EDCs from diet, household or agricultural pesticides, and cleaning products in daily life. The pervasive of EDCs and their association with chronic diseases caused potential human health concerns and considerable public health problems[9].

Several EDCs including polychlorinated biphenyls (PCBs), poly-brominated diphenyl ethers (PBDEs), per- and polyfluoroalkyl substances (PFAS), and phthalates (PAEs) have been reported to be associated with impaired glucose metabolism and T2DM[10]. Growing evidence supports the notion that human exposure to EDCs is particularly concerning during pregnancy, the effects of which on the developing fetus may result in long-term postnatal pathologies[11]. Previous studies have indicated that exposure to EDCs of various classes may be closely associated with the occurrence and development of GDM[12, 13]. For instance, some researches indicated exposure to PAEs may be correlated with the occurrence of gestational impaired glucose tolerance [14] and GDM[15]. However, due to the varying adjustment model variables, such as population selections, measurement approaches, and definition of outcome events, epidemiological evidences for the relationship between EDCs and GDM are inconsistent.

Humans are widely exposed to various EDCs, which may influence the regulation of glucose homeostasis. However, the current studies linking EDCs exposure to glucose homeostasis during pregnancy were inconsistent and have not been well systematically reviewed. The present study was aimed to conduct a comprehensive systematic review and meta-analysis to evaluate the relationship between EDCs exposure and risk of GDM. The purposes of the present study are as follows: (i) to confirm the association between EDCs and the risk of GDM and to provide up-to-date epidemiological clues on this association. (ii) To determine the pooled data on different kinds of EDCs (including PCBs, PBDEs, PAEs, and PFAS) and their impact on the risk of GDM.

Methods

This meta-analysis was performed according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[16] and the Meta-analysis of Observational Studies in Epidemiology (MOOSE)[17]. The PRISMA checklist for this study can be seen in Additional file 1. This study is registered with the PROSPERO registration number CRD42021226856.

Data sources

A comprehensive electronic search was carried out at EMBASE, PubMed, and Web of Science databases for relevant studies from their inception to November 2021. Search terms included exposure (endocrine disruptor OR endocrine disrupting chemicals OR environmental pollutants OR persistent toxic substance OR polychlorinated biphenyls OR phthalates) and outcomes (gestational diabetes mellitus). The detailed search strategy is presented in the Additional file 2. We also checked the references of relevant articles to search for additional researches.

Study selection

The titles and abstracts of the search results were screened independently by two investigators (DDY and YJ) according to the inclusion criteria as following: (1) observational epidemiological studies (i.e., cohort, cross-sectional, or case-control studies) on the relationship between EDCs exposure and risk of GDM; (2) the level of EDCs exposure in humans is determined in biological samples (plasma, serum, or urine); (3) outcome data reported the effect size with 95% confidence interval (CI) or sufficient data to calculate the effect size and 95% CI; (4) provided the data on sub-group EDCs exposure, which have been studied in at least three researches, thus the extracted data can be integrated. Studies that detected the level of EDCs through questionnaires or environmental measurements were excluded. Reviews, editorials, letters, and nonhuman studies were excluded, as they could not provide the effect size and 95% CI on the correlations between EDCs and risk of GDM. The studies whose results could not be extracted or the results could not be translated into odds ratio (OR) or 95% CI were also excluded.

Data extraction and quality assessment

Data extraction was done independently by two researchers using the standardized data extraction sheet. The detailed data extraction sheet including the following items: first author, year of publication, location, study time period, design, sample size, covariates adjustment, diagnostic criteria for GDM, effect sizes, and 95% CIs. The comparison value between the highest versus the lowest EDCs concentration category was selected to calculate the summary OR. The quality of the included studies was assessed independently by two investigators using the Newcastle-Ottawa Scale [18]. It evaluates the selection of participants (4 questions), the comparability (2 questions), and the assessment of exposure/outcome (3 questions). According to these parameters, the quality was divided into three grades increasing from low to high, where 0–4 points indicated low quality research, 5–6 points denoted moderate quality research, and 7–9 points represented high quality research.

Data analysis

In the meta-analyses, the effect estimates were pooled if at least two original studies reported the same kinds of EDCs as follow: a) risk per unit increase in continuous exposure and b) risk of high versus low exposure level in individual study. The OR and 95% CI were used as the primary measures to assess the relationship between EDCs and risk of GDM. The summary OR was calculated by using categorical exposure defined as high versus low, as this method has been previously used in researches of environmental exposures[19]. Cochran Q and I^2 statistics were used to evaluate the possible heterogeneity among the included studies, $P < 0.10$ and $I^2 > 50\%$ represents a significant level of heterogeneity[20, 21]. When the overall summary OR revealed no obvious heterogeneity, a fixed-effect model was performed. Otherwise, a random-effect model was used. Publication bias among the included studies were assessed with Egger's test and Begg's test. Sensitivity analyses were used to assess the sensitivity of our results. The statistical analyses were performed by Stata software (version 12.0), and the statistically significant was recognized when $P < 0.05$ (two-sided).

Results

Search results and study characteristics

A total of 392 researches were identified from three electronic databases using the search strategy, and 5 additional records were identified through citation review. Among those 397 literatures, 152 of which were left after removing duplicates. According to the titles and abstracts, 25 studies were enrolled with a total of sample size of 23,796. The screening flow chart is displayed in Fig. 1.

Among those included articles, 16 were cohort studies, 7 were case-control studies, and 2 were cross-sectional studies. In terms of study location, 11 studies were conducted in China, 7 in the USA, 2 in Canada, 2 in Spain, one in Iran, one in Norway, and one in the UK. More than half of those studies assessed the level of EDCs in serum (15 articles), 6 studies evaluated EDCs in urine, 3 studies detected EDCs in plasma, and one study assessed EDCs in meconium. In terms of laboratory technique, liquid chromatography was used in 17 studies and gas chromatography was used in 8 studies. The general characteristics of the selected articles are displayed in Table 1. The assessment scores of the selected studies are in the range of 7–9 points, yielded an average of 7.9 score, suggesting a relatively high quality for all included articles. The results are shown in Additional file 3.

Table 1

Characteristics of included studies investigating the association between environmental endocrine disruptors and gestational diabetes mellitus.

References (time period)	Location	Design	Used sample	Method	Sample size	Adjusting variables	Diagnostic criteria for GDM	Comparison categories	Endocrine disrupter	OR (95% CI)
Zhang et al. 2015 (2005-2009)	China	Cohort	Serum	HPLC-MS/MS	258	Age (y), BMI (kg/m ²), parity conditional on gravidity (never pregnant/ pregnant without live birth/ pregnant with previous birth), race/ethnicity (white/ nonwhite) and smoking (yes/no).	Self-report	Per SD increment	PFOS	1.01 (0.99, 1.03)
									PFNA	1.01 (0.99, 1.03)
									PFDA	1.01 (0.99, 1.03)
									PFOA	1.01 (0.99, 1.03)
Eslami et al. 2016 (2013.09-2015.08)	Iran	Case-control	Serum	GC/MS	140	Maternal age (yrs), pre-pregnancy BMI (kg/m ²), gestational age (wks), and total lipids in maternal serum (mg/dL)	GDM diagnoses were made when two or more of the fast plasma glucose $\geq$ 92 mg/dL, $\geq$ 180 mg/dL at 1h-OGTT or $\geq$ 153 mg/dL at 2 h-OGTT	Per unit increase in ln	PBDEs	2.01 (1.01, 3.99)
									PBDE-99	2.01 (1.01, 3.99)
									PBDE-28	2.01 (1.01, 3.99)
									PCBs	1.01 (0.99, 1.03)
									PCB-118	1.01 (0.99, 1.03)
									PCB-153	1.01 (0.99, 1.03)
									PCB-28	1.01 (0.99, 1.03)

Abbreviations: SD, standard deviation; BMI, body mass index; FPG, fasting plasma glucose; 1h-PG, 1h plasma glucose; 2h-PG, 2h plasma glucose; GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test; GC-MS, gas chromatography coupled to mass detection; GC/MS, gas chromatography mass spectrometry; LC-MS/MS, liquid chromatography coupled to mass spectrometry; GC-MS/MS, gas chromatograph triple quadrupole mass spectrometer; UPLC-MS/MS, ultra-performance liquid chromatography coupled with triple quadrupole tandem mass spectrometry; HPLC, high performance liquid chromatography; GC-HRMS, gas chromatography high resolution mass spectrometry; LC-MS/MS, liquid chromatography coupled with triple quadrupole tandem mass spectrometry; UPLC-Q/TOF MS, ultra-performance liquid chromatography coupled to quadrupole time-of-flight mass spectrometry; T2D, type 2 diabetes; ppBMI, pre-pregnancy BMI; PBDEs, Polybrominated diphenylethers; PCBs, Polychlorinated biphenyls; PAEs, phthalates; PFAS, Per- and polyfluoroalkyl substances; PFNA, Perfluorononanoic acid; PFOA, Perfluorooctanoic acid; PFDA, Perfluorodecanoic acid; PFHxS, Perfluorohexanesulfonic acid; PFOS, Perfluorooctanesulfonic acid; PFUnDA, Perfluoroundecanoic acid; PFDoA, Perfluorododecanoic acid; PFBS, perfluorobutane sulfonate; EtFOSAA, 2-(N-ethyl-perfluorooctane sulfonamide) acetate; MeFOSAA, 2-(N-methyl-perfluorooctane sulfonamide) acetate; DEHP, diethylhexyl phthalate; MBP, mono-n-butyl phthalate; MBzP, mono-benzyl phthalate; MCPP, mono-3-carboxypropyl phthalate; MEHP, mono-2-ethylhexyl phthalate; MIBP, mono-isobutyl phthalate; MEHP, mono-(2-ethylhexyl) phthalate.

References (time period)	Location	Design	Used sample	Method	Sample size	Adjusting variables	Diagnostic criteria for GDM	Comparison categories	Endocrine disrupter	Cases (n)
Vafeidi et al. 2016 (2007.02-2008.02)	Spain	Cohort	Serum	GC-MS/MS	939	Gestational age at sampling (weeks), maternal age (b30 years, 30 years), pre-pregnancy BMI (kilograms per meter squared), parity (primiparous, multiparous), maternal educational level [low (9 years of mandatory schooling), medium (N9 years of schooling up to attending postsecondary school education), high (attending university or having a university/technical college degree)], smoking during pregnancy (never, ever), gestational weight gain (kilograms) and maternal serum triglycerides and cholesterol	GDM diagnoses were made when two or more of the fast plasma glucose ≥ 95 mg/dL, ≥ 180 mg/dL at 1 h-OGTT, ≥ 155 mg/dL at 2 h-OGTT, or ≥ 140 mg/dL at 3 h-OGTT	Per 10-fold increase	PCBs	4 (2
Wang et al. 2018a (2013.01-2013.03)	China	Case-control	Serum	UPLC	252	BMI, gestational weight gain, ethnic groups, maternal education, parity, maternal drinking during pregnancy, and household income	GDM diagnoses were made when the fast plasma glucose ≥ 95 mg/dL, ≥ 180 mg/dL at 1 h-OGTT, ≥ 155 mg/dL at 2 h-OGTT, or ≥ 140 mg/dL at 3 h-OGTT	Per 1 ng/mL increase in serum PFASs	PFOA	1 (1
									PFNA	1 (2
									PFDA	0 (2
									PFOS	0 (1
									PFUnDA	1 (2
									PFHxS	1 (1
Liu et al. 2018 (2013.08-2015.06)	China	Case-control	Serum	GC-HRMS	439	Pregnancy BMI, serum triglyceride and total cholesterol	GDM was defined if a woman had any of the following plasma glucose values: (1) Fasting: ≥ 5.1 mmol/L; (2) 1 h: ≥ 10.0 mmol/L; and (3) 2 h: ≥ 8.5 mmol/L in the 75-g oral glucose tolerance test (OGTT)	Q4 vs. Q1	PBDE-28	2 (3
									PBDE-47	2 (2
									PBDE-99	2 (2
									PBDE-100	2 (2

Abbreviations: SD, standard deviation; BMI, body mass index; FPG, fasting plasma glucose; 1h-PG, 1h plasma glucose; 2h-PG, 2h plasma glucose; GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test; GC-MS, gas chromatography coupled to mass detection; GC/MS, gas chromatography mass spectrometry; MS, liquid chromatography coupled to mass spectrometry; GC-MS/MS, gas chromatograph triple quadrupole mass spectrometer; UPLC-MS/MS, ultra-performance liquid chromatography coupled with triple quadrupole tandem mass spectrometry; HPLC, high performance liquid chromatography; GC-HRMS, gas chromatography high resolution mass spectrometry; LC-MS/MS, liquid chromatography coupled with triple quadrupole tandem mass spectrometry; UPLC-Q/TOF MS, ultra-performance liquid chromatography coupled to quadrupole time-of-flight mass spectrometry; T2D, type 2 diabetes; ppBMI, pre-pregnancy BMI; PBDEs, Polybrominated diphenylethers; PCBs, Polychlorinated biphenyls; PAEs, phthalates; PFAS, Per- and polyfluoroalkyl substances; PFNA, Perfluorononanoic acid; PFOA, Perfluorooctanoic acid; PFDA, Perfluorodecanoic acid; PFHxS, Perfluorohexanesulfonic acid; PFOS, Perfluorooctanesulfonic acid; PFUnDA, Perfluoroundecanoic acid; PFDoA, perfluorododecanoic acid; PFBS, perfluorobutane sulfonate; EtFOSAA, 2-(N-ethyl-perfluorooctane sulfonamide) acetate; MeFOSAA, 2-(N-methyl-perfluorooctane sulfonamide) acetate; DEHP, diethylhexyl phthalate; MBP, mono-n-butyl phthalate; MBzP, mono-benzyl phthalate; MCPP, mono-3-carboxypropyl phthalate; MEHP, mono-2-ethylhexyl phthalate; MIBP, mono-isobutyl phthalate; MEHP, mono-(2-ethylhexyl) phthalate.

References (time period)	Location	Design	Used sample	Method	Sample size	Adjusting variables	Diagnostic criteria for GDM	Comparison categories	Endocrine disrupter	C ()
									PBDE-153	3 ()
									PBDE-154	1 ()
									PBDEs	2 ()
Zhang et al. 2018 (2013.08-2015.06)	China	Case-control	Serum	GC-HRMS	231	no	GDM diagnoses were made when the fast plasma glucose ≥ 5.1 mmol/L; ≥ 10 mmol/L at 1 h-OGTT, ≥ 8.5 mmol/L at 2 h-OGTT	Na	PCB-28	1 3
									PCB-52	1 2
									PCB-101	1 2
									PCB-138	1 2
									PCB-153	1 1
									PCB-180	1 1
									PCBs	4 2
Shapiro et al. 2015 (2008-2010)	Canada	Cohort	Urine	LC-MS/MS	1274	Maternal age, race, pre-pregnancy BMI, education and specific gravity	GDM was defined if ≥ 2 of the following plasma glucose values: (1) Fasting: ≥ 5.3 mmol/L; (2) 1 h: ≥ 10.6 mmol/L; (3) 2 h: ≥ 9.2 mmol/L in the 75-g oral glucose tolerance test (OGTT)	Q4 vs. Q1	MEP	0 (1
									MBP	0 (2
									MBzP	1 (2
									MCP	0 (1
									DEHP	0 (2
Shapiro et al. 2016 (2008-2010)	Canada	Cohort	Urine	GC/MSMS and UPLC-MS-MS	1274	Maternal age, race, pre-pregnancy BMI and education; analyses for organophosphorus pesticide metabolites are additionally adjusted for urinary specific gravity; analyses for PCBs and organochlorine pesticides are additionally adjusted for total lipids.	GDM was defined if ≥ 2 of the following plasma glucose values: (1) Fasting: ≥ 5.3 mmol/L; (2) 1 h: ≥ 10.6 mmol/L; (3) 2 h: ≥ 9.2 mmol/L in the 75-g oral glucose tolerance test (OGTT)	Q4 vs. Q1	PFOA	0 (2
									PFOS	0 (1
									PFHxS	1 (3
									PCB-118	1 (2
									PCB-138	1 (2

Abbreviations: SD, standard deviation; BMI, body mass index; FPG, fasting plasma glucose; 1h-PG, 1h plasma glucose; 2h-PG, 2h plasma glucose; GDM, gesta diabetes mellitus; OGTT, oral glucose tolerance test; GC-MS, gas chromatography coupled to mass detection; GC/MS, gas chromatography mass spectrometry; MS, liquid chromatography coupled to mass spectrometry; GC-MS/MS, gas chromatograph triple quadrupole mass spectrometer; UPLC-MS/MS, ultra-perform liquid chromatography coupled with triple quadrupole tandem mass spectrometry; HPLC, high performance liquid chromatography; GC-HRMS, gas chromatography high resolution mass spectrometry; LC-MS/MS, liquid chromatography coupled with triple quadrupole tandem mass spectrometry; UPLC-Q/TOF MS, ultra-performance liquid chromatography coupled to quadrupole time-of-flight mass spectrometry; T2D, type 2 diabetes; ppBMI, pre-pregnancy BMI; PBDEs, Polybrominated diphenylethers; PCBs, Polychlorinated biphenyls; PAEs, phthalates; PFAS, Per- and polyfluoroalkyl substances; PFNA, Perfluorononanoic acid; PFOA, Perfluorooctanoic acid; PFDA, Perfluorodecanoic acid; PFHxS, Perfluorohexanesulfonic acid; PFOS, Perfluorooctanesulfonic acid; PFUnDA, Perfluoroundecanoic acid; PFDoA, perfluorododecanoic acid; PFBS, perfluorobutane sulfonate; EtFOSAA, 2-(N-ethyl-perfluorooctane sulfonamide) acetate; MeFOSAA, 2-(N-methyl-perfluorooctane sulfonamide) acetate; DEHP, diethylhexyl phthalate; MBP, mono-n-butyl phthalate; MBzP, mono-benzyl phthalate; MCP, mono-3-carboxypropyl phthalate; MEHP, mono-2-ethylhexyl phthalate; MIBP, mono-isobutyl phthalate; MEHP, mono-(2-ethylhexyl) phthalate.

References (time period)	Location	Design	Used sample	Method	Sample size	Adjusting variables	Diagnostic criteria for GDM	Comparison categories	Endocrine disrupter	C (
									PCB-153	1 (2
									PCB-180	1 (2
									PCBs	1 (2
Jaacks et al.2016 (2005-2007)	USA	Cohort	Serum	HPLC– MS/MS	258	Total serum lipids estimated, age, and waist-to-height ratio, all specified continuously	GDM was identified from medical record	Na	PCBs	0 (1
									PCB-28	0 (2
									PCB-101	1 (1
									PCB-118	0 (1
									PCB-138	0 (0
									PCB-153	0 (0
									PCB-180	0 (0
Smarr et al. 2016 (2005- 2009)	USA	Cohort	Serum	GC/MS	258	Serum lipids, age, BMI, non-white race, smoking, and the sum of remaining chemicals in the relevant class of compounds	GDM was identified from medical record	Na	PBDE-28	0 (1
									PBDE-47	0 (1
									PBDE-99	0 (1
									PBDE-100	2 (2
									PBDE-153	1 (2
									PBDE-154	1 (2
Rahman et al.2019 (2009.07- 2013.01)	USA	Cohort	Plasma	UPLC	2334	Maternal age (continuous), enrollment BMI (19–24.9; 25–29.9), education (<college; some college/undergraduate; graduate/post graduate), parity	GDM was defined if fasting plasma glucose (FPG)≥ 5.3mmol/L, or 1-hour plasma glucose (1h-	Per SD increment	PCB-101	1 (1
									PCB-118	0 (1

Abbreviations: SD, standard deviation; BMI, body mass index; FPG, fasting plasma glucose; 1h-PG, 1h plasma glucose; 2h-PG, 2h plasma glucose; GDM, gesta diabetes mellitus; OGTT, oral glucose tolerance test; GC-MS, gas chromatography coupled to mass detection; GC/MS, gas chromatography mass spectrometry; LC-MS/MS, liquid chromatography coupled to mass spectrometry; GC-MS/MS, gas chromatograph triple quadrupole mass spectrometer; UPLC-MS/MS, ultra-perform liquid chromatography coupled with triple quadrupole tandem mass spectrometry; HPLC, high performance liquid chromatography; GC-HRMS, gas chromatography coupled with high resolution mass spectrometry; LC-MS/MS, liquid chromatography coupled with triple quadrupole tandem mass spectrometry; UPLC-Q/TOF MS, ultra-performance liquid chromatography coupled to quadrupole time-of-flight mass spectrometry; T2D, type 2 diabetes; ppBMI, pre-pregnancy BMI; PBDEs, Polybrominated diphenylethers; PCBs, Polychlorinated biphenyls; PAEs, phthalates; PFAS, Per- and polyfluoroalkyl substances; PFNA, Perfluorononanoic acid; PFOA, Perfluorooctanoic acid; PFDA, Perfluorodecanoic acid; PFHxS, Perfluorohexanesulfonic acid; PFOS, Perfluorooctanesulfonic acid; PFUnDA, Perfluoroundecanoic acid; PFDoA, perfluorododecanoic acid; PFBS, perfluorobutane sulfonate; EtFOSAA, 2-(N-ethyl-perfluorooctane sulfonamide) acetate; MeFOSAA, 2-(N-methyl-perfluorooctane sulfonamide) acetate; DEHP, diethylhexyl phthalate; MBP, mono-n-butyl phthalate; MBzP, mono-benzyl phthalate; MCPP, mono-3-carboxypropyl phthalate; MEHP, mono-isobutyl phthalate; MIBP, mono-isobutyl phthalate; MEHP, mono-(2-ethylhexyl) phthalate.

References (time period)	Location	Design	Used sample	Method	Sample size	Adjusting variables	Diagnostic criteria for GDM	Comparison categories	Endocrine disrupter	C 9
						(nulliparous; multiparous), race/ethnicity (white, African American, Hispanic, Asian), family history of type 2 diabetes among first degree relatives, serum cotinine level (continuous), and serum total lipids (continuous, mg/dL)	PG) ≥ 10.0 mmol/L, or 2- hour plasma glucose (2h- PG) ≥ 8.6 mmol/L, or 3- hour plasma glucose ≥ 7.8 mmol/L		PCB-138	0 (1
									PCB-153	1 (1
									PCB-180	1 (1
									PCB-28	1 (1
									PCB-52	1 (1
									PCBs	0 (1
									PFDA	0 (1
									PFHxS	0 (1
									PFNA	0 (1
									PFOA	0 (1
									PFOS	0 (1
									PFUnDA	0 (1
									PBDE-28	1 (1
									PBDE-100	0 (1
									PBDE-153	0 (1
									PBDE-154	1 (1
									PBDE-47	1 (1
									PBDE-99	1 (1

Abbreviations: SD, standard deviation; BMI, body mass index; FPG, fasting plasma glucose; 1h-PG, 1h plasma glucose; 2h-PG, 2h plasma glucose; GDM, gesta diabetes mellitus; OGTT, oral glucose tolerance test; GC-MS, gas chromatography coupled to mass detection; GC/MS, gas chromatography mass spectrometry; LC-MS/MS, liquid chromatography coupled to mass spectrometry; GC-MS/MS, gas chromatograph triple quadrupole mass spectrometer; UPLC-MS/MS, ultra-perform liquid chromatography coupled with triple quadrupole tandem mass spectrometry; HPLC, high performance liquid chromatography; GC-HRMS, gas chromatography coupled with high resolution mass spectrometry; LC-MS/MS, liquid chromatography coupled with triple quadrupole tandem mass spectrometry; UPLC-Q/TOF MS, ultra-performance liquid chromatography coupled to quadrupole time-of-flight mass spectrometry; T2D, type 2 diabetes; ppBMI, pre-pregnancy BMI; PBDEs, Polybrominated diphenylethers; PCBs, Polychlorinated biphenyls; PAEs, phthalates; PFAS, Per- and polyfluoroalkyl substances; PFNA, Perfluorononanoic acid; PFOA, Perfluorooctanoic acid; PFDA, Perfluorodecanoic acid; PFHxS, Perfluorohexanesulfonic acid; PFOS, Perfluorooctanesulfonic acid; PFUnDA, Perfluoroundecanoic acid; PFDoA, perfluorododecanoic acid; PFBS, perfluorobutane sulfonate; EtFOSAA, 2-(N-ethyl-perfluorooctane sulfonamide) acetate; MeFOSAA, 2-(N-methyl-perfluorooctane sulfonamide) acetate; DEHP, diethylhexyl phthalate; MBP, mono-n-butyl phthalate; MBzP, mono-benzyl phthalate; MCPP, mono-3-carboxypropyl phthalate; MEHP, mono-isobutyl phthalate; MIBP, mono-isobutyl phthalate; MEHP, mono-(2-ethylhexyl) phthalate.

References (time period)	Location	Design	Used sample	Method	Sample size	Adjusting variables	Diagnostic criteria for GDM	Comparison categories	Endocrine disrupter	OR (95% CI)
Matilla-Santander et al. 2017 (2003-2008)	Spain	Cohort	Serum	HPLC–MS/MS	1240	Subcohort, country of birth, prepregnancy body mass index, previous breastfeeding, parity, gestational week at blood extraction, physical activity, and relative Mediterranean Diet Score.	Results of the OGTT are routinely used to classify women as having GDM if two or more of the baseline or postchallenge blood glucose concentrations exceed National Diabetes Data Group (NDDG) reference values	Per 10-fold increase	PFOA	1 (0.2–2)
									PFOS	2 (0.6–6)
									PFHxS	1 (0.3–3)
									PFNA	0 (0–1)
Valvi et al. 2017 (1997-2000)	Norway	Cohort	Serum	HPLC–MS/MS	604	Maternal age at delivery, education, parity, pre-pregnancy BMI (continuous) and smoking during pregnancy	GDM was identified from medical record	Per unit increase.	PCBs	0 (0–1)
									PFOS	0 (0–1)
									PFOA	0 (0–1)
									PFHxS	1 (0–1)
									PFDA	1 (0–1)
									PFNA	0 (0–1)
Neblett et al. 2020 (2012-2015)	USA	Cross-sectional	Serum	GC/MS	254	Age (current age & age at pregnancy), BMI, and total lipid levels.	Self-report	Na	PCBs	1 (0–1)
Fisher et al. 2018 (2001-2009)	UK	Case-control	Serum	LC–MS	232	Age, pre-pregnancy body mass index (log-transformed), IMD (log-transformed), and parity	GDM was diagnosed if they meet one or more of the following criteria: Fasting plasma glucose ≥ 5.1 mmol/l, 60-min plasma glucose ≥ 10.0 mmol/l, or 120-min plasma glucose ≥ 8.5 mmol/l	Q4 vs. Q1	MEP	1 (0.3–3)
									MIBP	4 (0–1)
									MBP	1 (0.3–3)
Shaffer et al. 2019 (2010-2012)	USA	Cohort	Urine	HPLC–MS/MS		Na	GDM is diagnosed in women with two or more abnormal values in the OGTT: fasting: 95mg/dL; 1h: 180mg/dL; 2h:	Per interquartile-range increase	MEP	1 (0.2–2)
									MBP	1 (0–1)

Abbreviations: SD, standard deviation; BMI, body mass index; FPG, fasting plasma glucose; 1h-PG, 1h plasma glucose; 2h-PG, 2h plasma glucose; GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test; GC-MS, gas chromatography coupled to mass detection; GC/MS, gas chromatography mass spectrometry; LC-MS, liquid chromatography coupled to mass spectrometry; GC-MS/MS, gas chromatograph triple quadrupole mass spectrometer; UPLC-MS/MS, ultra-performance liquid chromatography coupled with triple quadrupole tandem mass spectrometry; HPLC, high performance liquid chromatography; GC-HRMS, gas chromatography high resolution mass spectrometry; LC-MS/MS, liquid chromatography coupled with triple quadrupole tandem mass spectrometry; UPLC-Q/TOF MS, ultra-performance liquid chromatography coupled to quadrupole time-of-flight mass spectrometry; T2D, type 2 diabetes; ppBMI, pre-pregnancy BMI; PBDEs, Polybrominated diphenylethers; PCBs, Polychlorinated biphenyls; PAEs, phthalates; PFAS, Per- and polyfluoroalkyl substances; PFNA, Perfluorononanoic acid; PFOA, Perfluorooctanoic acid; PFDA, Perfluorodecanoic acid; PFHxS, Perfluorohexanesulfonic acid; PFOS, Perfluorooctanesulfonic acid; PFUnDA, Perfluoroundecanoic acid; PFDoA, perfluorododecanoic acid; PFBS, perfluorobutane sulfonate; EtFOSAA, 2-(N-ethyl-perfluorooctane sulfonamide) acetate; MeFOSAA, 2-(N-methyl-perfluorooctane sulfonamide) acetate; DEHP, diethylhexyl phthalate; MBP, mono-n-butyl phthalate; MBzP, mono-benzyl phthalate; MCPP, mono-3-carboxypropyl phthalate; MEHP, mono-(2-ethylhexyl) phthalate; MIBP, mono-isobutyl phthalate; MEHP, mono-(2-ethylhexyl) phthalate.

References (time period)	Location	Design	Used sample	Method	Sample size	Adjusting variables	Diagnostic criteria for GDM	Comparison categories	Endocrine disrupter	Cases (n)
							155 mg/dL; and 3h: 140 mg/dL		MCP	1 (1)
									MBP	1 (1)
									DEHP	1 (1)
									MEHP	1 (2)
									MIBP	1 (1)
Zhang et al.2017 (2013.05-2014.09)	China	Cohort	Urine	HPLC-MS/MS	3009	The FPG level of early stages pregnancy, maternal age, pre-pregnancy BMI, monthly household income, reproductive history, gestational weeks, concentration of urinary creatinine	GDM was diagnosed if fasting plasma glucose (FPG) ≥ 5.1 mmol/L (≥ 92 mg/dL), or 1h plasma glucose (1 h-PG) ≥ 10.0 mmol/L (≥ 180 mg/dL), or 2h plasma glucose (2 h-PG) ≥ 8.5 mmol/L (≥ 153 mg/dL)	Na	MEP	1 (1)
Xu et al.2020 (2017.01-2019.01)	China	Case-control	Serum	UPLC-Q/TOF MS	1575	Maternal age, sampling time, parity, BMI, educational level, and serum lipids	GDM was diagnosed if fasting plasma glucose (FPG) ≥ 5.1 mmol/L, or 1h plasma glucose (1 h-PG) ≥ 10.0 mmol/L, or 2h plasma glucose (2 h-PG) ≥ 8.5 mmol/L	Per 10-fold increase	PFOA	1 (3)
									PFOS	1 (1)
									PFDA	1 (2)
									PFNA	1 (2)
									PFHxS	1 (3)
									PFBS	1 (2)
									PFDaA	2 (3)
Preston et al.2020 (1999-2002)	USA	Cohort	Plasma	HPLC-MS/MS	1540	Maternal age, pre-pregnancy BMI, prior history of GDM, parity, race, ethnicity, smoking, education	GDM is diagnosed in women with two or more abnormal values in the OGTT: fasting:	Q4 vs. Q1	PFOA	1 (2)

Abbreviations: SD, standard deviation; BMI, body mass index; FPG, fasting plasma glucose;1h-PG, 1h plasma glucose; 2h-PG, 2h plasma glucose; GDM, gesta diabetes mellitus; OGTT, oral glucose tolerance test; GC-MS, gas chromatography coupled to mass detection; GC/MS, gas chromatography mass spectrometry; LC-MS/MS, liquid chromatography coupled to mass spectrometry; GC-MS/MS, gas chromatograph triple quadrupole mass spectrometer; UPLC-MS/MS, ultra-perform liquid chromatography coupled with triple quadrupole tandem mass spectrometry; HPLC, high performance liquid chromatography; GC-HRMS, gas chromatography coupled with high resolution mass spectrometry; LC-MS/MS, liquid chromatography coupled with triple quadrupole tandem mass spectrometry; UPLC-Q/TOF MS, ultra-performance liquid chromatography coupled to quadrupole time-of-flight mass spectrometry; T2D, type 2 diabetes; ppBMI, pre-pregnancy BMI; PBDEs, Polybrominated diphenylethers; PCBs, Polychlorinated biphenyls; PAEs, phthalates; PFAS, Per- and polyfluoroalkyl substances; PFNA, Perfluorononanoic acid; PFOA, Perfluorooctanoic acid; PFDA, Perfluorodecanoic acid; PFHxS, Perfluorohexanesulfonic acid; PFOS, Perfluorooctanesulfonic acid; PFUnDA, Perfluoroundecanoic acid; PFDaA, perfluorododecanoic acid; PFBS, perfluorobutane sulfonate; EtFOSAA, 2-(N-ethyl-perfluorooctane sulfonamide) acetate; MeFOSAA, 2-(N-methyl-perfluorooctane sulfonamide) acetate; DEHP, diethylhexyl phthalate; MBP, mono-n-butyl phthalate; MBzP, mono-benzyl phthalate; MCP, mono-3-carboxypropyl phthalate; MEHP, mono-(2-ethylhexyl) phthalate; MIBP, mono-isobutyl phthalate; MEHP, mono-(2-ethylhexyl) phthalate.

References (time period)	Location	Design	Used sample	Method	Sample size	Adjusting variables	Diagnostic criteria for GDM	Comparison categories	Endocrine disrupter	Cases (n)
							95mg/dL; 1h: 180mg/dL; 2h: 155 mg/dL; and 3h: 140 mg/dL	Q3 vs. Q1	PFOS	1 (3)
									PFNA	1 (2)
									PFHxS	1 (2)
Wang et al.2018b (2013.09- 2014.12)	China	Cohort	Serum	UPLC- Q/TOF MS	560	Pregnant age, diabetes mellitus history of relatives, husband smoking status, family per capita income, baby sex, averaged intake of meat,	GDM was diagnosed if fasting plasma glucose (FPG) ≥ 5.1 mmol/L, or 1h plasma	Q3 vs. Q1	PFOS	2 (5)
									PFOA	0 (1)
Gao et al. 2021 (2013.05- 2019.05)	China	Cohort	Urine	LC-MS	3273	Maternal age, pre- pregnancy BMI, income and primiparous	GDM was diagnosed if fasting plasma glucose (FPG) ≥ 5.1 mmol/L (≥ 92 mg/dL), or 1h plasma glucose (1 h- PG) ≥ 10.0 mmol/L (≥ 180 mg/dL), or 2h plasma glucose (2 h- PG) ≥ 8.5 mmol/L (≥ 153 mg/dL)	Per 10-fold increase	MEP	1 (1)
									MBP	1 (1)
									MBzP	0 (1)
									MEHP	0 (1)
									DEHP	0 (1)
Guo et al. 2020 (2013.07- 2014.07)	China	Cross- sectional	Meconium	LC- MS/MS	251	Mother's age, pre- pregnancy BMI and gestational age	GDM was diagnosed if fasting plasma glucose (FPG) ≥ 5.1 mmol/L (≥ 92 mg/dL), or 1h plasma glucose (1 h- PG) ≥ 10.0 mmol/L (≥ 180 mg/dL),	Per unit increase in ln	MEP	1 (2)
									MBP	3 (1)
									MIBP	2 (5)

Abbreviations: SD, standard deviation; BMI, body mass index; FPG, fasting plasma glucose; 1h-PG, 1h plasma glucose; 2h-PG, 2h plasma glucose; GDM, gesta diabetes mellitus; OGTT, oral glucose tolerance test; GC-MS, gas chromatography coupled to mass detection; GC/MS, gas chromatography mass spectrometry; LC-MS/MS, liquid chromatography coupled to mass spectrometry; GC-MS/MS, gas chromatograph triple quadrupole mass spectrometer; UPLC-MS/MS, ultra-perform liquid chromatography coupled with triple quadrupole tandem mass spectrometry; HPLC, high performance liquid chromatography; GC-HRMS, gas chromatography coupled with high resolution mass spectrometry; LC-MS/MS, liquid chromatography coupled with triple quadrupole tandem mass spectrometry; UPLC-Q/TOF MS, ultra-performance liquid chromatography coupled to quadrupole time-of-flight mass spectrometry; T2D, type 2 diabetes; ppBMI, pre-pregnancy BMI; PBDEs, Polybrominated diphenylethers; PCBs, Polychlorinated biphenyls; PAEs, phthalates; PFAS, Per- and polyfluoroalkyl substances; PFNA, Perfluorononanoic acid; PFOA, Perfluorooctanoic acid; PFDA, Perfluorodecanoic acid; PFHxS, Perfluorohexanesulfonic acid; PFOS, Perfluorooctanesulfonic acid; PFUnDA, Perfluoroundecanoic acid; PFDoA, perfluorododecanoic acid; PFBS, perfluorobutane sulfonate; EtFOSAA, 2-(N-ethyl-perfluorooctane sulfonamide) acetate; MeFOSAA, 2-(N-methyl-perfluorooctane sulfonamide) acetate; DEHP, diethylhexyl phthalate; MBP, mono-n-butyl phthalate; MBzP, mono-benzyl phthalate; MCPP, mono-3-carboxypropyl phthalate; MEHP, mono-(2-ethylhexyl) phthalate; MIBP, mono-isobutyl phthalate; MEHP, mono-(2-ethylhexyl) phthalate.

References (time period)	Location	Design	Used sample	Method	Sample size	Adjusting variables	Diagnostic criteria for GDM	Comparison categories	Endocrine disrupter	C (((
							or 2h plasma glucose (2 h- PG) $\geq$ 8.5 mmol/L ($\geq$ 153 mg/dL)		MEHP	3 ((
Zukin et al. 2021 (1999- 2000)	USA	Cohort	Urine		415	Maternal age, income, maternal education, marital status, sugar- sweetened beverage consumption, country of birth, and maternal pre-pregnancy BMI.	GDM was diagnosis if either (1) maternal plasma glucose levels on the OGTT exceeded at least two of the following plasma levels: fasting 95 mg/dL (5.3 mmol/L), 1 h 180 mg/dL (10.0 mmol/L); 2 h 155 mg/dL (8.6 mmol/L); 3hr 140 mg/dL (7.8 mmol/L) or (2) a diagnosis of GDM in the maternal medical records	Na	MEP MBP MIBP MBzP DEHP MCP	1 (1 1 (1 1 (1 1 (1
Liu et al. 2019 (2013.08- 2015.06)	China	Case- control	Serum	GC-HRMS	439	Maternal age, pregnancy BMI, fetal sex, and serum triglyceride and total cholesterol.	GDM was defined if a woman had any of the following plasma glucose values: (1) Fasting: $\geq$ 5.1 mmol/L; (2) 1 h: $\geq$ 10.0 mmol/L; and (3) 2 h: $\geq$ 8.5 mmol/L in the 75-g oral glucose tolerance test (OGTT)	Per unit increase in ln	PFOS PFOA	1 (2 1 (1
Yu et al.2021(2013- 2016)	China	Cohort	Plasma	HPLC- MS/MS	2747	Maternal age, pre- pregnant BMI, maternal education, smoking status, parity, averaged physical activity and economic status.	GDM was diagnosed if fasting plasma glucose (FPG) $\geq$ 5.1 mmol/L, or 1h plasma glucose (1 h- PG) $\geq$ 10.0 mmol/L, or 2h plasma glucose (2 h- PG) $\geq$ 8.5 mmol/L	Per 10-fold increase	PFOA PFOS PFNA PFDA PFHxS	1 (1 1 (1 1 (1 1 (1

Abbreviations: SD, standard deviation; BMI, body mass index; FPG, fasting plasma glucose; 1h-PG, 1h plasma glucose; 2h-PG, 2h plasma glucose; GDM, gesta diabetes mellitus; OGTT, oral glucose tolerance test; GC-MS, gas chromatography coupled to mass detection; GC/MS, gas chromatography mass spectrometry; MS, liquid chromatography coupled to mass spectrometry; GC-MS/MS, gas chromatograph triple quadrupole mass spectrometer; UPLC-MS/MS, ultra-perform liquid chromatography coupled with triple quadrupole tandem mass spectrometry; HPLC, high performance liquid chromatography; GC-HRMS, gas chromatography high resolution mass spectrometry; LC-MS/MS, liquid chromatography coupled with triple quadrupole tandem mass spectrometry; UPLC-Q/TOF MS, ultra-performance liquid chromatography coupled to quadrupole time-of-flight mass spectrometry; T2D, type 2 diabetes; ppBMI, pre-pregnancy BMI; PBDEs, Polybrominated diphenylethers; PCBs, Polychlorinated biphenyls; PAEs, phthalates; PFAS, Per- and polyfluoroalkyl substances; PFNA, Perfluorononanoic acid; PFOA, Perfluorooctanoic acid; PFDA, Perfluorodecanoic acid; PFHxS, Perfluorohexanesulfonic acid; PFOS, Perfluorooctanesulfonic acid; PFUnDA, Perfluoroundecanoic acid; PFDoA, Perfluorododecanoic acid; PFBS, perfluorobutane sulfonate; EtFOSAA, 2-(N-ethyl-perfluorooctane sulfonamide) acetate; MeFOSAA, 2-(N-methyl-perfluorooctane sulfonamide) acetate; DEHP, diethylhexyl phthalate; MBP, mono-n-butyl phthalate; MBzP, mono-benzyl phthalate; MCP, mono-3-carboxypropyl phthalate; MEHP, mono-(2-ethylhexyl) phthalate; MIBP, mono-isobutyl phthalate; MEHP, mono-(2-ethylhexyl) phthalate.

References (time period)	Location	Design	Used sample	Method	Sample size	Adjusting variables	Diagnostic criteria for GDM	Comparison categories	Endocrine disrupter	C
									PFUnDA	(1
									PFDaA	(1
									PFBS	1 (1

Abbreviations: SD, standard deviation; BMI, body mass index; FPG, fasting plasma glucose; 1h-PG, 1h plasma glucose; 2h-PG, 2h plasma glucose; GDM, gesta diabetes mellitus; OGTT, oral glucose tolerance test; GC-MS, gas chromatography coupled to mass detection; GC/MS, gas chromatography mass spectrometry; MS, liquid chromatography coupled to mass spectrometry; GC-MS/MS, gas chromatograph triple quadrupole mass spectrometer; UPLC-MS/MS, ultra-perform liquid chromatography coupled with triple quadrupole tandem mass spectrometry; HPLC, high performance liquid chromatography; GC-HRMS, gas chromatography high resolution mass spectrometry; LC-MS/MS, liquid chromatography coupled with triple quadrupole tandem mass spectrometry; UPLC-Q/TOF MS, ultra-performance liquid chromatography coupled to quadrupole time-of-flight mass spectrometry; T2D, type 2 diabetes; ppBMI, pre-pregnancy BMI; PBDEs, Polybrominated diphenylethers; PCBs, Polychlorinated biphenyls; PAEs, phthalates; PFAS, Per- and polyfluoroalkyl substances; PFNA, Perfluorononanoic acid; PFOA, Perfluorooctanoic acid; PFDA, Perfluorodecanoic acid; PFHxS, Perfluorohexanesulfonic acid; PFOS, Perfluorooctanesulfonic acid; PFUnDA, Perfluoroundecanoic acid; PFDaA, perfluorododecanoic acid; PFBS, perfluorobutane sulfonate; EtFOSAA, 2-(N-ethyl-perfluorooctane sulfonamide) acetate; MeFOSAA, 2-(N-methyl-perfluorooctane sulfonamide) acetate; DEHP, diethylhexyl phthalate; MBP, mono-n-butyl phthalate; MBzP, mono-benzyl phthalate; MCP, mono-3-carboxypropyl phthalate; MEHP, mono-ethyl phthalate; MIBP, mono-isobutyl phthalate; MEHP, mono-(2-ethylhexyl) phthalate.

Accordance to the items in inclusion criteria (the summary effect estimates were calculated if the endocrine-disrupting chemicals exposure have been examined in ≥ 2 studies as follow: a) risk per unit increase in continuous exposure and b) risk of high versus low exposure level in individual study) and the searching results, the EDCs evaluated in this paper are: PBDEs, PCBs, PAEs, PFAS, perfluorononanoic acid (PFNA), perfluorooctanoic acid (PFOA), perfluorodecanoic acid (PFDA), perfluorohexanesulfonic acid (PFHxS), perfluorooctanesulfonic acid (PFOS), perfluoroundecanoic acid (PFUnDA), perfluorododecanoic acid (PFDaA), perfluorobutane sulfonate (PFBS), 2-(N-ethyl-perfluorooctane sulfonamide) acetate (EtFOSAA), 2-(N-methyl-perfluorooctane sulfonamide) acetate (MeFOSAA), diethylhexyl phthalate (DEHP), mono-n-butyl phthalate(MBP), mono-benzyl phthalate(MBzP), mono-3-carboxypropyl phthalate (MCP), mono-ethyl phthalate (MEP), mono-isobutyl phthalate (MIBP), and mono-(2-ethylhexyl) phthalate (MEHP).

Polychlorinated biphenyls and the risk of GDM

Eight studies[22–29] were included in the analysis of PCBs and the risk of GDM. The EDCs of PCBs including PCB-101, PCB-118, PCB-138, PCB-153, PCB-180, PCB-28, PCB-52, and total PCBs were enrolled in this study. The result of heterogeneity test indicated significant heterogeneity among the included studies ($P=0.000$, $I^2 = 64.0\%$). Thus, a random-effect model was used, the overall estimated OR exhibited a significant association between PCBs and the risk of GDM (OR = 1.14; 95% CI = 1.00-1.31, $n=8$), indicating that PCBs is a risk factor for GDM. The forest plot is displayed in Fig. 2. In the subgroup analysis, no significant association was observed between the eight PCBs congeners and GDM risk. When the subgroup analysis was classified by the design of studies, the summary OR from cohort and non-cohort studies were 0.99 (95% CI = 0.91-1.09; $n = 5$) and 1.60 (95% CI = 1.23-2.09; $n = 3$), respectively (Table 2).

Table 2
Endocrine-disrupting chemicals and the risk of gestational diabetes mellitus: the summary ORs of cohort and non-cohort studies and the results of publication bias.

ECDs	Type	No. of studies	Effect size, pooled OR (95% CI)	Heterogeneity		Publication bias	
				<i>P</i> value	I^2 value, %	Egger <i>P</i> value	Begg <i>P</i> value
PCBs	Cohort	5	0.99 (0.91-1.09)	0.394	5.0	0.539	0.933
	Non-cohort	3	1.60 (1.23-2.09)	0.000	68.2	0.790	0.631
PBDEs	Cohort	2	1.12 (1.00-1.26)	0.006	57.8	0.221	0.15
	Non-cohort	2	2.21 (1.83-2.68)	0.993	0.0	0.639	0.721
PAEs	Cohort	5	1.08 (1.02-1.15)	0.391	0.0	0.666	0.597
	Non-cohort	2	2.17 (1.45-3.26)	0.353	0.0	0.609	0.368
PFASs	Cohort	8	1.06 (1.00-1.12)	0.574	0.0	0.848	0.395
	Non-cohort	3	1.22 (1.04-1.44)	0.010	59.1	0.263	0.621

Abbreviations: PCBs, polychlorinated biphenyls; PBDEs, poly-brominated diphenyl ethers; PFAS, per- and polyfluoroalkyl substances; PAEs, phthalates; CI, confidence interval; OR, odds ratio.

Polybrominated diphenyl ethers and risk of GDM

Four literatures[23, 27, 30, 31] were enrolled to investigate the association between PBDEs and risk of GDM. The subgroup analysis was performed according to PBDE congeners. Six PBDE congeners were included: PBDE-100, PBDE-153, PBDE-154, PBDE-28, PBDE-47, PBDE-99, and total PBDEs. A random-effect model was used to estimate the summary OR, the result displayed a remarkable correlation between PBDEs and risk of GDM (OR = 1.32; 95% CI = 1.15-1.53; $n=4$), with significant heterogeneity among the included studies ($P=0.00$, $I^2 = 72.3\%$). The forest plot is displayed in Fig. 3. The subgroup analysis displayed

that PBDE-154 produced a significantly contribution to the risk of GDM (OR =1.23; 95% CI = 1.13-1.35), indicating that PBDE-154 may be a risk factor for GDM. Meanwhile, the pooled OR of total PBDEs was 2.21 (95% CI = 1.55-3.16), suggesting the total PBDEs is a risk factor for GDM. While, the summary ORs for the most other PBDE congeners (PBDE-100, PBDE-153, PBDE-28, PBDE-47, and PBDE-99) did not show significant association. When the subgroup analysis was classified by the design of studies, the summary OR from cohort and non-cohort studies were 1.12 (95% CI = 1.00-1.26; n = 2) and 2.21 (95% CI = 1.83-2.68; n=2), respectively (Table 2).

Phthalates and risk of GDM

Seven literatures [13, 15, 32–36] were selected to assess the association between PAEs and GDM, and the subgroup analysis was performed according to the PAEs metabolites. Seven metabolites including DEHP, MBP, MBzP, MCPP, MEHP, MEP, and MiBP were enrolled. The heterogeneity test proved that the I^2 of the summary PAEs was 9.6% ($P=0.311$), thus a fixed-effect model was used to combine data, the forest plot is shown in Fig. 4. The summary OR indicated a significantly positive association between PAEs and risk of GDM (OR = 1.10; 95% CI = 1.04-1.16; n = 7). In subgroup analysis, MBP and MEP exposure were markedly associated with the risk of GDM (OR =1.21; 95% CI = 1.05-1.39 for MBP; OR =1.17; 95% CI = 1.03-1.32 for MBP), while the OR values of the other five PAEs metabolites indicated no statistical significance. When the subgroup analysis was classified according to the design of studies, the summary OR from cohort and non-cohort studies were 1.08 (95% CI = 1.02-1.15; n = 5) and 2.17 (95% CI = 1.45-3.26; n = 2), respectively (Table 2).

Per- and polyfluoroalkyl substances and risk of GDM

Eleven articles[23, 26, 29, 37–44] were included in the analysis of PFAS and the risk of GDM. The PFAS congeners enrolled in this study included PFDA, PFHxS, PFNA, PFOA, PFOS, PFUnDA, PFBS, PFDoA, EtFOSAA, and MeFOSAA. Heterogeneity among the enrolled articles indicated no statistical significance ($P = 0.011$ and $I^2 = 48.5\%$), suggesting that the results of the included literatures were statistically homogeneous. Thus, a fixed-effect model was used to evaluate the overall estimated OR and 95% CIs. The summary OR of PFAS and the risk of GDM was 1.09 (95% CI = 1.02-1.16; n = 11), indicating an additive effect on the risk of GDM, the forest plot is displayed in Fig. 5. In the subgroup analysis, the pooled OR value of the PFBS was markedly associated with the risk of GDM (OR =1.37; 95% CI = 1.17-1.53). While the pooled OR values of the other nine PFAS congeners and risk of GDM exhibited no significant association. When the subgroup analysis was classified according to the design of studies, the summary OR from cohort and non-cohort studies were 1.06 (95% CI = 1.00-1.12; n = 8) and 1.22 (95% CI = 1.04-1.44; n = 3), respectively (Table 2).

Publication bias and sensitivity analyses

As shown in Table 3. For PCBs, the Egger and Begg tests provided no evidence of substantial publication bias ($P=0.305$ for Egger test; $P= 0.591$ for Begg test). For PBDEs, neither the Egger test nor the Begg test reached significance ($P=0.130$ for Egger test; $P= 0.195$ for Begg test). For PAEs, the P value of Egger and Begg tests were 0.069 and 0.198 respectively, these results were not statistically significant. For PFAS, the Egger and Begg tests also provided no publication bias($P=0.535$ for Egger test; $P= 0.416$ for Begg test). Thus, no publication bias was observed in the included studies. Sensitivity analyses were evaluated by leave-one-out-method. We omitted each literatures from the analysis one-by-one. As shown in Additional Fig. 1, the results of PCBs, PBDEs, PAEs and PFAS were either marginal significant or significance, indicating that the results of the present meta-analysis were stable.

Table 3
Endocrine-disrupting chemicals and the risk of gestational diabetes mellitus: Summary ORs and the results of publication bias.

ECDs	No. of studies	Effect size, pooled OR (95% CI)	Heterogeneity		Publication bias	
			<i>P</i> value	I^2 value, %	Egger <i>P</i> value	Begg <i>P</i> value
PCBs	8	1.14 (1.00-1.31)	0.000	64.0	0.305	0.591
PBDEs	4	1.32 (1.15-1.53)	0.000	72.3	0.130	0.195
PAEs	7	1.10 (1.03-1.16)	0.302	9.6	0.069	0.198
PFAS	11	1.09 (1.02-1.16)	0.011	48.5	0.535	0.416
Abbreviations: PCBs, polychlorinated biphenyls; PBDEs, poly-brominated diphenyl ethers; PFAS, per- and polyfluoroalkyl substances; PAEs, phthalates; CI, confidence interval; OR, odds ratio.						

Discussion

EDCs are a special type of chemical capable of interfering with many hormone actions. Humans are exposed to EDCs via air inhalation, drinking water, and dermal absorption due to their widespread and worldwide use[45]. Several EDCs including PCBs, PBDEs, and PAEs have been shown to increase the risk of T2DM via different mechanisms[46–48]. However, these results did not necessarily generalizable to GDM because of the significant physiological changes that occur during pregnancy. Thus, the potential link between EDCs and GDM risk remains obscure. In the present systematic review and meta-analysis, we explored the relationship between EDCs (including PCBs, PBDEs, PAEs, and PFAS) and risk of GDM. The data indicated that certain kinds of EDCs exposure, including PCBs, PBDEs, PAEs, and PFASs are risk factors for GDM. As far as we know, this is the first comprehensive meta-analysis research creating the group modes according to its congeners to assess the possible association between EDCs and GDM, and our results suggest the opinion that exposure to certain kinds of EDCs are one of the modifying risk factors for GDM.

PCBs belong to the persistent organic pollutants, which can bioaccumulate and biomagnify within the food chain. PCB congeners are usually detected in human milk and serum due to their persistent characteristics. Previous epidemiology studies have indicated that PCBs differ in their effects on obesity, insulin resistance, or diabetes depending on the number of chlorine atoms, and heavily chlorinated PCBs were more likely to be associated with these effects, but such patterns were not consistent among researches [23, 49, 50]. Generally, individuals are exposed to various complex mixtures, and these complex exposure

models may produce synergistic, additive or antagonistic effects on human health. In our present study, although single PCBs congeners presented null associations in subgroup analysis, the synergistic effect of multiple PCBs congeners demonstrated a significant impact on the prevalence of GDM. Currently, there are limited experimental data exploring the risk of GDM with prenatal PCBs exposure. A previous study indicated that the activation of peroxisome proliferator-activated receptor alpha (PPAR α) via interacting with the aryl hydrocarbon receptor is a potential biological mechanisms of the association between PCBs and diabetes[51]. Another research using animal subjects demonstrated that sub-chronic exposure to PCBs disrupted the glucose homeostasis, suppressed the functions of pancreatic β -cells and reduced insulin levels in mice[46]. Although these mechanisms were not necessarily generalizable to GDM due to the significant physiological changes occurred during pregnancy, these results still provide some relevant evidences. Therefore, we can speculate that PCBs exposure might have a significant impact on the prevalence of GDM, but the underline mechanisms need to be further investigated.

PBDEs are a class of persistent organic pollutants that commonly used as flame retardants in household consumer products such as electronics and furniture. PBDEs can leach into the environment and enter the human body, it is associated with the endocrine and numerous health problems[52]. The result of PBDEs in the present study was in line with the enrolled literatures, which support the notion that PBDEs exposure is a risk factor of GDM. Dysglycemia displayed as continuum hyperglycemia during pregnancy is the main pathophysiological changes in GDM. Mechanistically, the main pathways of PBDEs leading to GDM may be multifaceted. A previous study used animal subjects to explore the biological plausibility for an association between PBDEs and GDM found a dose-response hyperglycemia and significant oxidative damage after exposure to PBDEs congener for 8 weeks[53]. Analogously, according to an in vitro study, exposure to PBDEs congeners (BDE-47 and BDE-85) can directly stimulate insulin secretion via activating thyroid receptor and Akt signaling in pancreatic β -cells[54]. T2D and GDM may be two clinical features of the same entity, the pathogenesis of both conditions are attributed to the continuum dysglycemia with the development of insulin resistance or impaired insulin secretion[30]. These data suggested that there are similar biologic pathways explaining EDCs exposure as it is associated with diabetes in both the general and gravid populations. Although, the precise underlying mechanisms between PBDE exposure and GDM have not been elucidated, our findings together with these biological evidences indicated that PBDEs can potentially contribute to the development of GDM.

PAEs are plasticizers used in many consumer applications such as food packaging, personal care products, and medical devices numerous. It can migrate into food and enter the human body, several metabolites of PAEs can be detected in the urine of >75% of the general population [55]. The result of PAEs in the present study showed that it is a risk factor of GDM, indicating the metabolic process of PAEs in the body could impair glucose metabolism and induce continuum hyperglycemia. Currently, the main mechanisms of PAEs and their metabolites contributing to the development of GDM are multifaceted. First, PAEs are a kind of endocrine disruptors associated with the alterations of steroid hormones, several PAEs have been found to be capable to bind with estrogen receptor α and possess estrogenic activity specifically [56]. There is considerable evidence to suggest that changes in estrogens level are associated with insulin resistance, alterations in adipocytes, and metabolic disorders in women[57–59]. Second, the prolonged activation of PAEs-induced estrogen could lead to excess insulin release, pancreatic β -cell exhaustion, and peripheral insulin resistance, which may result in glucose metabolism disorder and contributing to the development of diabetes[60]. Moreover, PAEs can selectively regulate PPAR α and in turn affect lipid modulation and glucose homeostasis, result in insulin resistance, which also contributing to the development of diabetes[61]. Subgroup analysis of our present study showed that five single PAE metabolites presented no risk, except for MBP, but the synergistic effect of the six PAE metabolites on GDM verified this viewpoint in the aforementioned mechanism researches. Thus, we can speculate that PAEs metabolites might contribute to the development of GDM, and future studies are needed to assess and determine the precise underlying mechanisms.

PFASs have been extensively used in a series of industrial applications, such as products surfactants, paper and textile coatings, nonstick frying pan coatings, and repellents, which resulted in ubiquitous contamination and worldwide exposure[62]. It can biomagnify in the food chain and bioaccumulate in human tissues due to their persistence characteristic. PFASs are structurally homologous to fatty acids and possess endocrine-disrupting properties, which may be associated with the development of lipid alterations and energy metabolism dysfunction[63]. Currently, evidence on the relationship between PFASs exposures and risk of GDM remains puzzling. Data from animal studies indicated that PFASs exposure can inhibit the phosphatidylinositol 3-kinase- serine/ threonine protein kinase signaling, which may interfere with the metabolic actions of insulin[64]. In general population, PFASs have been proved to be related to β -cell function, glycated hemoglobin, fasting proinsulin, and insulin secretion[65]. Coincidentally, in our present study, exposure to PFASs did have an additive effect on the risk of GDM. Human beings are generally exposed to a series of PFASs mixtures. The sufficiently wide range of exposure and a large sample size are critical to assess the relationship between PFASs exposure and risk of GDM[39]. In our present study, the summary OR from cohort and case-control studies were both indicated an additive effect on the risk of GDM. Thus, we can speculate that PFASs metabolites might contribute to the development of GDM, and future studies are needed to assess and determine the precise underlying mechanisms.

At present, the biological mechanisms of the potential relationship between EDCs exposure and risk of GDM are not fully elucidated. As previously mentioned, GDM may share certain of the similar pathways for development in common with T2DM in respect of EDCs exposure, as both of them are characterized by continuum hyperglycemia and insulin resistance. Women with GDM are more likely to development with T2DM in later life. Therefore, certain hypothesized mechanisms such as mitochondrial dysfunction, oxidative stress, inflammation response, and insulin resistance, which have been considered to be associated with the development of diabetes may also be applicable to GDM[66]. The highlights of the present study are as follows. Firstly, this is the first comprehensive meta-analysis research to explore the potential association between EDCs exposure and the risk of GDM. The second advantage is that the estimated scores of all the included studies are higher than or equal to 7, indicating a relatively high quality of the original literatures. The third advantage is that the results of sensitivity analysis did not significantly modify the conclusions of the present study, and no publication bias was observed in the included studies. Moreover, the results of the present meta-analysis reveal trends that may not be apparent in a single epidemiological study, and the persuasiveness of the results can be enhanced with large sample size.

However, several limitations should be recognized in our present study. Firstly, due to the insufficient number of relevant literatures and the failure of data extraction, the types of EDCs enrolled in this study are limited. Secondly, the dose-response relationship between individual pollutants and the risk of GDM was not established in the present study, as humans are generally exposed to a complex mixtures of pollutants, it is difficult to distinguish the effects of individual

compounds. Thirdly, since the unpublished data were not retrieved, the publication bias may be inevitable, even though no publication bias was observed in the Egger and Begg tests. Moreover, due to the limited number of included studies, we didn't perform subgroup analysis to assess the relationship between the EDCs and risk of GDM in different gestational stages (different trimesters). Lastly, in the results of PBDEs and PCBs, we did not investigate the possible sources of heterogeneity among the included studies due to the insufficient number of references.

Conclusion

In conclusion, the results of our present meta-analysis indicates that PCBs, PBDEs, PAEs, and PFASs exposure have significant effects on the risk of GDM, and these results given powerful evidence supporting the hypothesis that certain EDCs (especially the PCBs, PBDEs, PAEs, and PFASs) exposure are related to an increased risk of GDM. Further large-sample and high-quality epidemiologic researches with improved methods for documenting cases of GDM, as well as in vivo and in vitro studies are needed to verify the potential relationship and biological mechanisms.

List Of Abbreviations

GDM, gestational diabetes mellitus; EDCs, Endocrine-disrupting chemicals; T2D, type 2 diabetes; PBDEs, Polybrominated diphenylethers; PCBs, Polychlorinated biphenyls; PAEs, phthalates; PFAS, Per-and polyfluoroalkyl substances; PFNA, Perfluorononanoic acid; PFOA, Perfluorooctanoic acid; PFDA, Perfluorodecanoic acid; PFHxS, Perfluorohexanesulfonic acid; PFOS, Perfluorooctanesulfonic acid; PFUnDA, Perfluoroundecanoic acid; PFDoA, perfluorododecanoic acid; PFBS, perfluorobutane sulfonate; EtFOSAA, 2-(N-ethyl-perfluorooctane sulfonamide) acetate; MeFOSAA, 2-(N-methyl-perfluorooctane sulfonamide) acetate; DEHP, diethylhexyl phthalate; MBP, mono-n-butyl phthalate; MBzP, mono-benzyl phthalate; MCPP, mono-3-carboxypropyl phthalate; MEP, mono-ethyl phthalate; MIBP, mono-isobutyl phthalate; MEHP, mono-(2-ethylhexyl) phthalate.

Declarations

Authors' Contributions

DY, HY and JY designed of the study; DY and YJ performed the literature search; DY and TL did the study selection; DY and HY performed data extraction and checking. DY and HY performed meta-analyses; DY drafted the article. HY and JY revised the manuscript; All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available as Additional file 4.

Conflicts of Interest

The authors declare that they have no conflicts of Interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

Not applicable.

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Figures

Figure 1

Flowchart of assessment of eligible studies.

Figure 2

Forest plot of PCBs exposure and risk of GDM. The points represent the study- specific odds ratios (ORs) and the horizontal lines correspond to 95% confidence intervals (CIs). The study-specific weight is presented as the grey areas. The pooled ORs and 95% CIs are presented as the diamonds. The vertical dashed line represents an OR of 1.14.

Figure 3

Forest plot of PBDEs exposure and risk of GDM. The points represent the study- specific odds ratios (ORs) and the horizontal lines correspond to 95% confidence intervals (CIs). The study-specific weight is presented as the grey areas. The pooled ORs and 95% CIs are presented as the diamonds. The vertical dashed line represents an OR of 1.32.

Figure 4

Forest plot of PAEs exposure and risk of GDM. The points represent the study- specific odds ratios (ORs) and the horizontal lines correspond to 95% confidence intervals (CIs). The study-specific weight is presented as the grey areas. The pooled ORs and 95% CIs are presented as the diamonds. The vertical dashed line represents an OR of 1.10.

Figure 5

Forest plot of PFAS exposure and risk of GDM. The points represent the study- specific odds ratios (ORs) and the horizontal lines correspond to 95% confidence intervals (CIs). The study-specific weight is presented as the grey areas. The pooled ORs and 95% CIs are presented as the diamonds. The vertical dashed line represents an OR of 1.04.

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