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Gestational Exposure to Endocrine-Disrupting Chemicals of Emerging Concern and the Risk of Developing Gestational Diabetes Mellitus: A Comprehensive Investigation of Sex-Specific and Trimester-Specific Associations

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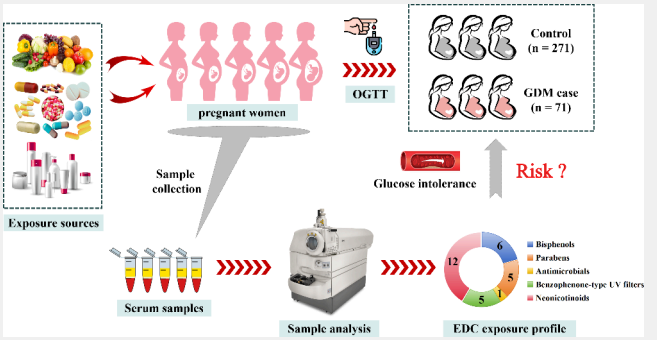
ABSTRACT: Gestational diabetes mellitus (GDM) is a type of diabetes that arises during pregnancy, leading to long-term adverse consequences for maternal health and fetal development. However, the specific role of endocrine-disrupting chemicals (EDCs) in the pathogenesis of GDM remains controversial. This prospective cohort study sought to investigate how coexposure to bisphenols, parabens, triclosan (TCS), benzophenone-type UV filters, and neonicotinoids (NEOs) affects the odds of GDM. Quantile-based g-computation and Bayesian kernel machine regression showed a significant inverse relationship between EDC mixtures and the reduced risk of GDM (OR = 0.34, 95% CI: 0.13−0.87), which was mainly explained by bisphenol (OR = 0.49, 95% CI: 0.29−0.80) and paraben (OR = 0.60, 95% CI: 0.40−0.91) exposure. Bisphenol S (BPS), bisphenol Z (BPZ), ethylparaben (EtP), propylparaben (PrP), and butylparaben (BuP) were identified as key contributors to the joint effect. In addition, subgroup analyses suggested that the bisphenols-GDM association was more pronounced in younger/normal-weight participants. The sex-specific impact of exposure to bisphenols on the development of GDM was observed, whereas the second trimester represented a critical window for EDC exposure. Continued research efforts, focusing on causal pathways and nonmonotonic relationships, will be crucial to elucidate the complex influence of EDC exposure on the development of GDM.



KEYWORDS: *Gestational diabetes mellitus, Endocrine-disrupting chemicals, Mixture exposure analyses, Sex specificity, Sensitive windows*

1. INTRODUCTION

Gestational diabetes mellitus (GDM) is a common pregnancy complication,[1] characterized by varying degrees of impaired glucose tolerance and hyperglycemia,[2] which is first recognized during pregnancy. Maternal hormones, like placental lactogens and progesterone, have been proven to reduce insulin sensitivity in pregnant women,[3] and this is counteracted by increased insulin biosynthesis and secretion triggered by glucose.[4,5] GDM occurs if the pancreatic β-cell fails to adapt to the higher insulin demand of pregnancy.[6] Affecting approximately 14% of pregnant women worldwide,[7] GDM has become a global public health issue and is linked to various adverse birth outcomes, including preeclampsia, miscarriage, macrosomia, respiratory distress, and neonatal hypoglycemia.[4,8] Importantly, it may also increase the risk of developing type 2 diabetes mellitus (T2DM) and cardiovascular disease for mothers later in life, along with metabolic syndrome and glucose intolerance for their offspring.[9−11] Known risk factors for GDM include advanced age, obesity, ethnicity, smoking, hypertension, unhealthy lifestyle, and family history of diabetes.[12] Also, emerging evidence indicates that environmental endocrine-disrupting chemicals (EDCs) may be responsible for the risk of developing GDM.[13−15]

EDCs are a combination of natural or synthetic chemicals with similar structure to certain endogenous hormones.[11,16] Bisphenols, parabens, triclosan (TCS), benzophenone-type UV filters, and neonicotinoids (NEOs) are well-known EDCs, widely utilized in daily consumer goods.[17−19] Bisphenols are basic components for manufacturing plastic bottles, food packing materials, can linings, and thermal paper.[20] As broad-spectrum antimicrobial preservatives, parabens, and TCS have extensive applications in personal care products (PCPs),

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pharmaceuticals, and food processing.[21,22] Benzophenone-type UV filters are often added to cosmetics and sunscreens for their excellent UV-absorbing properties,[23] whereas NEOs are novel insecticides used for crop protection and pest control.[24] Given the broad applications, hormonal disorders and subsequent health issues caused by EDCs have attracted substantial attention.

Considerable epidemiological studies have linked EDC exposure to the development of GDM, with controversial or inconsistent results. For example, a cohort study quantified four bisphenols in urine samples from 1841 pregnant women, and found that bisphenol AF (BPAF) was related to elevated odds of GDM, as well as a positive correlation between bisphenol S (BPS) and fasting plasma glucose (FPG) levels.[25] In contrast, maternal urinary concentration of bisphenol A (BPA) was reported to have a protective effect against the development of GDM.[26] Two prospective studies from China revealed that exposure to ethylparaben (EtP) and TCS may accelerate the pathogenesis of GDM.[21,27] Available information on NEOs and UV filters is limited. Only one nested case-control study has discovered a potential link between exposure to NEOs and GDM,[24] while perinatal exposure to 2-hydroxy-4-methoxybenzophenone (BP-3) may contribute to the reduction in pregnancy glucose levels among subfertile women.[23] Most studies have focused on the effects of a specific class of chemicals on the development of GDM or blood glucose levels. Interestingly, recent studies conducted in US have addressed phenols and parabens as mixtures to explore the associations of exposure to EDC mixtures with GDM risk, considering the complexity of practical exposure.[28,29] In addition, researchers also emphasized variations in EDC-GDM links stratified by maternal age, prepregnancy body mass index (BMI), fetal sex, and pregnancy.[30−33]

Experimental evidence has indicated that EDC-induced abnormalities in blood glucose levels are mainly ascribed to epigenetic alternations and disruptions in hormonal signaling pathways, including estrogen, androgens, and thyroid hormones.[34−37] It is well-established that certain EDCs can interfere with the hypothalamic-pituitary-thyroid axis, causing thyroid dysfunction, which in turn leads to glucose intolerance, insulin resistance, and β-cell dysfunction.[2] Oxidative stress and inflammation may also promote metabolic disorders and facilitate the development of GDM.[8] Moreover, the impact of EDCs on lipid levels could be an essential mediator of the increased risk of GDM.[10] However, the precise pathogenesis of glucose fluctuations and GDM remains unclear.

Owing to variations in research method, sample size, target chemicals, and population characteristics,[38−42] the existing literature on the effects of EDCs on GDM and blood glucose levels shows substantial discrepancies, making it challenging to draw definitive conclusions. Besides, studies focusing on a single selected group of chemicals fail to explore the joint effects of combined exposure to multiple types of EDCs and lack a comprehensive understanding of the realistic exposure profile.[43] Thus, in this study, we measured the concentrations of five typical categories of EDCs (bisphenols, parabens, TCS, benzophenone-type UV filters, and NEOs) in maternal serum and investigated how coexposure to EDC mixtures affects the development of GDM and blood glucose levels. Additionally, subgroup analyses were conducted to probe the potential modifications of maternal characteristics and fetal sex on the EDCs-GDM relationships, along with the window of susceptibility.

2. MATERIALS AND METHODS

2.1. Study Population

In this prospective cohort study, pregnant women were recruited between April to May 2022 when they came to Longgang District Maternity & Child Healthcare Hospital of Shenzhen City for prenatal care. Eligibility criteria included: (1) ≥ 18 years old; (2) singleton pregnancy; (3) no reported diagnosis of type 1 or type 2 diabetes or a family history of diabetes (4) no severe chronic or infectious disease. After informed consent was provided, all participants were asked to undergo a physical examination and complete a structured questionnaire primarily designed to collect demographic information (e.g., maternal age, educational status, and residential area). During maternal check-ups, blood samples were collected from participants by a trained nurse. After centrifugation, the upper serum layer was transferred to new EP tubes and stored at −20 °C before analysis. This study was approved by the Ethics Committee of the School of Public Health (Shenzhen) at the Shenzhen Campus of Sun Yat-Sen University, Shenzhen, China.

A 75 g oral glucose tolerance test (OGTT)[44] was performed to screen for GDM between 24 and 28 weeks of pregnancy, and participants were diagnosed with GDM if they met any of the recommended criteria: (1) fasting plasma glucose (FPG) ≥ 5.1 mmol/L; (2) 1-h plasma glucose (1-h PG) ≥ 10.0 mmol/L; (3) 2-h plasma glucose (2-h PG) ≥ 8.5 mmol/L. After delivery, detailed information on pregnancy complications, related indices, and birth outcomes was extracted from medical records. Out of the 610 participants enrolled, 73 pregnant women were diagnosed with GDM, and each case was randomly matched with four controls based on maternal age and fetal sex.[43,44] Moreover, 2 cases and 21 controls were ruled out because of the missing information and inadequate blood samples. Finally, 71 GDM cases and 271 controls were included in the subsequent analyses.

2.2. Sample Collection and Measurement

For sample preparation, three cycles of liquid−liquid extraction were performed to extract target EDCs,[45−47] including six bisphenols (BPA, BPS, bisphenol P [BPP], bisphenol Z [BPZ], BPAF, bisphenol AP [BPAP]), five parabens (methylparaben [MeP], EtP, propylparaben [PrP], butylparaben [BuP], benzyl paraben [BzP]), TCS, five benzophenone-type UV filters (2,4-dihydroxybenzophenone [BP-1], 2,2′,4,4′-tetrahydroxybenzophenone [BP-2], BP-3, 2,2′-dihydroxy-4-methoxybenzophenone [BP-8], 4-hydroxybenzophenone [4-OH-BP]), and 12 neonicotinoids and associated metabolites (thiacloprid [THD], imidacloprid [IMI], thiamethoxam [THM], acetamiprid [ACE], dinotefuran [DIN], clothianidin [CLO], 5-hydroxy-imidacloprid [5-OH-IMI], olefin-imidacloprid [Of-IMI], N-desmethyl-acetamiprid [N-dm-ACE], 1-methyl-3-(tetrahydro-3-furylmethyl) urea [UF], N-desmethyl-thiamethoxam [N-dm-THM], and 6-chloronicotinic acid [6-CNA]). Briefly, 500 μL of serum was spiked with mixed internal standards (50 μL, 100 ng/mL), ammonium acetate buffer solution (3 mL, 1.0 mol/L), and β-glucuronidase (20 μL, > 100,000 units/mL), and incubated at 37 °C overnight. Following enzymatic hydrolysis, the mixture was extracted thrice with 3 mL of ethyl acetate. Subsequently, the supernatant was combined, concentrated, redissolved in 0.5 mL of methanol/water (6:4, v/v), and filtered through a 0.22-μm organic membrane.

The separation and quantification of target chemicals was performed on a 20A high-performance liquid chromatography (HPLC) system (Shimadzu, Kyoto, Japan) and a Q-trap 6500 triple quadrupole mass spectrometer (MS/MS, Applied Biosystems, Waltham, MA, USA), respectively. The mobile phase for NEOs consisted of 0.1% formic acid (A) and acetonitrile (B), whereas deionized water (A) and methanol (B) were used to separate the other chemicals (Table S1−S2). More details on precursor ions, tandem fragments, specific parameters, and the limit of detection (LOD) for each target EDC are presented in Table S3−S4. Information on quality assurance and quality control is also provided in Supporting Information.

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Environ. Health 2025, 3, 271−281

Table 1. Demographic Characteristics and Plasma Glucose Levels of Participants in This Study (n = 342)

	Total (n = 342)	GDM cases (n = 71)	Controls (n = 271)	
	Mean ± SD[a] or N (%)	Mean ± SD or N (%)	Mean ± SD or N (%)	P values
Age (years)	30.4 ± 4.08	30.9 ± 4.11	30.3 ± 4.06	0.309
<30	146 (43)	28 (39)	118 (44)	0.781
30−35	145 (42)	31 (44)	114 (42)	
≥35	51 (15)	12 (17)	39 (14)	
Prepregnancy BMI[b] (kg/m^2)	21.3 ± 2.85	21.9 ± 3.48	21.1 ± 2.64	0.036
<18.5	43 (13)	7 (10)	36 (13)	0.062
18.5−23.9	251 (73)	48 (68)	203 (75)	
≥24	48 (14)	16 (23)	32 (12)	
Gestational weight gain (kg)	12.6 ± 4.74	11.6 ± 4.19	12.9 ± 4.85	0.065
Educational status				
Less than high school	52 (15)	14 (20)	38 (14)	0.490
High school	42 (12)	8 (11)	34 (13)	
College and above	248 (73)	49 (69)	199 (73)	
Pregnancy on inclusion				
First trimester	57 (17)	16 (23)	41 (15)	0.592
Second trimester	156 (46)	34 (48)	122 (45)	
Third trimester	129 (38)	21 (30)	108 (40)	
Residential area				
Urban	183 (54)	38 (54)	145 (54)	0.998
Rural	159 (47)	33 (47)	126 (47)	
Ethnicity				
Han nationality	327 (96)	69 (97)	258 (95)	0.469
Minority nationality	15 (4)	2 (3)	13 (5)	
Parity				
Nulliparous	139 (41)	36 (51)	103 (38)	0.040
Multiparous	192 (56)	32 (45)	160 (59)	
Missing	11 (3)	3 (4)	8 (3)	
Neonatal sex				
Male	184 (54)	36 (51)	148 (55)	0.557
Female	158 (46)	35 (49)	123 (45)	
Random blood glucose (mmol/L)	4.72 ± 0.65	4.81 ± 0.60	4.69 ± 0.67	0.042
Fasting plasma glucose (mmol/L)	4.64 ± 0.51	4.87 ± 0.44	4.56 ± 0.51	<0.001
1-h plasma glucose (mmol/L)	8.15 ± 1.63	9.63 ± 1.52	7.77 ± 1.44	<0.001
2-h plasma glucose (mmol/L)	7.19 ± 1.60	8.11 ± 1.62	6.90 ± 1.49	<0.001

[a]SD: standard deviation. [b]BMI: body mass index.

2.3. Covariates

At enrollment, demographic data and socioeconomic factors of pregnant women were collected by well-trained staff using structured questionnaires, and birth outcomes of the fetus, pregnancy complications, and blood glucose levels were obtained from medical records. Guided by biological plausibility and existing literature,[28,39,48] the following covariates were chosen regardless of statistical significance: maternal age (continuous), prepregnancy BMI (continuous), educational status (less than high school, high school, college and above), place of residence (urban, rural), ethnicity (Han nationality, minority nationality), and neonatal sex (male, female). The self-reported prepregnancy weight and height, which were verified by a nurse, were used to derive prepregnancy BMI. Also, parity (nulliparous, multiparous) was selected as a covariate due to the statistical significance between groups (GDM cases and controls) (Table 1).

2.4. Statistical Analysis

Baseline characteristics of pregnant women were summarized as mean ± standard deviation (SD) for continuous variables and frequencies and percentages for categorical variables. Concentrations below the limit of detection (LOD) were adjusted by assigning a value equivalent to LOD/$\sqrt{2}$.[31,43] Due to the skewed distribution, concentrations of target analytes were log-transformed to mitigate interferences introduced by extreme values in subsequent analyses. Differences between GDM cases and controls were compared using the Mann−Whitney U test (continuous variables) and Pearson's Chi-squared test (categorical variables). Spearman's correlation analysis was applied to evaluate pairwise associations among the measured EDCs.

Quantile-based g-computation (QGC), a combination of weighted quantile sum (WQS) regression and g-calculation, is designed to assess the joint effects of multiple exposures on a single outcome and estimate weights for each exposure variable.[49] Unlike traditional linear models that assume linearity and independence, QGC captures nonlinear effects and allows for greater flexibility in quantifying the relative contributions of each factor to the outcome, accommodating both positive and negative impacts.[50−52] WQS requires directional homogeneity of effects for all exposures, which limits its applicability in certain cases. Similarly, Bayesian kernel machine regression (BKMR) model is fitted to explore complex nonlinear relationships and interactions among exposure variables in high-dimensional data, providing a deeper insight into how each chemical contributes to the overall effect.[53,54] The overall effect of the mixture is exhibited as the observed variation in outcome probability when all chemicals are at a given percentile compared to those at the median level. Considering the multiple classes of EDCs in this study, the skewed distribution of target analytes, and the interactions among these chemicals, we employed QGC to investigate how combined exposure to bisphenols, parabens, TCS, benzophenone-type UV filters, and NEOs affects the

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Environ. Health 2025, 3, 271−281

Table 2. Distribution of Serum Concentrations (ng/mL) of Bisphenols, Parabens, Triclosan, Benzophenone-Type UV Filters, and Neonicotinoids among Pregnant Women with Gestational Diabetes Mellitus (GDM) and Control Subjects from South China

	Total (n = 342)		GDM cases (n = 71)		Controls (n = 271)		
Exposure	Median (P_{25}, P_{75})	DR[a] (%)	Median (P_{25}, P_{75})	DR (%)	Median (P_{25}, P_{75})	DR (%)	P values
Plasticizers							
BPA	0.02 (<LOD[b], 0.07)	57	0.02 (<LOD, 0.06)	52	0.03 (<LOD, 0.07)	58	0.830
BPS	0.04 (0.02, 0.06)	100	0.03 (0.02, 0.04)	100	0.04 (0.03, 0.07)	100	<0.001
BPP	0.07 (0.04, 0.12)	94	0.06 (0.03, 0.12)	94	0.07 (0.04, 0.13)	94	0.369
BPZ	0.06 (0.04, 0.10)	100	0.06 (0.03, 0.08)	100	0.07 (0.04, 0.11)	100	0.120
BPAF	0.01 (0.01, 0.01)	100	0.01 (0.01, 0.01)	100	0.01 (0.01, 0.01)	100	0.076
BPAP	0.04 (0.03, 0.06)	92	0.04 (0.02, 0.07)	89	0.04 (0.03, 0.06)	92	0.350
∑bisphenols[c]	0.31 (0.23, 0.42)	100	0.28 (0.19, 0.40)	100	0.32 (0.24, 0.43)	100	0.024
Preservatives							
MeP	0.27 (0.13, 0.95)	100	0.26 (0.11, 0.65)	100	0.28 (0.14, 1.00)	100	0.354
EtP	0.10 (0.03, 0.52)	100	0.05 (0.02, 0.29)	100	0.12 (0.03, 0.56)	100	0.032
PrP	0.17 (0.09, 0.47)	100	0.17 (0.08, 0.37)	100	0.17 (0.09, 0.48)	100	0.561
BuP	0.01 (0.01, 0.02)	100	0.01 (0.01, 0.02)	100	0.02 (0.01, 0.02)	100	0.622
BzP	0.002 (0.001, 0.003)	83	0.002 (0.001, 0.003)	86	0.002 (0.001, 0.003)	83	0.053
∑parabens[d]	0.98 (0.49, 2.42)	100	0.91 (0.43, 1.63)	100	1.02 (0.53, 2.50)	100	0.083
Antimicrobials							
TCS	0.20 (0.09, 0.41)	100	0.24 (0.12, 0.49)	100	0.19 (0.08, 0.40)	100	0.377
Benzophenone-type UV filters							
BP-1	0.002 (0.001, 0.005)	85	0.002 (0.001, 0.004)	82	0.002 (0.001, 0.005)	86	0.539
BP-2	0.03 (0.02, 0.05)	100	0.04 (0.02, 0.05)	100	0.03 (0.02, 0.05)	100	0.412
BP-3	0.54 (0.32, 1.11)	100	0.43 (0.30, 0.83)	100	0.56 (0.34, 1.20)	100	0.145
BP-8	0.04 (0.03, 0.06)	100	0.04 (0.03, 0.05)	100	0.04 (0.03, 0.06)	100	0.134
4-OH-BP	0.04 (0.02, 0.06)	100	0.04 (0.02, 0.05)	100	0.04 (0.02, 0.06)	100	0.227
∑BPs[e]	0.68 (0.45, 1.27)	100	0.53 (0.37, 0.99)	100	0.74 (0.45, 1.37)	100	0.080
Neonicotinoids							
THD	0.02 (0.01, 0.03)	100	0.02 (0.01, 0.03)	100	0.02 (0.01, 0.03)	100	0.681
THM	0.18 (0.06, 0.24)	89	0.18 (0.05, 0.26)	89	0.17 (0.06, 0.23)	90	0.624
CLO	0.08 (0.05, 0.13)	86	0.08 (0.04, 0.13)	79	0.08 (0.06, 0.13)	88	0.366
IMI	0.05 (0.03, 0.08)	76	0.04 (<LOD, 0.06)	72	0.06 (0.03, 0.09)	77	0.003
ACE	0.01 (0.01, 0.02)	87	0.01 (0.01, 0.02)	87	0.02 (0.01, 0.03)	87	0.098
DIN	0.26 (0.16, 0.43)	88	0.24 (0.15, 0.37)	90	0.27 (0.18, 0.45)	87	0.166
5-OH-IMI	0.17 (0.10, 0.27)	82	0.17 (0.09, 0.28)	77	0.17 (0.10, 0.26)	83	0.797
Of-IMI	0.07 (<LOD, 0.12)	70	0.06 (<LOD, 0.12)	61	0.08 (<LOD, 0.13)	72	0.068
N-dm-ACE	0.14 (0.08, 0.27)	92	0.15 (0.06, 0.26)	87	0.14 (0.08, 0.27)	94	0.425
UF	0.02 (<LOD, 0.03)	65	0.02 (<LOD, 0.03)	54	0.02 (<LOD, 0.03)	68	0.028
N-dm-THM	0.34 (0.21, 5.26)	100	0.32 (0.22, 4.58)	100	0.34 (0.21, 5.27)	100	0.938
6-CNA	0.04 (0.03, 0.07)	87	0.04 (0.03, 0.07)	90	0.04 (0.03, 0.07)	86	0.875
∑NEOs[f]	2.23 (1.40, 6.75)	100	1.94 (1.35, 6.63)	100	2.34 (1.43, 6.81)	100	0.667

[a]DR: detection rate. [b]LOD: limit of detection. [c]∑bisphenols: the sum concentration of BPA, BPS, BPP, BPZ, BPAF, and BPAP. [d]∑parabens: the sum concentration of MeP, EtP, PrP, BuP, and BzP. [e]∑BPs: the sum concentration of BP-1, BP-2, BP-3, BP-8, and 4-OH-BP. [f]∑NEOs: the sum concentration of THD, THM, CLO, IMI, ACE, DIN, 5-OH-IMI, Of-IMI, N-dm-ACE, UF, N-dm-THM, and 6-CNA.

risk of developing GDM, and to identify major drivers responsible for the overall effect; these were further verified by BKMR (combined effect) and WQS (risk factor) to ensure the robustness of the results. The P values obtained from QGC model were adjusted using the Benjamini-Hochberg (BH) method. TCS was incorporated into parabens when mixture analyses were performed based on specific chemical classes. Besides, the single EDC-GDM links, as well as linear and nonlinear relationships, were analyzed using the restricted cubic spline (RCS) model.

Subgroup analyses were conducted, with pregnant women grouped by demographic characteristics (maternal age and prepregnancy BMI), infant sex, and pregnancy; this allowed for the exploration of vulnerable population, sex-specificity, and the critical window for EDC exposure. At last, we developed the structural equation model (SEM) to probe the mediating role of blood glucose level in the relationship between EDC exposure and the risk of developing GDM. All analyses were performed using R (version 4.3.1), and a two-sided $P < 0.05$ was adopted as the threshold for statistical significance.

3. RESULTS

3.1. Study Population Characteristics

Demographic features and blood glucose levels of pregnant women are displayed in Table 1. Out of the 342 participants, the majority had a normal prepregnancy BMI and a high educational attainment (college and above), with a mean age of 30.4 years. The average levels for random blood glucose, fasting plasma glucose, 1-h plasma glucose, and 2-h plasma glucose were 4.72 mmol/L, 4.64 mmol/L, 8.15 mmol/L, and 7.19 mmol/L, respectively. Compared to non-GDM women, GDM cases had higher prepregnancy BMI (21.9 vs 21.1 kg/m^2) and blood glucose levels, and were more likely to be

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Environ. Health 2025, 3, 271−281

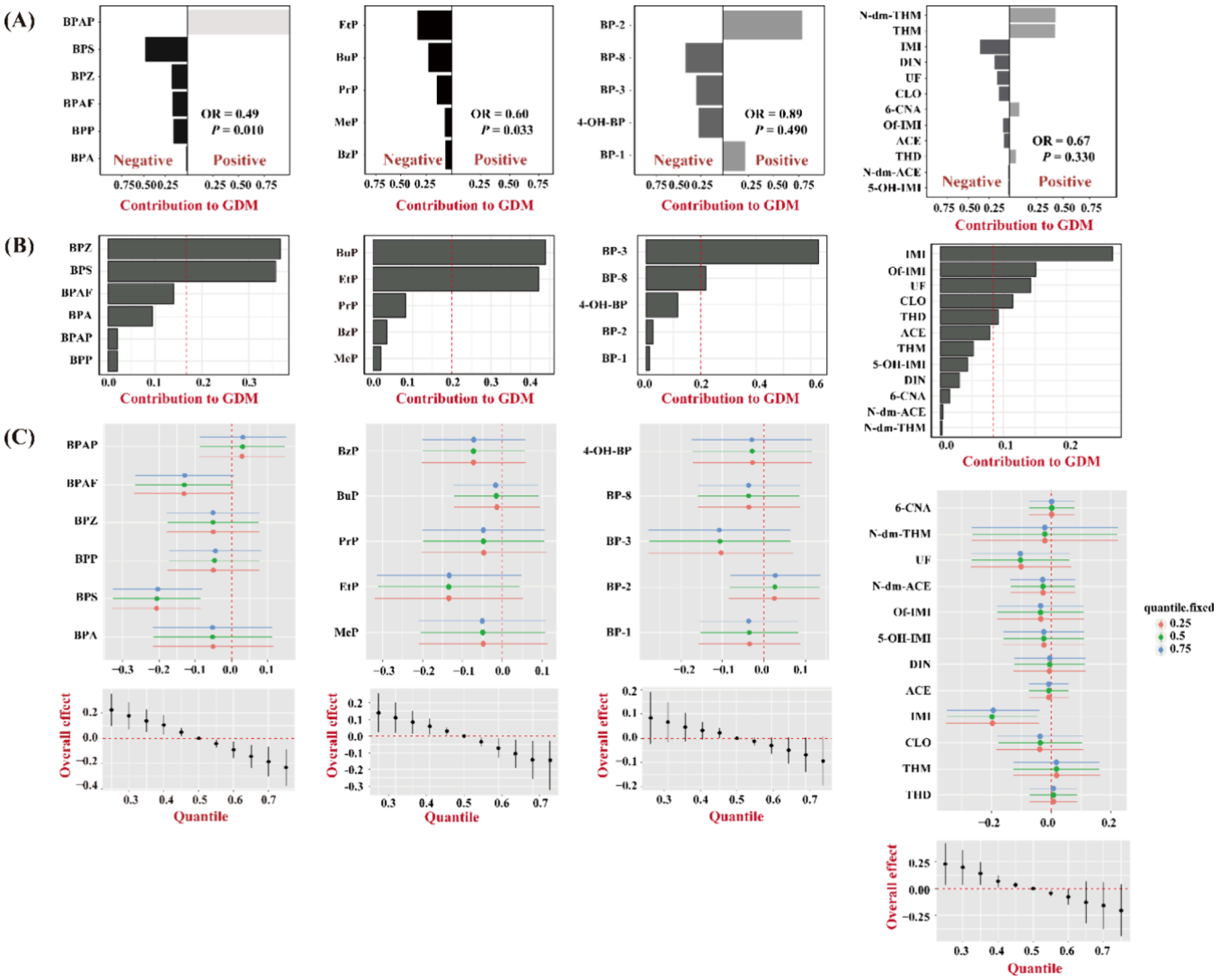

Figure 1. Overall effect of bisphenols, parabens, benzophenone-type UV filters, and neonicotinoids (log-transformed) on the risk of gestational diabetes mellitus (GDM), and weights of the positive or negative effects for each chemical on the overall effect, as assessed by quantile-based g-computation (A), weighted quantile sum regression (B), and Bayesian kernel machine regression (C) models.

nulliparous (51% vs 38%). No significant differences were found between GDM cases and healthy controls in maternal age, educational status, pregnancy, residential area, gestational weight gain, ethnicity, and neonatal sex.

3.2. Maternal Exposure Status

The distributions of bisphenols, parabens, TCS, benzophenone-type UV filters, and NEOs in serum from cases and controls are summarized in Table 2. Among the target analytes, detection rates were greater than 80%, except for BPA (57%), IMI (76%), Of-IMI (70%), and UF (65%), and median values varied from 0.002 (BzP) to 0.54 ng/mL (BP-3). Of the five studied classes of EDCs, the exposure profiles were dominated by NEOs (median: 2.23 ng/mL), followed by parabens (0.98 ng/mL), benzophenone-type UV filters (0.68 ng/mL), bisphenols (0.31 ng/mL), and TCS (0.20 ng/mL). BPP, MeP, BP-3, and N-dm-THM represented the most abundant chemicals in the classes of bisphenols, parabens, benzophenone-type UV filters, and NEOs, respectively. Generally, the GDM cases exhibited lower median levels of BPS, EtP, IMI, and UF than those in controls, and no significant differences were observed between cases and controls for the remaining EDCs (Figure S1 and Table 2). After stratifying by pregnancy, variations in EDC levels between GDM cases and controls were noted only in the second trimester, where the concentrations of bisphenols and benzophenone-type UV filters were higher in the control group (Table S5). The pairwise correlations between bisphenols and parabens in serum samples were consistently weak (Figure S2), with correlation coefficients below 0.3, whereas several pairs of UV filters and NEOs showed moderate degree of correlations (coefficients >0.4, $P < 0.05$), e.g., BP-3 and BP-8 ($r = 0.58$), BP-3 and 4-OH-BP ($r = 0.55$), BP-8 and 4-OH-BP ($r = 0.49$), THM and 5-OH-IMI ($r = 0.43$), and DIN and N-dm-THM ($r = 0.51$).

3.3. Associations between EDC Exposure and GDM Risk

The overall effects of the different classes of EDC mixtures on the risk of GDM, as well as the major contributors, are presented in Figure 1. In QGC model, a quantile increase in exposure to six bisphenols was associated with reduced risk of GDM (OR = 0.49, 95% CI: 0.29−0.80, $P = 0.010$), whereas BPS (weight: 48%) and BPZ (18%) contributed most to the joint effects. Comparable results were noted for BKMR model.

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Environ. Health 2025, 3, 271−281

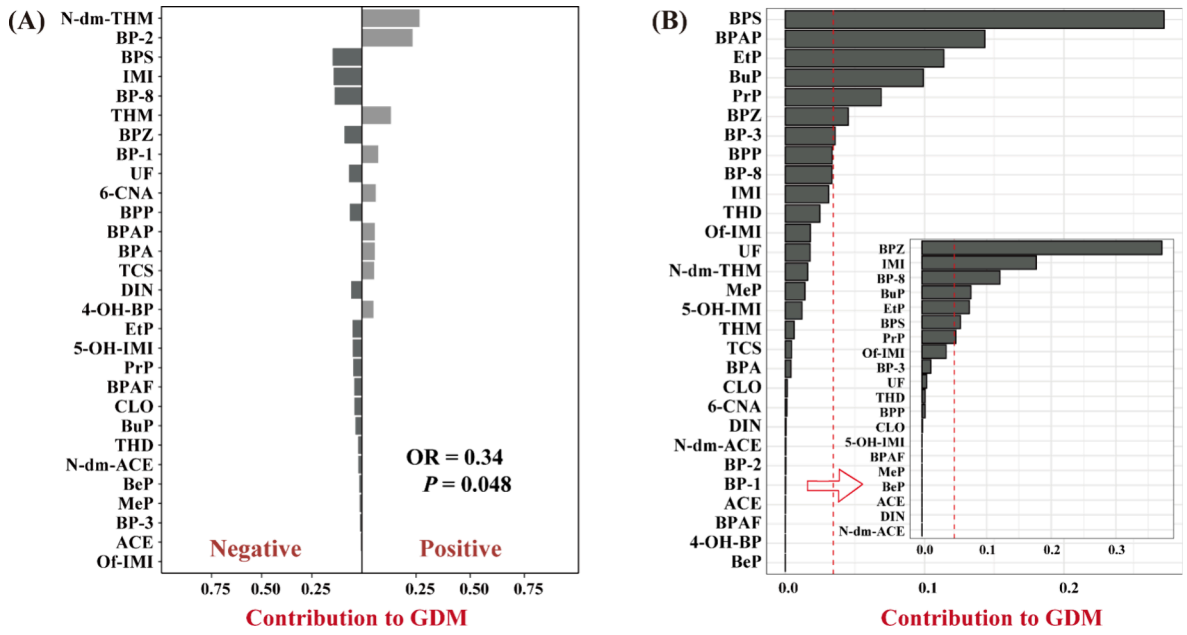

Figure 2. Associations between coexposure to all target chemicals (log-transformed) and the risk of gestational diabetes mellitus (GDM), as assessed by quantile-based g-computation (A) and Weighted quantile sum regression (B) models.

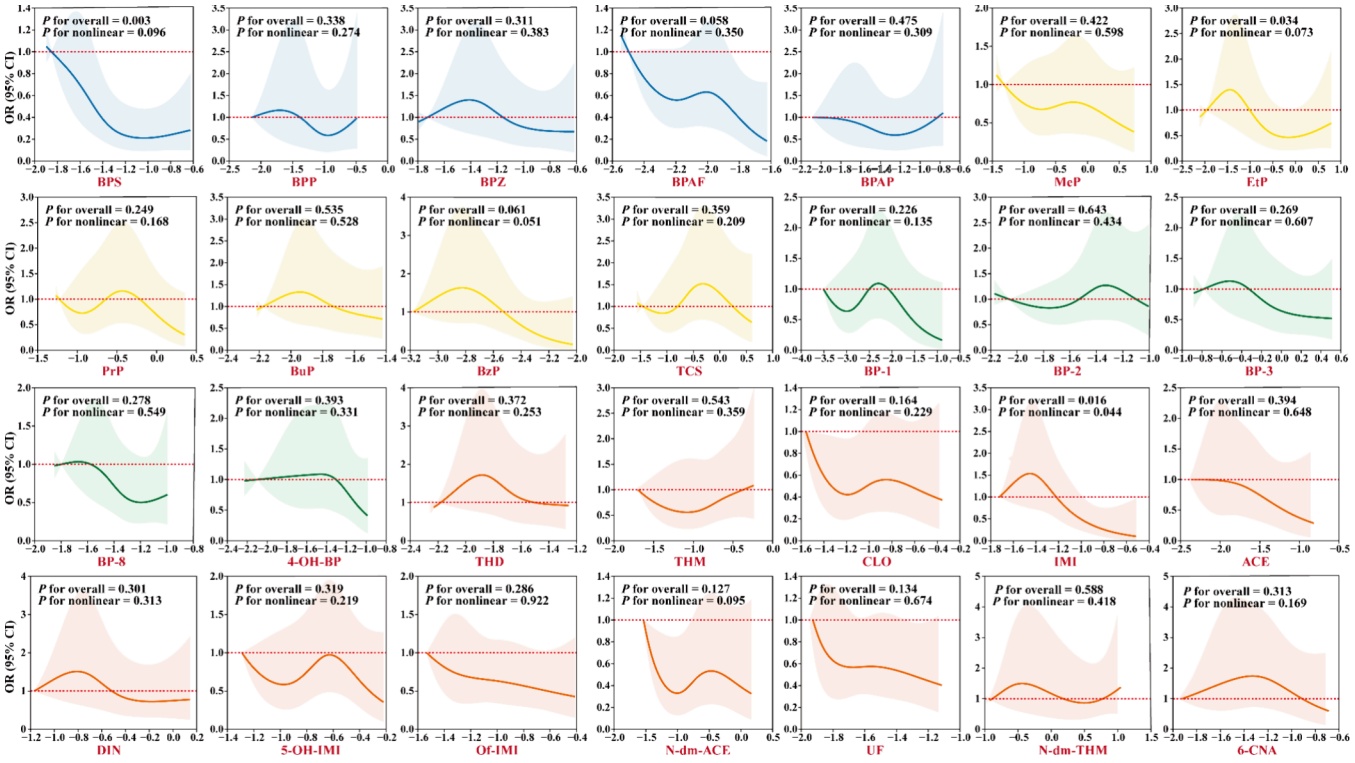

Figure 3. Dose−response relationships between target chemicals (log-transformed) and the risk of gestational diabetes mellitus (GDM), fitted with restricted cubic spline models (RCS). Four knots were located at the fifth, 35th, 65th, and 95th percentiles.

Specifically, when exposure to bisphenols was fixed at the 75th percentile relative to the median value, the odds of GDM decreased by 23%. For parabens, a one-quantile elevation of exposure to a mixture of five parabens inversely correlated to GDM risk (OR = 0.60, 95% CI: 0.40−0.91, P = 0.033), which was mainly attributed to EtP (40%), BuP (27%), and PrP (18%) exposure. The BKMR model also suggested that increasing paraben mixtures from the 50th to 75th percentile coincided with a 14% reduction in GDM risk. When TCS was incorporated into parabens (Figure S3), the association of TCS and parabens with GDM lost statistical significance (OR = 0.60, 95% CI: 0.37−0.95, P = 0.062). Despite the lack of significant associations of UV filters and NEOs with the risk of GDM in QGC, fixing the levels of UV filters and NEOs at the 75th percentile resulted in estimated 8% and 23% reductions in GDM risk, respectively, in comparison with the median status.

When all the examined chemicals were included in QGC (Figure 2), a notable and negative relationship was observed

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Environ. Health 2025, 3, 271−281

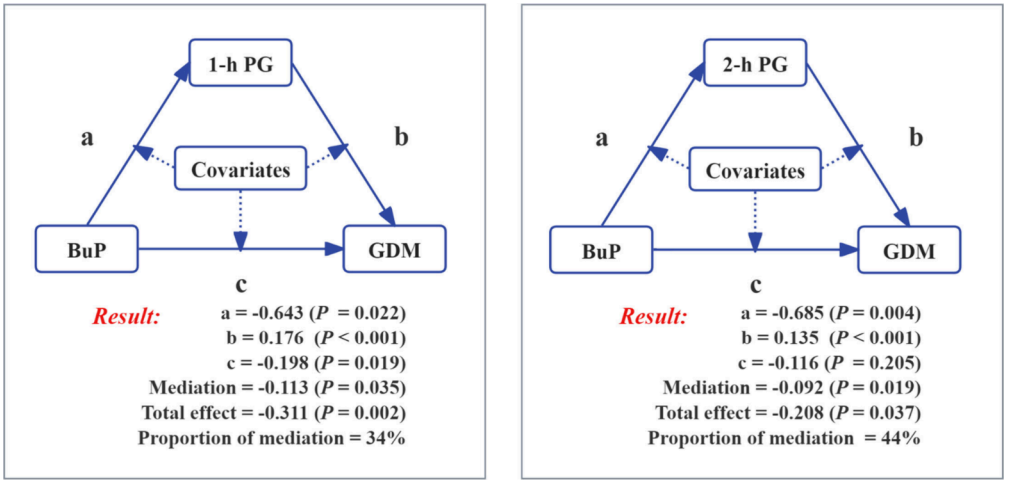

Figure 4. Mediating effect of plasma glucose levels on the relationship between single exposure to one of the target chemicals and the risk of gestational diabetes mellitus (GDM), as determined using structural equation models (SEM). 1-h PG: 1-h plasma glucose; 2-h PG: 2-h plasma glucose.

between exposure to EDC mixtures and the odds of GDM (OR = 0.34, 95% CI: 0.13−0.87, P = 0.049). We further incorporated target EDCs with negative weight into WQS, and found that bisphenols (BPZ and BPS) and parabens (BuP, EtP, and PrP) were the key contributors driving the combined effects of EDCs on GDM risk. Although the QGC model showed that UV filters-GDM and NEOs-GDM links were null (P > 0.05), IMI and BP-8 were recognized as potential protective factors in the WQS. Additionally, Figure 3 illustrates the correlations between single EDC exposure and GDM risk, and BPA was excluded owing to the low detection rate. The levels of BPS and EtP demonstrated significant and negative linear relationships with the risk of developing GDM, whereas an inverse U-shape association was found between IMI and GDM. It is worth noting that BPAF (P = 0.058) and BzP (P = 0.061) exhibited marginal negative correlations with GDM risk.

3.4. Subgroup Analysis and Mediation Effect

An exploratory analysis regarding the potential effect modification of maternal characteristics on the mixture-GDM link is presented in Table S6. The associations between exposure to bisphenols and GDM risk maintained statistical significance among pregnant women aged <30 years, as well as in the group with normal prepregnancy BMI. Also, the significant relationship between bisphenols and GDM risk (OR = 0.41, 95% CI: 0.19−0.86, P = 0.038) was observed among pregnant women with female offsprings, while the significance of the link became null (P > 0.05) in male offsprings. In trimester-stratified analyses, each quantile increase in bisphenols was inversely related to the odds of GDM among pregnant women in the second trimester (OR = 0.46, 95% CI: 0.23−0.93, P = 0.042). The bisphenol-GDM link remained notable when combined with the first and second trimesters.

Notably, parabens were found to have a negative influence on 2-h plasma glucose level (Table S7), whereas no other EDCs were linked to blood glucose indicators. We further conducted mediation analyses to investigate the mediating role of blood glucose indicators in the relationship between EDC mixtures and GDM risk. The results (Figure 4) indicated that BuP may mitigate the development of GDM by regulating the increase in 1-h plasma glucose and 2-h plasma glucose levels, with the proportion of mediation of 34% and 44%, respectively.

4. DISCUSSION

In this prospective cohort, we measured the levels of five classes of EDCs in maternal serum (e.g., bisphenols, parabens, TCS, benzophenone-type UV filters, and NEOs), and discovered that coexposure to a mixture of EDCs was linked to a decreased risk of developing GDM. This confounding effect was mainly attributed to bisphenols (BPS and BPZ) and parabens (EtP, BuP, and PrP), while IMI and BP-8 were also identified as important contributors. In subgroup analysis, the negative relationship between bisphenols and GDM risk was more pronounced in pregnant women who were younger and experienced a normal prepregnancy BMI. Furthermore, pregnant women carrying female fetuses were found to be more susceptible to bisphenol exposure compared to those carrying male babies, whereas the second trimester was identified as a critical window for EDC exposure. The results from mediation analyses suggested that BuP may manage the development of GDM by slowing down the increase in blood glucose levels.

Numerous epidemiological studies have focused on exposure to EDCs in relation to GDM risk, yielding controversial and inconclusive results. In this study, QGC and BKMR demonstrated negative combined effects of EDC exposure on GDM risk, which were driven by the groups of bisphenols and parabens. In line with our findings, a nested case-control study involving 500 pregnant women discovered that exposure to a mixture of five bisphenols resulted in a decreased risk of GDM.[44] Another birth cohort from China showed that one unit increase in log-transformed BPA level was related to 27% reduction in the odds of GDM.[26] Likewise, the protective effect of BPA on the development of GDM has been reported in a probit-BKMR analysis, which addressed multiple phenols and parabens as mixtures.[29] Conversely, several previous studies have reached quite different conclusions, proposing that bisphenol, paraben, and TCS were potential risk factors associated with the elevated risk of GDM.[21,27,28] Evidence also emerged regarding a null association of bisphenol and paraben with GDM risk and blood glucose levels.[12,55] Although the UV filters-GDM and NEOs-GDM links were insignificant in this

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Environ. Health 2025, 3, 271−281

study, BP-8 and IMI were still found to have a protective effect against the development of GDM. Research focusing on the effects of exposure to UV filters and NEOs on GDM remains scarce. Only one study revealed a positive association of coexposure to NEOs and their metabolites with the odds of GDM, with oxidative stress serving as the underlying mechanism.[24] When it comes to UV filters, only three reports have investigated the impact of BP-3 on GDM and blood glucose levels, yielding conflicting results.[23,28,29]

Heterogeneity across studies and inconsistent results can be attributed to various factors, including study design (case-control or cohort), population characteristic, biological sample (urine or blood), small sample size, target chemical (single or mixture exposure), and window of exposure assessment. Currently, most studies have generally examined a single or class of selected EDCs, and ignored to address the mixed effects, e.g., synergistic or antagonistic interactions, arising from coexposure to multiple EDCs; this may lead to a lack of compressive characterization of gestational EDC exposure and variations in the EDCs-GDM links.[43] Interestingly, two studies were conducted among subfertile women recruited from a fertility center, and this group faced a greater risk of GDM compared to those conceived naturally.[23,56] In addition, potential confounding factors may also have modified the exposure-outcome relationship. For instance, exposure to NEOs was accompanied by nutritional benefits from fruit and vegetable consumption,[57] while the use of PCPs was tied to higher health awareness.[58] Differences in diagnostic criteria for GDM among countries may be an additional reason for the inevitable discrepancies.[12]

Significant effect modifications of maternal age and prepregnancy BMI on bisphenols-GDM correlations were observed in this study, with protective effects being more pronounced in younger/normal-weight women relative to older/obese women. Supported by the available evidence, advanced age and obesity are typical risk factors for GDM.[21,24] In particular, being overweight coincides with decreased insulin sensitivity and elevated oxidative stress in the body.[25] We speculate that the instability of pancreatic β cell and the interaction of lipids with the effects of EDCs may account for the observed alternations elicited by prepregnancy BMI. Consistent with our results, the sex-specific influence of EDCs has been confirmed in prior work,[25,27,32] which could be explained by discrepancies in sex hormone levels and sensitivity to diverse hormones.[44] Furthermore, it has been proposed that the midpregnancy might be a window of sensitivity for EDC exposure, owing to the full formation of the placenta during this period, along with the subsequent elevation in placental lactogen and growth hormones.[56]

The existing experimental data concerning the pathogenesis of GDM induced by EDC exposure remain fragmented and inadequate. Hypothesized molecular mechanisms, such as impaired hormonal homeostasis, oxidative stress, inflammation, epigenetic modifications, and alternations in gut microbiota, are believed to result in pancreatic β-cell dysfunction, insulin resistance, and metabolic disorders.[7,8,59] It is worth noting that nonmonotonic does-response relationship between EDCs and outcome has been described in animal and cell-based studies;[60,61] this nonlinear pattern indicates that EDCs-induced biological and physiological impacts may vary depending on the exposure does. An *in vivo* experiment, in which pregnant rats were exposed to BPA via drinking water, found that low-dose BPA (0.5 μg/kg BW/day) evoked a rapid increase in insulin secretion, while high-dose BPA (50 μg/kg BW/day) resulted in a 40% reduction in insulin secretion.[61] Similar trends of low-dose stimulation and high-dose inhibition have been detected in other trials.[62−64] Sharing comparable molecular structure to estrogen, some EDCs stimulate insulin synthesis and modulate glucose homeostasis by binding to estrogen receptors.[26] Low-dose EDC exposure could enhance insulin secretion without triggering β-cell depletion and peripheral insulin resistance, which alleviated the reduced insulin sensitivity and higher insulin demand of pregnant women.[3] These mechanisms provide a plausible explanation for the protective impact of EDC exposure on GDM risk identified in this study. However, it should be note that if EDCs were present in doses beyond the physiological range or in long-term exposure scenarios, adverse effects may occur, like insulin resistance and disturbances in glucose metabolism, accelerating the development of GDM.[65] Thus, the health effects of EDCs in response to different exposure levels and durations require further validation in laboratory studies.

By analyzing the combined influence of five typical classes of EDCs on the risk of GDM, our study provided a holistic insight into gestational exposure to EDCs building on the existing literature. Also, the application of novel models (QGC, BKMR, and WQS) that allowed for multicollinearity among chemicals, strengthened the robustness of the results. Nevertheless, this study presents several limitations that warrant further discussion. First, the exposure assessment relied on the collection of single-spot serum samples. Given the short half-life of the target chemicals, a single measurement is unable to accurately reflect cumulative exposure throughout pregnancy, while fluctuations in EDC concentrations increase the likelihood of exposure misclassification. Second, some confounding factors, like diet and physical activity, and other unmeasured chemicals, which were not included in our study, may have altered the exposure-outcome relationship. Hence, we cannot neglect the possibility of residual confounding. Finally, the limited sample size in stratified analyses restricted the statistical power and resulted in relatively wide confidence intervals, thereby affecting the reliability and precision of the results. As such, it is imperative for future research to establish conclusive evidence on the potential protective or detrimental effects of EDC exposure on the pathogenesis of GDM through repeated measurements, larger sample sizes, comprehensive confounding controls, and exploration of underlying mechanisms.

5. CONCLUSIONS

Maternal exposure to a mixture of bisphenols, parabens, TCS, benzophenone-type UV filters, and NEOs was correlated with a decreased risk of GDM, in which bisphenols (BPS and BPZ) and parabens (EtP, BuP, and PrP) represented the major contributors. Moreover, the bisphenol-GDM relationships were modified by maternal age and prepregnancy BMI, being more prominent in younger/normal-weight pregnant women. Sex-specific and trimester-specific effects of bisphenol exposure on GDM risk were also observed. In light of the small sample size, these results should be interpreted with caution, and further epidemiological and experimental work is needed to validate our findings and to delve deeper into the causal relationship between exposure to a mixture of EDCs and outcomes, together with biological pathways.

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Environ. Health 2025, 3, 271−281

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/envhealth.4c00202.

Mobile phase gradient, mass spectral information, standard curves and limits of detection of target chemicals, subgroup analyses, and sensitive analyses (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Ehrlich, S.; Lambers, D.; Baccarelli, A.; Khoury, J.; Macaluso, M.; Ho, S.-M. Endocrine Disruptors: A Potential Risk Factor for Gestational Diabetes Mellitus. *Am. J. Perinatol.* **2016**, *33*, 1313−1318.

(2) Wu, W.; Ren, J.; Wang, J.; Wang, J.; Yu, D.; Zhang, Y.; Zeng, F.; Huang, B. Metalloestrogens Exposure and Risk of Gestational Diabetes Mellitus: Evidence Emerging from the Systematic Review and Meta-Analysis. *Environ. Res.* **2024**, *248*, No. 118321.

(3) Salazar-Petres, E. R.; Sferruzzi-Perri, A. N. Pregnancy-Induced Changes in β-Cell Function: What Are the Key Players? *J. Physiol.* **2022**, *600* (5), 1089−1117.

(4) Eberle, C.; Stichling, S. Environmental Health Influences in Pregnancy and Risk of Gestational Diabetes Mellitus: A Systematic Review. *BMC Public Health* **2022**, *22* (1), 1572.

(5) Yan, D.; Jiao, Y.; Yan, H.; Liu, T.; Yan, H.; Yuan, J. Endocrine-Disrupting Chemicals and the Risk of Gestational Diabetes Mellitus: A Systematic Review and Meta-Analysis. *Environ. Health* **2022**, *21* (1), 53.

(6) Varshavsky, J.; Smith, A.; Wang, A.; Hom, E.; Izano, M.; Huang, H.; Padula, A.; Woodruff, T. J. Heightened Susceptibility: A Review of How Pregnancy and Chemical Exposures Influence Maternal Health. *Reprod. Toxicol. Elmsford N* **2020**, *92*, 14−56.

(7) Mitra, T.; Gulati, R.; Ramachandran, K.; Rajiv, R.; Enninga, E. A. L.; Pierret, C. K.; Kumari R, S.; Janardhanan, R. Endocrine Disrupting Chemicals: Gestational Diabetes and Beyond. *Diabetol. Metab. Syndr.* **2024**, *16* (1), 95.

(8) Yao, X.; Geng, S.; Zhu, L.; Jiang, H.; Wen, J. Environmental Pollutants Exposure and Gestational Diabetes Mellitus: Evidence from Epidemiological and Experimental Studies. *Chemosphere* **2023**, *332*, No. 138866.

(9) Lin, J.-Y.; Yin, R.-X. Exposure to Endocrine-Disrupting Chemicals and Type 2 Diabetes Mellitus in Later Life. *Expo. Health* **2023**, *15* (1), 199−229.

(10) Akash, M. S. H.; Sabir, S.; Rehman, K. Bisphenol A-Induced Metabolic Disorders: From Exposure to Mechanism of Action. *Environ. Toxicol. Pharmacol.* **2020**, *77*, No. 103373.

(11) Padmanabhan, V.; Song, W.; Puttabyatappa, M. Praegnatio Perturbatio—Impact of Endocrine-Disrupting Chemicals. *Endocr. Rev.* **2021**, *42* (3), 295−353.

(12) Hou, Y.; Li, S.; Xia, L.; Yang, Q.; Zhang, L.; Zhang, X.; Liu, H.; Huo, R.; Cao, G.; Huang, C.; Tian, X.; Sun, L.; Cao, D.; Zhang, M.; Zhang, Q.; Tang, N. Associations of Urinary Phenolic Environmental Estrogens Exposure with Blood Glucose Levels and Gestational Diabetes Mellitus in Chinese Pregnant Women. *Sci. Total Environ.* **2021**, *754*, No. 142085.

(13) Puche-Juarez, M.; Toledano, J. M.; Moreno-Fernandez, J.; Gálvez-Ontiveros, Y.; Rivas, A.; Diaz-Castro, J.; Ochoa, J. J. The Role of Endocrine Disrupting Chemicals in Gestation and Pregnancy Outcomes. *Nutrients* **2023**, *15* (21), 4657.

(14) Madore, M. P.; Sakaki, J. R.; Chun, O. K. Protective Effects of Polyphenols against Endocrine Disrupting Chemicals. *Food Sci. Biotechnol.* **2022**, *31* (8), 905−934.

(15) Taheri, E.; Riahi, R.; Rafiei, N.; Fatehizadeh, A.; Iqbal, H. M. N.; Hosseini, S. M. Bisphenol A Exposure and Abnormal Glucose Tolerance during Pregnancy: Systematic Review and Meta-Analysis. *Environ. Sci. Pollut. Res.* **2021**, *28* (44), 62105−62115.

(16) Rolfo, A.; Nuzzo, A. M.; De Amicis, R.; Moretti, L.; Bertoli, S.; Leone, A. Fetal-Maternal Exposure to Endocrine Disruptors: Correlation with Diet Intake and Pregnancy Outcomes. *Nutrients* **2020**, *12* (6), 1744.

(17) Filardi, T.; Panimolle, F.; Lenzi, A.; Morano, S. Bisphenol A and Phthalates in Diet: An Emerging Link with Pregnancy Complications. *Nutrients* **2020**, *12* (2), 525.

(18) Milanović, M.; Đurić, L.; Milošević, N.; Milić, N. Comprehensive Insight into Triclosan—from Widespread Occurrence to Health Outcomes. *Environ. Sci. Pollut. Res.* **2023**, *30* (10), 25119−25140.

(19) Kahn, L. G.; Philippat, C.; Nakayama, S. F.; Slama, R.; Trasande, L. Endocrine-Disrupting Chemicals: Implications for Human Health. *Lancet Diabetes Endocrinol.* **2020**, *8* (8), 703.
(20) Yang, J.; Wang, H.; Du, H.; Xu, L.; Liu, S.; Yi, J.; Chen, Y.; Jiang, Q.; He, G. Serum Bisphenol A, Glucose Homeostasis, and Gestational Diabetes Mellitus in Chinese Pregnant Women: A Prospective Study. *Environ. Sci. Pollut. Res.* **2021**, *28* (10), 12546−12554.
(21) Liu, W.; Zhou, Y.; Li, J.; Sun, X.; Liu, H.; Jiang, Y.; Peng, Y.; Zhao, H.; Xia, W.; Li, Y.; Cai, Z.; Xu, S. Parabens Exposure in Early Pregnancy and Gestational Diabetes Mellitus. *Environ. Int.* **2019**, *126*, 468−475.
(22) Shapiro, G. D.; Arbuckle, T. E.; Ashley-Martin, J.; Fraser, W. D.; Fisher, M.; Bouchard, M. F.; Monnier, P.; Morisset, A.-S.; Ettinger, A. S.; Dodds, L. Associations between Maternal Triclosan Concentrations in Early Pregnancy and Gestational Diabetes Mellitus, Impaired Glucose Tolerance, Gestational Weight Gain and Fetal Markers of Metabolic Function. *Environ. Res.* **2018**, *161*, 554−561.
(23) Wang, Z.; Mínguez-Alarcón, L.; Williams, P. L.; Bellavia, A.; Ford, J. B.; Keller, M.; Petrozza, J. C.; Calafat, A. M.; Hauser, R.; James-Todd, T. Perinatal Urinary Benzophenone-3 Concentrations and Glucose Levels among Women from a Fertility Clinic. *Environ. Health* **2020**, *19* (1), 45.
(24) Mahai, G.; Wan, Y.; Wang, A.; Qian, X.; Li, J.; Li, Y.; Zhang, W.; He, Z.; Li, Y.; Xia, W.; Xu, S. Exposure to Multiple Neonicotinoid Insecticides, Oxidative Stress, and Gestational Diabetes Mellitus: Association and Potential Mediation Analyses. *Environ. Int.* **2023**, *179*, No. 108173.
(25) Zhang, W.; Xia, W.; Liu, W.; Li, X.; Hu, J.; Zhang, B.; Xu, S.; Zhou, Y.; Li, J.; Cai, Z.; Li, Y. Exposure to Bisphenol a Substitutes and Gestational Diabetes Mellitus: A Prospective Cohort Study in China. *Front. Endocrinol.* **2019**, DOI: 10.3389/fendo.2019.00262.
(26) Wang, X.; Wang, X.; Chen, Q.; Luo, Z.-C.; Zhao, S.; Wang, W.; Zhang, H.-J.; Zhang, J.; Ouyang, F. Urinary Bisphenol A Concentration and Gestational Diabetes Mellitus in Chinese Women. *Epidemiology* **2017**, *28*, S41.
(27) Ouyang, F.; Tang, N.; Zhang, H.-J.; Wang, X.; Zhao, S.; Wang, W.; Zhang, J.; Cheng, W. Maternal Urinary Triclosan Level, Gestational Diabetes Mellitus and Birth Weight in Chinese Women. *Sci. Total Environ.* **2018**, *626*, 451−457.
(28) Zhu, Y.; Hedderson, M. M.; Calafat, A. M.; Alexeeff, S. E.; Feng, J.; Quesenberry, C. P.; Ferrara, A. Urinary Phenols in Early to Midpregnancy and Risk of Gestational Diabetes Mellitus: A Longitudinal Study in a Multiracial Cohort. *Diabetes* **2022**, *71* (12), 2539−2551.
(29) Chen, W.-J.; Robledo, C.; Davis, E. M.; Goodman, J. R.; Xu, C.; Hwang, J.; Janitz, A. E.; Garwe, T.; Calafat, A. M.; Peck, J. D. Assessing Urinary Phenol and Paraben Mixtures in Pregnant Women with and without Gestational Diabetes Mellitus: A Case-Control Study. *Environ. Res.* **2022**, *214*, No. 113897.
(30) Gao, H.; Zhu, B.; Huang, K.; Zhu, Y.; Yan, S.; Wu, X.; Han, Y.; Sheng, J.; Cao, H.; Zhu, P.; Tao, F. Effects of Single and Combined Gestational Phthalate Exposure on Blood Pressure, Blood Glucose and Gestational Weight Gain: A Longitudinal Analysis. *Environ. Int.* **2021**, *155*, No. 106677.
(31) Wang, X.; Tang, N.; Nakayama, S. F.; Fan, P.; Liu, Z.; Zhang, J.; Ouyang, F. Maternal Urinary Bisphenol A Concentration and Thyroid Hormone Levels of Chinese Mothers and Newborns by Maternal Body Mass Index. *Environ. Sci. Pollut. Res.* **2020**, *27* (10), 10939−10949.
(32) Guo, J.; Wu, M.; Gao, X.; Chen, J.; Li, S.; Chen, B.; Dong, R. Meconium Exposure to Phthalates, Sex and Thyroid Hormones, Birth Size and Pregnancy Outcomes in 251 Mother−Infant Pairs from Shanghai. *Int. J. Environ. Res. Public. Health* **2020**, *17* (21), 7711.
(33) Bellavia, A.; Cantonwine, D. E.; Meeker, J. D.; Hauser, R.; Seely, E. W.; McElrath, T. F.; James-Todd, T. Pregnancy Urinary Bisphenol-A Concentrations and Glucose Levels across BMI Categories. *Environ. Int.* **2018**, *113*, 35−41.
(34) Addo, K. A.; Palakodety, N.; Hartwell, H. J.; Tingare, A.; Fry, R. C. Placental microRNAs: Responders to Environmental Chemicals and Mediators of Pathophysiology of the Human Placenta. *Toxicol. Rep.* **2020**, *7*, 1046−1056.
(35) Xiao, T.; Huang, Z.; Zheng, C.; Quach, B.; Zhu, Y.; Li, F.; Liang, W.; Baker, J.; Reichetzeder, C.; Hocher, B.; Yang, Y. Associations of Bisphenol A Exposure with Metabolic Syndrome and Its Components: A Systematic Review and Meta-Analysis. *Obes. Rev.* **2024**, *25* (6), No. e13738.
(36) Merrill, A. K.; Anderson, T.; Conrad, K.; Marvin, E.; James-Todd, T.; Cory-Slechta, D. A.; Sobolewski, M. Protracted Impairment of Maternal Metabolic Health in Mouse Dams Following Pregnancy Exposure to a Mixture of Low Dose Endocrine-Disrupting Chemicals, a Pilot Study. *Toxics* **2021**, *9* (12), 346.
(37) Hua, X.; Cao, X.-Y.; Wang, X.-L.; Sun, P.; Chen, L. Exposure of Pregnant Mice to Triclosan Causes Insulin Resistance via Thyroxine Reduction. *Toxicol. Sci.* **2017**, *160* (1), 150−160.
(38) Chen, W.; He, C.; Liu, X.; An, S.; Wang, X.; Tao, L.; Zhang, H.; Tian, Y.; Wu, N.; Xu, P.; Liao, D.; Liao, J.; Wang, L.; Fang, D.; Xiong, S.; Liu, Y.; Tian, K.; Li, Q.; Huang, J.; Yuan, H.; Chen, X.; Zhang, L.; Shen, X.; Zhou, Y. Effects of Exposure to Phthalate during Early Pregnancy on Gestational Diabetes Mellitus: A Nested Case−Control Study with Propensity Score Matching. *Environ. Sci. Pollut. Res.* **2023**, *30* (12), 33555−33566.
(39) Wang, H.; Chen, R.; Gao, Y.; Qu, J.; Zhang, Y.; Jin, H.; Zhao, M.; Bai, X. Serum Concentrations of Phthalate Metabolites in Pregnant Women and Their Association with Gestational Diabetes Mellitus and Blood Glucose Levels. *Sci. Total Environ.* **2023**, *857*, No. 159570.
(40) James-Todd, T.; Ponzano, M.; Bellavia, A.; Williams, P. L.; Cantonwine, D. E.; Calafat, A. M.; Hauser, R.; Quinn, M. R.; Seely, E. W.; McElrath, T. F. Urinary Phthalate and DINCH Metabolite Concentrations and Gradations of Maternal Glucose Intolerance. *Environ. Int.* **2022**, *161*, No. 107099.
(41) Liang, Q.-X.; Lin, Y.; Fang, X.-M.; Gao, Y.-H.; Li, F. Association Between Phthalate Exposure in Pregnancy and Gestational Diabetes: A Chinese Cross-Sectional Study. *Int. J. Gen. Med.* **2022**, *15*, 179−189.
(42) Zukin, H.; Eskenazi, B.; Holland, N.; Harley, K. G. Prenatal Exposure to Phthalates and Maternal Metabolic Outcomes in a High-Risk Pregnant Latina Population. *Environ. Res.* **2021**, *194*, No. 110712.
(43) Huang, W.; Pan, X.-F.; Tang, S.; Sun, F.; Wu, P.; Yuan, J.; Sun, W.; Pan, A.; Chen, D. Target Exposome for Characterizing Early Gestational Exposure to Contaminants of Emerging Concern and Association with Gestational Diabetes Mellitus. *Environ. Sci. Technol.* **2023**, *57* (36), 13408−13418.
(44) Tang, P.; Liang, J.; Liao, Q.; Huang, H.; Guo, X.; Lin, M.; Liu, B.; Wei, B.; Zeng, X.; Liu, S.; Huang, D.; Qiu, X. Associations of Bisphenol Exposure with the Risk of Gestational Diabetes Mellitus: A Nested Case−Control Study in Guangxi, China. *Environ. Sci. Pollut. Res.* **2023**, *30* (10), 25170−25180.
(45) Bai, X.; Zhang, B.; He, Y.; Hong, D.; Song, S.; Huang, Y.; Zhang, T. Triclosan and Triclocarbon in Maternal-Fetal Serum, Urine, and Amniotic Fluid Samples and Their Implication for Prenatal Exposure. *Environ. Pollut.* **2020**, *266*, No. 115117.
(46) Song, S.; He, Y.; Zhang, T.; Zhu, H.; Huang, X.; Bai, X.; Zhang, B.; Kannan, K. Profiles of Parabens and Their Metabolites in Paired Maternal-Fetal Serum, Urine and Amniotic Fluid and Their Implications for Placental Transfer. *Ecotoxicol. Environ. Saf.* **2020**, *191*, No. 110235.
(47) Zhang, B.; He, Y.; Zhu, H.; Huang, X.; Bai, X.; Kannan, K.; Zhang, T. Concentrations of Bisphenol A and Its Alternatives in Paired Maternal−Fetal Urine, Serum and Amniotic Fluid from an e-Waste Dismantling Area in China. *Environ. Int.* **2020**, *136*, No. 105407.
(48) Soomro, M. H.; England-Mason, G.; Reardon, A. J. F.; Liu, J.; MacDonald, A. M.; Kinniburgh, D. W.; Martin, J. W.; Dewey, D. Maternal Exposure to Bisphenols, Phthalates, Perfluoroalkyl Acids,

and Trace Elements and Their Associations with Gestational Diabetes Mellitus in the APrON Cohort. *Reprod. Toxicol.* **2024**, *127*, No. 108612.
(49) Kalloo, G.; Wellenius, G. A.; McCandless, L.; Calafat, A. M.; Sjodin, A.; Romano, M. E.; Karagas, M. R.; Chen, A.; Yolton, K.; Lanphear, B. P.; Braun, J. M. Exposures to Chemical Mixtures during Pregnancy and Neonatal Outcomes: The HOME Study. *Environ. Int.* **2020**, *134*, No. 105219.
(50) Zeng, J.-Y.; Zhang, M.; Chen, X.-H.; Liu, C.; Deng, Y.-L.; Chen, P.-P.; Miao, Y.; Cui, F.-P.; Shi, T.; Lu, T.-T.; Liu, X.-Y.; Wu, Y.; Li, C.-R.; Liu, C.-J.; Zeng, Q. Prenatal Exposures to Phthalates and Bisphenols in Relation to Oxidative Stress: Single Pollutant and Mixtures Analyses. *Environ. Sci. Pollut. Res.* **2024**, *31* (9), 13954−13964.
(51) Eatman, J. A.; Dunlop, A. L.; Barr, D. B.; Corwin, E. J.; Hill, C. C.; Brennan, P. A.; Ryan, P. B.; Panuwet, P.; Taibl, K. R.; Tan, Y.; Liang, D.; Eick, S. M. Exposure to Phthalate Metabolites, Bisphenol A, and Psychosocial Stress Mixtures and Pregnancy Outcomes in the Atlanta African American Maternal-Child Cohort. *Environ. Res.* **2023**, *233*, No. 116464.
(52) Eick, S. M.; Tan, Y.; Taibl, K. R.; Barry Ryan, P.; Barr, D. B.; Hüls, A.; Eatman, J. A.; Panuwet, P.; D'Souza, P. E.; Yakimavets, V.; Lee, G. E.; Brennan, P. A.; Corwin, E. J.; Dunlop, A. L.; Liang, D. Prenatal Exposure to Persistent and Non-Persistent Chemical Mixtures and Associations with Adverse Birth Outcomes in the Atlanta African American Maternal-Child Cohort. *J. Expo. Sci. Environ. Epidemiol.* **2024**, *34*, 570.
(53) Kim, S.; Park, E.; Park, E.-K.; Lee, S.; Kwon, J.-A.; Shin, B.-H.; Kang, S.; Park, E.-Y.; Kim, B. Urinary Concentrations of Bisphenol Mixtures during Pregnancy and Birth Outcomes: The MAKE Study. *Int. J. Environ. Res. Public. Health* **2021**, *18* (19), 10098.
(54) Ryva, B. A.; Pacyga, D. C.; Anderson, K. Y.; Calafat, A. M.; Whalen, J.; Aung, M. T.; Gardiner, J. C.; Braun, J. M.; Schantz, S. L.; Strakovsky, R. S. Associations of Urinary Non-Persistent Endocrine Disrupting Chemical Biomarkers with Early-to-Mid Pregnancy Plasma Sex-Steroid and Thyroid Hormones. *Environ. Int.* **2024**, *183*, No. 108433.
(55) Robledo, C.; Peck, J. D.; Stoner, J. A.; Carabin, H.; Cowan, L.; Koch, H. M.; Goodman, J. R. Is Bisphenol-A Exposure During Pregnancy Associated with Blood Glucose Levels or Diagnosis of Gestational Diabetes? *J. Toxicol. Environ. Health A* **2013**, *76* (14), 865−873.
(56) Chiu, Y.-H.; Mínguez-Alarcón, L.; Ford, J. B.; Keller, M.; Seely, E. W.; Messerlian, C.; Petrozza, J.; Williams, P. L.; Ye, X.; Calafat, A. M.; Hauser, R.; James-Todd, T. Trimester-Specific Urinary Bisphenol A Concentrations and Blood Glucose Levels Among Pregnant Women From a Fertility Clinic. *J. Clin. Endocrinol. Metab.* **2017**, *102* (4), 1350−1357.
(57) Shapiro, G. D.; Dodds, L.; Arbuckle, T. E.; Ashley-Martin, J.; Ettinger, A. S.; Fisher, M.; Taback, S.; Bouchard, M. F.; Monnier, P.; Dallaire, R.; Morisset, A.-S.; Fraser, W. Exposure to Organophosphorus and Organochlorine Pesticides, Perfluoroalkyl Substances, and Polychlorinated Biphenyls in Pregnancy and the Association with Impaired Glucose Tolerance and Gestational Diabetes Mellitus: The MIREC Study. *Environ. Res.* **2016**, *147*, 71−81.
(58) Fisher, B. G.; Frederiksen, H.; Andersson, A.-M.; Juul, A.; Thankamony, A.; Ong, K. K.; Dunger, D. B.; Hughes, I. A.; Acerini, C. L. Serum Phthalate and Triclosan Levels Have Opposing Associations With Risk Factors for Gestational Diabetes Mellitus. *Front. Endocrinol* **2018**, DOI: 10.3389/fendo.2018.00099.
(59) Martínez-Ibarra, A.; Martínez-Razo, L. D.; Vázquez-Martínez, E. R.; Martínez-Cruz, N.; Flores-Ramírez, R.; García-Gómez, E.; López-López, M.; Ortega-González, C.; Camacho-Arroyo, I.; Cerbón, M. Unhealthy Levels of Phthalates and Bisphenol A in Mexican Pregnant Women with Gestational Diabetes and Its Association to Altered Expression of miRNAs Involved with Metabolic Disease. *Int. J. Mol. Sci.* **2019**, *20* (13), 3343.
(60) Pjanic, M. The Role of Polycarbonate Monomer Bisphenol-A in Insulin Resistance. *PeerJ.* **2017**, *5*, No. e3809.
(61) Manukyan, L.; Dunder, L.; Lind, P. M.; Bergsten, P.; Lejonklou, M. H. Developmental Exposure to a Very Low Dose of Bisphenol A Induces Persistent Islet Insulin Hypersecretion in Fischer 344 Rat Offspring. *Environ. Res.* **2019**, *172*, 127−136.
(62) Angle, B. M.; Do, R. P.; Ponzi, D.; Stahlhut, R. W.; Drury, B. E.; Nagel, S. C.; Welshons, W. V.; Besch-Williford, C. L.; Palanza, P.; Parmigiani, S.; vom Saal, F. S.; Taylor, J. A. Metabolic Disruption in Male Mice Due to Fetal Exposure to Low but Not High Doses of Bisphenol A (BPA): Evidence for Effects on Body Weight, Food Intake, Adipocytes, Leptin, Adiponectin, Insulin and Glucose Regulation. *Reprod. Toxicol.* **2013**, *42*, 256−268.
(63) Vandenberg, L. N. Non-Monotonic Dose Responses in Studies of Endocrine Disrupting Chemicals: Bisphenol A as a Case Study. *Dose-Response* **2014**, DOI: 10.2203/dose-response.13-020.Vandenberg.
(64) Bellavia, A.; Cantonwine, D. E.; Meeker, J. D.; Hauser, R.; Seely, E. W.; McElrath, T. F.; James-Todd, T. Pregnancy Urinary Bisphenol-A Concentrations and Glucose Levels across BMI Categories. *Environ. Int.* **2018**, *113*, 35−41.
(65) Nadal, A.; Alonso-Magdalena, P.; Soriano, S.; Ropero, A. B.; Quesada, I. The Role of Oestrogens in the Adaptation of Islets to Insulin Resistance. *J. Physiol.* **2009**, *587*, 5031−5037.