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Associations of Exposure to 24 Endocrine-Disrupting Chemicals with Perinatal Depression and Lifestyle Factors: A Prospective Cohort Study in Korea

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Abstract: During pregnancy, reproductive hormonal changes could affect the mental health of women, such as depression and anxiety. Previous studies have shown that exposure to endocrine disrupting chemicals (EDCs) is significantly associated with mental health symptoms; however, the results were inconsistent. We aimed to examine the association between 24 endocrine-disrupting chemicals (EDCs) in maternal urine and perinatal depression and their association with dietary and lifestyle factors. Participants were recruited from the "No Environmental Hazards for Mother–Child" cohort in Korea. Structured questionnaires asking dietary and lifestyle factors and evaluation of depressive symptoms were administered during antepartum (14 weeks of gestation) and postpartum (within four weeks after birth) periods. Urine samples were collected from 242 and 119 women during antepartum and postpartum periods, respectively. To assess perinatal depression, we used the Center for Epidemiological Studies-Depression Scale and the Edinburgh Postnatal Depression Scale. Antepartum depression and mono(2-ethyl-5-carboxypentyl) phthalate (MECPP) (1.50, 1.01–2.23) and 1-hydroxypyrene (1-OHP) (0.05, 0–0.89) showed significant positive association. Additionally, postpartum depression showed significant associations with mono(2-ethyl-5-oxohexyl) phthalate (MEOHP) (2.78, 1.00–7.70), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP) (2.79, 1.04–7.46), 2-hydroxynaphthalene (2-NAP) (7.22, 1.43–36.59), and 2-hydroxyfluorene (2-FLU) (<0.01, 0–0.004). Some dietary factors (consumption of fish, fermented foods, cup noodles, and popcorn) and consumer product factors (use of skin care, makeup, perfume, antibiotics, sunscreen, nail polish, new furniture, plastic tableware, detergent, polish, paint, and pesticide) were associated with the concentration level of chemicals. We found that exposure to several EDCs during pregnancy and the postpartum period was associated with perinatal depression and dietary–lifestyle factors. Women in childbirth need to actively seek out information about exposure to EDCs and make efforts to avoid them for their own and fetal health.

Keywords: perinatal depression; endocrine disrupting chemical; dietary factor; lifestyle factor

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Academic Editor: Carlos Carvalhais

Received: 5 December 2024
Revised: 23 December 2024
Accepted: 1 January 2025
Published: 6 January 2025

Citation: Moon, N.; Heo, S.J.; Kim, J.H. Associations of Exposure to 24 Endocrine-Disrupting Chemicals with Perinatal Depression and Lifestyle Factors: A Prospective Cohort Study in Korea. *Environments* **2025**, *12*, 15. https://doi.org/10.3390/environments12010015

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1. Introduction

The endocrinology of pregnancy is related to physiological changes during fetal development and growth [1]. During the perinatal period, when a woman is pregnant and gives birth, she undergoes significant hormonal changes. For example, as the placenta develops, the levels of human chorionic gonadotropin (hCG) and placental lactogen, which provide nutrients to the fetus, increase, as do the levels of estrogen and progesterone, which are essential for maintaining pregnancy [2]. However, after birth, the placenta, which secretes

reproductive hormones, is expelled, and the levels of these hormones drop rapidly [2]. The concentration of thyroid-stimulating hormone (TSH) in early pregnancy temporarily decreases due to the lowering effect of thyroid function caused by increased hCG levels and then begins to increase again [3]. This thyroid hormonal fluctuation may influence physiological changed that could be associated with mental health, including postpartum depression (PPD) [3]. In addition, pregnancy increases cardiac output and respiratory rate by approximately 30–40%, constituting a physical burden for women [2]. Due to these physical changes and fluctuations in reproductive hormones, women experience mental health symptoms such as anxiety, stress, and depression during the perinatal period [4–6]. Perinatal depression is defined as the occurrence of major depressive episodes, either during pregnancy (antenatal depression, AD) or within the first four weeks of postpartum (PPD). Exposure to EDCs in pregnant women can lead to endocrine disruptions, including immune activation and inflammatory responses [4]. According to a systematic review study, the biological and psychosocial predictors of PPD include hormonal dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis, inflammatory processes, genetic vulnerabilities, severe life events, chronic stress, and social support [7]. Among these, exposure to EDCs has been identified as a biologically significant factor [4,7]. The relationship between EDC concentrations in biological samples reflecting internal exposure in pregnant women and PPD has been the focus of recent research. A study conducted in Korea observed an association between EDC concentrations in breast milk and postpartum depression, underscoring the need for further research [8].

Phthalates, bisphenols, parabens, polycyclic aromatic hydrocarbons (PAHs), and volatile organic compounds (VOCs) are endocrine-disrupting chemicals (EDCs) that people may be ubiquitously exposed to in daily life through oral ingestion, dermal absorption, and inhalation [9,10]. These non-persistent chemicals are characterized by short half-lives ranging from 6 to 24 h, which leads to rapid metabolism and large within-person variability over time [9]. Despite their fast turnover, these chemicals are found consistently in human samples, such as urine or breast milk, indicating that most individuals face regularly daily exposure [4,11]. Although the mechanisms underlying the increased risk of perinatal depression following exposure to non-persistent EDCs are unclear, some possible explanations have been suggested. EDCs have estrogenic effects on the hippocampus and amygdala, regulating the hypothalamic–pituitary–adrenal axis (HPA) or influencing changes in neurotransmitters, causing anxiety and depressive behavioral disorders [12–14]. EDCs may cause depression by interfering with the production, transport, and release of neurotransmitters such as dopamine, causing synaptic plasticity [15,16]. Another mechanism is that EDCs act like fake thyroid hormones, which can induce thyroid dysfunction or hypothyroidism and cause psychopathological effects [4]. In other words, if exposed in early pregnancy, EDCs can interfere with thyroid function, reducing the fetus' neurological development and the mother's metabolic function [17,18]. Other possible mechanisms include elevated proinflammatory cytokine levels, oxidative stress, and epigenetic gene expression [19,20]. Epidemiological studies linking exposure to diverse EDCs and psychosocial disorders, such as depression and anxiety, have been reported in various populations, but the results are inconsistent [9,11,21–28]. Previous epidemiological studies have reported that exposure to phthalates and bisphenols increased the risk of postpartum depression by 1.03 (95% CI: 0.07, 1.99) times with bisphenol A (BPA) and bisphenol F (BPF) [11], 1.22 times (95% CI: 1.00–1.48) with mono(2-ethyl-5-carboxypentyl) phthalate (MECPP), 1.33 times (95% CI: 1.14–1.54) with mono-N-butyl phthalate (MnBP), 1.23 times (95% CI: 0.99–1.51) with mono-isobutyl phthalate (MiBP), and 1.29 times (95% CI: 1.00–1.67) with monobenzyl phthalate (MBzP) [24]; in contrast, several epidemiological studies reported that there was no significant difference between exposure to phthalates, bisphenols, and parabens

and postpartum depression [9,11,24]. Although women are vulnerable to depression and anxiety during pregnancy, few studies have reported on perinatal depression. Therefore, the purpose of this study was to determine the level of exposure to EDCs during pregnancy and the postpartum period and to determine the relationship between exposure to EDCs and ante- and postpartum depression. Additionally, we explored the relationship between pregnant women's diet, lifestyle habits, and exposure to 24 selected EDCs.

2. Materials and Methods

2.1. Study Design and Population

The No Environmental Hazards for Mother–Child (NoE-MoC) study is a prospective birth cohort in Korea established from the 1st trimester of pregnancy to three years after childbirth. Pregnant women were recruited from 2022 to 2023 in five hospitals in Korea (three in Seoul, one in Gyeonggi-do, and one in Gangwon-do) if they met the following inclusion criteria: (1) healthy Korean pregnant women at least 18 years of age; (2) 14 weeks of gestation (1st trimester of pregnancy); (3) receiving regular prenatal care from an obstetrician; (4) singleton pregnancy; (5) not taking any medications for mental health symptoms such as depression or anxiety; (6) not having any underlying disease such as hypertension, diabetes mellitus, thyroid, etc. All the participants were Koreans of the same ethnicity, maintained national insurance coverage, and lived with their husbands. They were invited to submit urine samples and answer a structured questionnaire covering sociodemographic and obstetric characteristics, dietary factors, consumer product factors, fetal growth records with ultrasonography, and depression symptoms when they visited the hospital for a medical checkup (1st, 2nd, and 3rd trimesters of pregnancy and within 4 weeks after childbirth). Considering the short half-life of EDCs, we investigated whether the study participant used food and personal care products within one to two days. We simultaneously conducted a structured questionnaire, urine collection, and assessment of depressive symptoms. Structured questionnaires and evaluation of depressive symptoms were conducted during pregnancy (around 14 weeks) and postpartum (within four weeks after birth), and urine samples were collected from 242 and 119 women, respectively, during each period. A total of 242 eligible pregnant women were enrolled in this cohort, and 197 were subsequently followed up, of whom 119 submitted postpartum depression scores. Written consent was obtained after participants received detailed explanations regarding this study from qualified nurses at the first visit. This study was approved by the Ethics and Human Committees of Kyung Hee University (KHSIRB-21-598) and Kangwon National University Hospital (KNUH-2022-02-001-001).

2.2. Perinatal Depression Assessment

Maternal ante- and postpartum depressive symptoms were assessed using a self-administered questionnaire, employing the Korean version of the Center for Epidemiological Studies-Depression Scale (CES-D) [29–31] for antepartum depression and the Korean version of the Edinburgh Postnatal Depression Scale (K-EPDS) [31,32] for postpartum depression. The Korean version of the CES-D consists of 20 items covering depressive mood, guilt, lack of self-valuation, hopelessness, and sleep disturbance. The total score ranges from 0 to 60, with a higher score indicating more depressive symptoms. A four-point Likert scale (0–3) was used, with 0 indicating "not at all" and 3 "severely". A total ≤ 20 was classified as "normal" and $\geq$21 was classified as "at risk, abnormal" based on the validated cut-off point for Korean women [30]. The K-EPDS consists of 10 items covering depressive mood, anxiety, hopelessness, and irritability. The total score ranges from 0 to 22, with a higher score indicating more depressive symptoms. The same four-point Likert scale was used, with a total ≤ 9 being classified as "normal" and $\geq$10 as "at risk, abnormal" based on

the validated cut-off point for postnatal Korean women [32]. Standardized z-scores were calculated and used to compare and analyze EPDS and CES-D scores.

2.3. Dietary and Lifestyle Factors Assessment

The questionnaire administered to pregnant women included items on sociodemographic and health information (gestational age, weight, height, marital status, educational level, monthly household income, occupation, residence, medical history, obstetric history, alcohol use, and smoking); dietary factors; and consumer product factors. All items in the dietary and consumer product questions were chosen based on a literature review that showed a significant association with exposure to EDCs. This questionnaire was validated by exposure assessment experts and used in our previous research [12]. Participants were required to indicate the frequency of food consumption and daily life product usage from the past 1 day to 4 weeks. Dietary factors consisted of meat with fat tissue, fish, dairy products, shellfish, fermented food, fried food, fast food, frozen food, cup noodles, ice cream, canned food, vinyl-packed food, and popcorn. Consumer product factors consisted of skincare products, makeup products, hair products, manicures, perfumes, antibiotics, sunscreen, new furniture, plastic bowls, disposable dishware, dishwasher, detergent, polish, water-proofing products, air freshener, glue, insect repellent, and mosquito repellent. Responses were recorded using a nine-point Likert scale interpreted as follows: 1 (none or rarely), 2 (once a month), 3 (2–3 times a month), 4 (once a week), 5 (2–4 times a week), 6 (5–6 times a week), 7 (once a day), 8 (twice a day), and 9 (3 times or more a day). All scores were added to calculate the total score in each domain.

2.4. Analysis of 24 Non-Persistent Chemicals in Urine Samples

We collected 20-mL maternal spot urine samples in polypropylene cups during each follow-up visit, which were directly stored at −80 °C until analysis. We measured the concentrations environmental pollutant chemicals, including nine phthalate metabolites (MnBP, MEP, MCPP, MBzP, MMP, MEOHP, MEHHP, MECPP, and MiBP) [8,10–12,14,21]; five phenols (BPA, BPF, BPS, TCS, and BP-3) [8,10–13,17,18]; four parabens (MP, EP, BP, and PP) [8,11,12,17]; four PAHs (1-OHP, 2-NAP, 1-PHE, and 2-FLU) [23,24,27,28]; and two VOCs (t, t-MA and BMA) [22,26] in the urine samples. The full names of these chemicals and the limit of detection (LOD) are presented in Table 1.

Detailed procedures for sample preparation, quality assurance, and quantification have been previously described [8,33]. Briefly, LC-MS/MS and the Thermo Scientific™ Vanquish™ ultra-high-performance liquid chromatography (UHPLC) system (Thermo Finnigan, San Jose, CA, USA) were used in the chemical analysis employing an ACE Excel 2 C18-AR column (150 mm × 2.1 mm I.D.; Advanced Chromatography Technology, Aberdeen, UK) and a TSQ Altis triple-quadrupole mass spectrometer (Thermo Finnigan) equipped with an electrospray ionization (ESI) source. The mobile phase consisted of water with 0.1% formic acid (solvent A) and acetonitrile with 0.1% formic acid (solvent B), with a gradient elution program optimized for target analytes. The spray voltage was 4500 V in the positive mode and 3500 V in the negative mode. The ion transfer tube temperature was 320 °C, and the vaporizer temperature was 340 °C in both modes. The column temperature was maintained at 35 °C. All experiments were performed in time-dependent reaction monitoring mode for simultaneous analysis. All chemicals used in this study were purchased from Sigma-Aldrich (St. Louis, MO, USA), Merck (Darmstadt, Germany), or Burdick and Jackson (Muskegon, MI, USA). *E. coli* β-glucuronidase (140 U/mg at 37 °C) was purchased from Roche (Mannheim, Germany). Standard reference materials (SRMs) 3672 and 3673 were purchased from the National Institute of Standards and Technology (NIST, Gaithersburg, MD, USA).

Table 1. Creatinine adjusted urinary concentration of chemicals in the ante- and postpartum periods (μg/g creatinine).

Groups	Analytes	Antepartum (14 Weeks of Gestation, n = 242)							Postpartum (One Month after Delivery, n = 119)						*t*-test *	*p*-Value
		DF (%)	LOD (μg/L)	GM	25th	50th	75th	Max	DF (%)	GM	25th	50th	75th	Max		
Phthalates	MnBP	100	0.11	14.45	7.72	15.34	26.11	232.82	100	24.95	14.51	22.33	39.44	192.25	−5.430	**<0.001**
	MEP	73.6	0.07	1.23	<LOD	1.80	6.35	684.50	100	3.28	1.11	2.52	8.04	711.64	−2.166	**0.031**
	MCPP	97.1	0.06	0.44	0.30	0.42	0.66	10.31	97.6	0.46	<LOD	0.49	0.63	3.14	−0.461	0.645
	MBzP	90.9	0.04	0.21	0.11	0.22	0.40	7.30	94.4	0.19	0.12	0.16	0.35	8.00	1.120	0.263
	MMP	100	0.01	0.33	0.17	0.33	0.62	11.51	37.3	0.03	<LOD	<LOD	0.21	79.21	2.019	**0.045**
	MEOHP	100	0.03	2.55	1.48	2.61	4.67	34.58	96.0	2.76	1.77	3.02	6.72	84.02	−1.958	0.052
	MEHHP	100	0.03	4.24	2.48	4.40	7.51	55.02	97.6	4.06	2.57	4.27	9.14	125.91	−0.640	0.523
	MECPP	92.1	0.03	3.40	2.48	5.08	10.32	53.47	98.4	8.87	5.63	8.65	18.24	196.18	−6.100	**<0.001**
	MiBP	98.8	0.07	5.35	2.54	5.69	12.00	178.70	82.5	3.34	1.01	5.32	18.30	300.41	0.288	0.774
Bisphenols	BPA	78.5	0.12	0.64	0.36	0.61	1.06	22.7	99.2	0.87	0.50	0.83	1.48	21.34	−5.118	**<0.001**
	BPF	42.1	0.08	0.47	0.09	0.26	2.48	19.9	48.4	0.11	<LOD	<LOD	0.19	2.78	4.100	**<0.001**
	BPS	98.8	0.01	0.30	0.13	0.25	0.63	22.1	100	0.77	0.37	0.64	1.74	86.62	−5.168	**<0.001**
Phenols	TCS	71.5	0.04	0.28	0.13	0.27	0.63	3.11	22.2	0.74	0.48	0.48	0.48	25.12	−6.855	**<0.001**
	BP-3	71.5	0.10	0.43	0.14	0.30	0.93	341	69.8	0.25	<LOD	0.15	0.52	156.64	0.022	0.983
Parabens	MP	100	0.15	6.70	2.77	4.82	9.07	1390	64.3	1.93	<LOD	1.81	13.90	682.09	2.307	**0.022**
	EP	99.6	0.14	32.80	10.2	40.30	126	2900	90.5	29.14	10.50	48.08	168.23	2492.72	−0.431	0.667
	PP	31	0.21	1.99	0.34	0.93	12.7	250	69.8	0.64	<LOD	0.32	1.44	303.40	−2.129	**0.034**
	BP	100	0.07	0.78	0.48	0.70	1.09	23.8	100	1.11	0.73	0.96	1.53	12.52	−3.567	**<0.001**
PAHs	1-OHP	85.5	0.03	0.14	0.07	0.13	0.23	4.08	98.4	0.10	0.07	0.11	0.15	0.97	2.652	**0.008**
	2-NAP	100	0.05	2.39	1.24	2.07	3.96	84.1	99.2	2.06	1.01	1.82	3.67	76.89	0.667	0.505
	1-PHE	77.3	0.02	0.07	0.04	0.06	0.09	37.0	84.9	0.05	0.03	0.05	0.08	0.53	2.077	**0.039**
	2-FLU	95	0.01	0.13	0.08	0.14	0.22	9.10	92.9	0.11	0.07	0.13	0.21	2.43	0.094	0.925
VOCs	t,t-MA	99.6	0.58	45.20	21.40	44.80	92.0	554	100	48.75	28.81	43.56	72.59	395.46	−0.869	0.386
	BMA	99.6	0.04	2.87	1.49	2.49	4.67	10100	99.2	5.57	3.24	5.21	9.43	791.21	−5.2132	**<0.001**

DF, detection frequency; LOD, limit of detection; GM, geometric mean; Min, minimum; Max, maximum; MnBP, mono-N-butyl phthalate; MEP, mono ethyl phthalate; MCPP, Mono(3-carboxypropyl) phthalate; MBzP, monobenzyl phthalate; MMP, mono(2-methylpropyl) phthalate; MEOHP, mono(2-ethyl-5-oxohexyl) phthalate; MEHHP, mono(2-ethyl-5-hydroxyhexyl) phthalate; MECPP, mono(2-ethyl-5-carboxypentyl) phthalate; MiBP, mono-isobutyl phthalate; BPA, Bisphenol A; BPF, Bisphenol F; BPS, Bisphenol S; MP, Methylparaben; EP, Ethylparaben; BP, Butylparaben; PP, Propylparaben; TCS, Triclosan; BP-3, Benzophenon-3; 1-OHP, 1-hydroxypyrene; 2-NAP, 2-hydroxynaphthalene; 1-PHE, 1-hydroxyphenanthrene; 2-FLU, 2-hydroxyfluorene; t,t-MA, trans, trans-muconic acid; BMA, benzylmercapturic acid; * *t*-test after natural log transformation; bold values are statistically significant ($p < 0.05$).

For quality control, a standard calibration curve with a regression coefficient > 0.99 was generated for all curves using 30% methanol in aqueous solution. The standard calibration curve ranged between 0.005 and 20 ng/mL. Urine samples were spiked with isotope-labeled standard material. The signal-to-noise ratio of the matrix used in this analysis was three. The average recovery rate for all targets in the matrix spike sample ranged between 86 and 105%, and the relative standard deviation ranged between 11 and 17%. Matrix spike urine samples with known concentrations (1, 10, and 20 ng/mL) and randomly selected procedural blank samples were used for experimental verification. No target analytes were detected in the blank sample. To evaluate the intra-day precision, the standard solution evaluated six times a day was compared with the target solution, and the inter-day precision was evaluated against the standard solution measured six days in a row. The overall quality and accuracy of the described analysis method were monitored through an interlaboratory comparison program.

2.5. Statistical Analyses

All chemicals were detected in >30% of urine samples. Values below the LOD were substituted with LOD/$\sqrt{2}$ [34]. The urinary creatinine levels were adjusted to reflect changes in the intra- and inter-subject variability in renal filtration dynamics [35]. Demographic characteristics were described as the mean, standard deviation, median, and minimum–maximum for continuous variables and numbers and percentages for categorical variables. A normality test (Kolmogorov–Smirnov test) was conducted for all data; because the level of chemical concentration in urine samples showed a right-skewed distribution, a natural log transformation was performed. The mean differences between the chemicals in both the ante- and postpartum periods were compared using a Student's *t*-test. Pearson's correlation coefficients were used to identify correlations among chemicals, depression scores, and dietary and lifestyle factors. To examine the association between each analyte (phthalates, phenols, parabens, PAHs, and VOCs) and ante- and postpartum depression, multiple logistic regression with the entry method was used to estimate odds ratios (ORs) and 95% confidence intervals. To confirm the association between each analyte and dietary and consumer product factors, bivariate linear regression was used. To evaluate the mixture effect between urinary chemicals and the perinatal depression score, we used Bayesian Kernel Machine Regression (BKMR). BKMR is a reliable method frequently used in the environmental health research field in which non-linear, non-additive, and mixture interaction effects of all substances are considered [36]. The overall cumulative mixture effects and dose–response effects of each of 24 urinary chemicals were evaluated in relation to the antepartum and postpartum depression scores. Subsequently, we evaluated the mixture effect of each chemical on the depression score by dividing the chemicals into subgroups according to phthalates, bisphenols, parabens, PAHs, and other chemicals. Maternal age, early pregnancy body mass index (BMI), education, income, parity, cotinine level in the urine, and neonatal sex were adjusted for as covariates following the previous studies [8,9,11,12]. Statistical significance was evaluated at $p < 0.05$. All statistical analyses were performed using R 4.1.0 (R Development Core Team, Vienna, Austria) and SPSS 28.0 (IBM SPSS Statistics, Armonk, NY, USA).

3. Results

3.1. Study Participants

The mean maternal age at the first visit was 33.8 years (range 21–42 years), and the mean early pregnancy BMI was 23.2 kg/m^2 (Table 2). Over 81% of the participants had a college or higher educational level, over 51% reported a more than 5000 USD household income monthly, about 65% were employed and lived in metropolitan areas, and over

57% were primipara mothers. The mean maternal urinary cotinine level was 25.4 μg/g creatinine. The mean cotinine level of non-smokers was 0.89 μg/g creatinine, while the mean cotinine level of six possible smokers was 995.76 μg/g creatinine (ranged from 544.88 to 1720 μg/g creatinine). The mean score of antepartum depression was 16.5 (range 1–36), and 23.6% of participants were classified as abnormal, with a score ≥ 21. The mean score of postpartum depression was 8.9 (range 0–22), and 45.4% of participants were classified as abnormal, with a score ≥ 9.

Table 2. Socioeconomic characteristics and ante- and postpartum depression of participants (n = 242).

Variables	Categories	n/M	%/SD	Median	Min	Max
Age (years)		33.8	4.0	34.0	21.0	42.0
Early-pregnancy BMI (kg/m^2)		23.2	4.2	22.5	14.8	40.2
Education	<college	44	18.2			
	≥college	198	81.8			
Household income ($/month)	≤5000	124	51.2			
	>5000	118	48.8			
Employment status	Yes	157	64.9			
	No	85	35.1			
Residence area	Metropolitan	155	64.0			
	Non-metropolitan	87	36.0			
Parity	Primipara	139	57.4			
	Multipara	103	42.6			
Cotinine level (μg/g creatinine) *		0.31	186.46	0.22	0.04	1720
Antepartum depression score		16.5	6.1	15.5	1	36
	Low (≤20)	185 (76.4)				
	High (≥21)	57 (23.6)				
Postpartum depression score (n = 119)		8.9	3.6	8	0	22
	Low (≤9)	65 (54.6)				
	High (≥10)	54 (45.4)				

M, mean; SD, standard deviation; Min, minimum; Max, maximum; BMI, body mass index; * detection frequency of cotinine was 84.3%.

3.2. Non-Persistent Urinary Chemical Concentrations in the Ante- and Postpartum Periods

Table 2 shows the detailed results for each tested chemical in 242 antepartum and 119 postpartum urine samples. The detection frequency, LOD, geometric mean (GM), median, minimum, and maximum values are shown. The detection frequency ranged from 22.2% for TCS in the postpartum period to 100% for MnBP, MMP, MEOHP, MEHHP, MP, BP, and 2-NAP in the antepartum period and for MnBP, MEP, BPS, BP, and t,t-MA during the postpartum period. Significant mean differences between the ante- and postpartum periods were present in MnBP, MEP, MMP, MECPP, BPA, BPF, BPS, TCS, MP, PP, BP, 1-OHP, 1-PHE, and BMA, with urinary concentrations decreasing from antepartum to postpartum (Figure 1). Each subject's urinary chemical concentration changes between ante the partum and postpartum periods are presented as line graphs (Figure 2). Some chemicals, including MEOHP, MEHHP, MECPP, BPA, BPS, TCS, and BMA, generally showed an increasing tendency, while BPF and 1-PHE showed a decreasing pattern in the postpartum period compared to antepartum period.

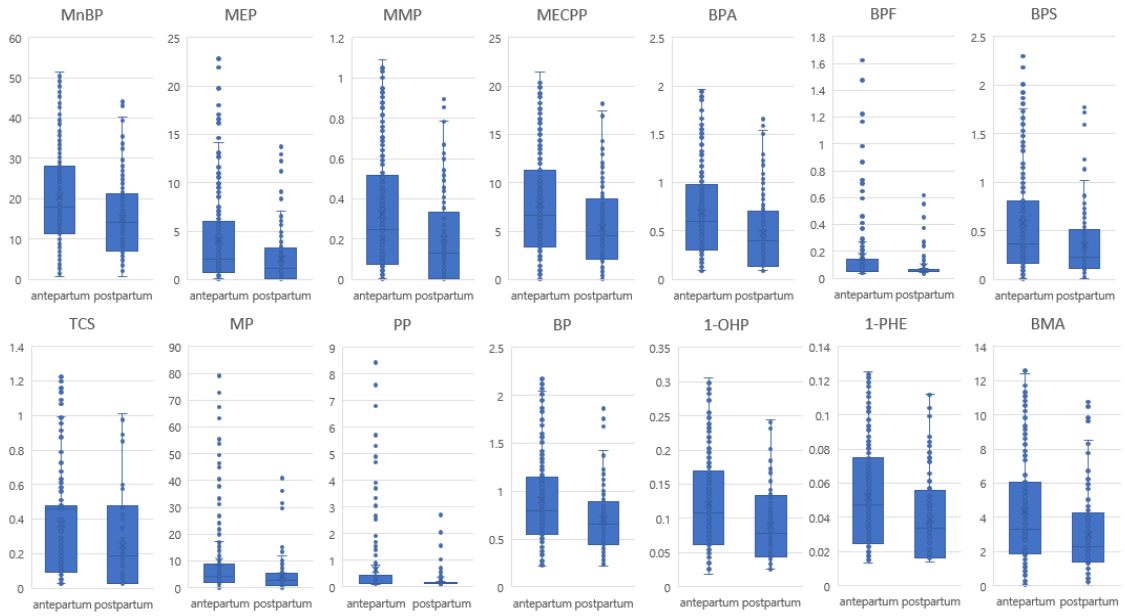


Figure 1. Concentration changes of chemicals in the ante- and postpartum periods. All boxplots show statistically significant higher median, mean, IQR, minimum, maximum, and outliers of chemicals in the antepartum period versus postpartum period. MnBP, mono-N-butyl phthalate; MEP, mono ethyl phthalate; MMP, mono(2-methylpropyl) phthalate; MECPP, mono(2-ethyl-5-carboxypentyl) phthalate; BPA, Bisphenol A; BPF, Bisphenol F; BPS, Bisphenol S; TCS, Triclosan; MP, Methylparaben; PP, Propylparaben; BP, Butylparaben; 1-OHP, 1-hydroxypyrene; 1-PHE, 1-hydroxyphenanthrene; BMA, benzylmercapturic acid. Extreme outliers (<Q1 − 5*IQR, >Q3 + 5*IQR) have been omitted.

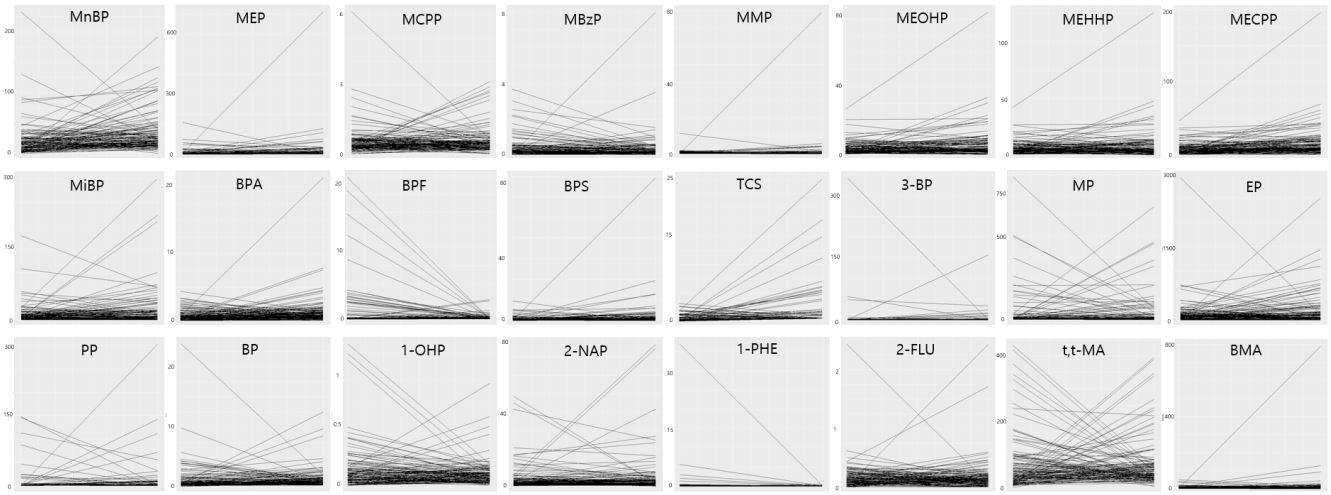


Figure 2. Difference of 24 non-persistent endocrine disrupting chemicals (EDCs) in maternal urine at the points of the 1st trimester and one month after delivery (n = 119). MnBP, mono-N-butyl phthalate; MEP, mono ethyl phthalate; MCPP, Mono(3-carboxypropyl) phthalate; MBzP, monobenzyl phthalate; MMP, mono(2-methylpropyl) phthalate; MEOHP, mono(2-ethyl-5-oxohexyl) phthalate; MEHHP, mono(2-ethyl-5-hydroxyhexyl) phthalate; MECPP, mono(2-ethyl-5-carboxypentyl) phthalate; MiBP, mono-isobutyl phthalate; BPA, Bisphenol A; BPF, Bisphenol F; BPS, Bisphenol S; MP, Methylparaben; EP, Ethylparaben; BP, Butylparaben; PP, Propylparaben; TCS, Triclosan; BP-3, Benzophenon-3; 1-OHP, 1-hydroxypyrene; 2-NAP, 2-hydroxynaphthalene; 1-PHE, 1-hydroxyphenanthrene; 2-FLU, 2-hydroxyfluorene; t,t-MA, trans, trans-muconic acid; BMA, benzylmercapturic acid.

3.3. Association Between Urinary Chemical Concentration and Ante- and Postpartum Depression

In the antepartum period, the depression score of mothers was statistically significantly correlated with MCPP (r = −0.18), MBzP (r = −0.11), MEHP (r = −0.07), and PP

(r = −0.06). In the postpartum period, some chemicals showed slight positive correlation with depression score, but there was no statistical significance at the significance level $p < 0.05$. The distribution of each depression score at the antepartum and postpartum periods is presented as scatter plots (Supplementary Figure S1).

In the adjusted multiple logistic regression model with covariates of maternal age, early pregnancy BMI, education, income, parity, gestational age, urine cotinine level, and neonatal sex, we observed a significant association with antepartum depression scores in MECPP (aOR = 1.50, 95% CI = 1.010–2.227) and 1-OHP (aOR = 0.05, 95% CI = 0.003–0.888) (Table 3). In the postpartum period, the antepartum depression score was adjusted with other covariates. Several phthalates and PAHs were significantly associated with maternal postpartum depression scores. In the phthalate group, this consisted of MEOHP (aOR = 2.78, 95% CI = 1.004–7.700) and MEHHP (aOR = 2.79, 95% CI = 1.040–7.459) and, in the PAH group, of 2-NAP (aOR = 7.22, 95% CI = 1.426–36.593) and 2-FLU (aOR <0.01, 95% CI = 0–0.004).

Table 3. Multiple logistic regression of the association between 24 chemicals and antepartum and postpartum depression.

		Antepartum Depression (n = 242)			**Postpartum Depression (n = 119)**		
Groups	**Chemical**	**aOR**	***p*-Value**	**95% CI**	**aOR**	***p*-Value**	**95% CI**
Phthalates	MnBP	0.97	0.863	0.682–1.379	0.46	0.185	0.144–1.455
	MEP	0.79	0.081	0.603–1.030	1.03	0.936	0.536–1.970
	MCPP	0.27	0.065	0.064–1.088	0.30	0.562	0.005–17.788
	MBzP	0.38	0.130	0.113–1.325	9.92	0.307	0.121–NA
	MMP	0.67	0.473	0.217–2.031	<0.01	0.180	0–NA
	MEOHP	1.04	0.874	0.645–1.675	**2.78**	**0.049**	**1.004–7.700**
	MEHHP	1.09	0.710	0.697–1.700	**2.79**	**0.042**	**1.040–7.459**
	MECPP	**1.50**	**0.045**	**1.010–2.227**	2.73	0.056	0.973–7.641
	MiBP	1.09	0.604	0.797–1.477	1.08	0.749	0.668–1.751
Bisphenols	BPA	0.87	0.731	0.400–1.901	1.00	1.000	0.106–9.446
	BPF	0.82	0.467	0.475–1.407	0.02	0.326	0–49.044
	BPS	0.99	0.984	0.523–1.886	0.41	0.296	0.078–2.174
Phenols	TCS	0.96	0.944	0.320–2.890	0.77	0.805	0.100–5.983
	BP-3	0.90	0.642	0.589–1.386	0.94	0.947	0.168–5.314
Parabens	MP	0.85	0.222	0.660–1.102	0.77	0.335	0.448–1.315
	EP	1.03	0.725	0.865–1.232	0.89	0.506	0.622–1.264
	PP	0.91	0.562	0.671–1.242	0.64	0.399	0.228–1.801
	BP	1.00	0.993	0.439–2.294	0.06	0.087	0.002–1.511
PAHs	1-OHP	**0.05**	**0.041**	**0.003–0.888**	0.01	0.511	0–NA
	2-NAP	1.10	0.660	0.727–1.654	**7.22**	**0.017**	**1.426–36.593**
	1-PHE	0.27	0.355	0.016–4.364	<0.01	0.144	0–NA
	2-FLU	0.37	0.423	0.032–4.217	**<0.01**	**0.017**	**0–0.004**
VOCs	t,t-MA	1.08	0.621	0.796–1.466	0.68	0.442	0.250–1.832
	BMA	0.97	0.852	0.691–1.356	0.67	0.603	0.148–3.027

Multiple logistic regression results adjusted for maternal age, early-pregnancy body mass index, education, income, parity, gestational age, and maternal urine cotinine level. Postpartum pregnancy depression score was adjusted for antepartum depression score and neonatal sex; bold characters indicate statistical significance ($p < 0.05$). MnBP, mono-N-butyl phthalate; MEP, mono ethyl phthalate; MCPP, Mono(3-carboxypropyl) phthalate; MBzP, monobenzyl phthalate; MMP, mono(2-methylpropyl) phthalate; MEOHP, mono(2-ethyl-5-oxohexyl) phthalate; MEHHP, mono(2-ethyl-5-hydroxyhexyl) phthalate; MECPP, mono(2-ethyl-5-carboxypentyl) phthalate; MiBP, mono-isobutyl phthalate; BPA, Bisphenol A; BPF, Bisphenol F; BPS, Bisphenol S; MP, Methylparaben; EP, Ethylparaben; BP, Butylparaben; PP, Propylparaben; TCS, Triclosan; BP-3, Benzophenon-3; 1-OHP, 1-hydroxypyrene; 2-NAP, 2-hydroxynaphthalene; 1-PHE, 1-hydroxyphenanthrene; 2-FLU, 2-hydroxyfluorene; t,t-MA, trans, trans-muconic acid; BMA, benzylmercapturic acid; aOR, adjusted odds ratio; CI, confidence interval.

We used the BKMR method to assess the mixture effects of 24 non-persistent EDCs on antepartum (Figure 3a) and postpartum (Figure 3d) depression. The overall effect regression models were adjusted for maternal age, early-pregnancy BMI, education, income, parity, gestational age, maternal urine cotinine level, and neonatal sex. Both antepartum

and postpartum depression scores showed no statistically significant association between urinary chemicals in terms of overall mixture effect when other chemical levels were fixed at similar percentiles from the 10th to 90th. Figure 3b,e show the dose–response relationship for the association between each non-persistent chemical level and antepartum and postpartum depression scores, with other chemical levels fixed at their median. Each chemical showed different dose–response results, including positive, negative, and non-linear patterns. Figure 3c,f show the estimated effect and 95% confidence intervals of interquartile change of each chemical and antepartum and postpartum depression scores after fixing the other chemical levels at their 25th (red), 50th (green), and 75th (blue) percentiles. No individual chemical showed a statistically significant interquartile change effect in this analysis.

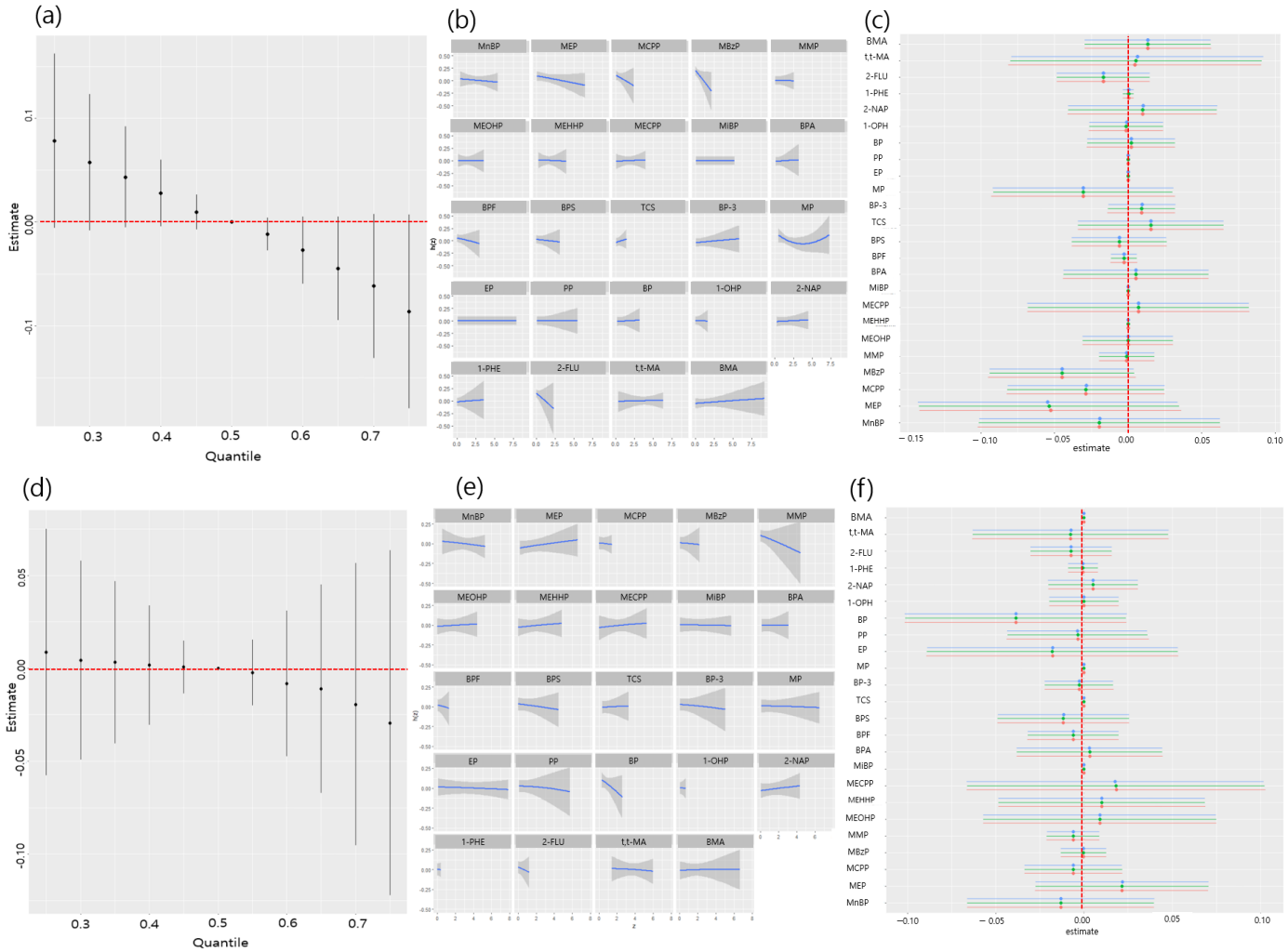


Figure 3. Bayesian Kernel Machine Regression between phthalates, bisphenols, parabens, PAHs, and other chemicals and antepartum and postpartum depression scores. (**a**) The overall effects of bisphenols; parabens; polycyclic aromatic hydrocarbons (PAHs); and other chemicals (TCS, BP-3, and VOCs) on the antepartum depression score were estimated using the Bayesian Kernel Machine Regression (BKMR) adjusted for maternal age, early-pregnancy body mass index, education, income, parity, gestational weeks, maternal urine cotinine level, and neonatal sex; ln: natural log. (**b**) Exposure–response relationship for the association between each chemical and antepartum depression score, fixing other chemical levels at their median. (**c**) The red, green, and blue bars and dots shows the estimated effect and 95% confidence intervals of an interquartile range change of each urinary chemical and antepartum depression score when the level of each of the other chemicals was held at

their corresponding 25th, 50th, and 75th percentiles, respectively. (**d**) The overall effects of bisphenols; parabens; polycyclic aromatic hydrocarbons (PAHs); and other chemicals (TCS, BP-3, and VOCs) on the postpartum depression score were estimated using the Bayesian Kernel Machine Regression (BKMR) adjusted for early pregnancy depression score, maternal age, early-pregnancy body mass index, education, income, parity, gestational weeks, maternal urine cotinine level, and neonatal sex; ln: natural log. (**e**) Exposure–response relationship for the association between each chemicals and postpartum depression score, fixing other chemical levels at their median. (**f**) The red, green, and blue bars and dots shows the estimated effect and 95% confidence intervals of an interquartile range change of each urinary chemical and postpartum depression score when the level of each of the other chemicals was held at their corresponding 25th, 50th, and 75th percentiles, respectively.

3.4. Association Between Dietary/Lifestyle Factors and Depression

In this study, the consumption of fish (MiBP), fermented food (MMP), cup noodle (MBzP), and popcorn (MEP) and use of manicure (MBzP), perfume (MiBP), plastic tableware (MMP), paint (MEHHP), and pesticides (MCPPs) were significantly associated with an increase in urinary phthalate concentration in pregnant women during the antepartum and postpartum periods. The increase in bisphenol levels was correlated with the consumption of fish (BPF) and popcorn (BPF) and the use of paint (BPA and BPF). TCS was significantly associated with the consumption of frozen food and use of new furniture. Increased paraben concentrations were significantly correlated with fermented foods (BP), consumption of cup noodles (MP and PP), skincare, makeup, sunscreen (EP), perfumes (PP), pesticides (MP), and the use of polishes (BP). Increased levels of PAHs in urine were significantly associated with the consumption of fermented and frozen foods; use of skin care, perfume, hand washer, and sunscreen products; and use of detergent, polish, air fresheners, and paint. There was a significant increase in VOCs in urine with the use of skincare products and polish (Tables 4 and 5).

Table 4. Associations between chemicals in maternal urine and dietary factors and consumer products in the antepartum period (n = 242).

Chemical		Dietary Factors									Consumer Products Factor							
		Fish	Dairy Products	Fermented Foods	Frozen Foods	Cup Noodle	Popcorn	Skincare Products	Makeup Products	Perfume	Antimicrobial Products	Sunscreen	New Furniture	Plastic Bowl	Detergent	Polish	Air Freshener	Paint	Pesticides
		B											B						
MnBP	beta	0.03	0.01	0.00	−0.06	−0.06	−0.05	−0.01	−0.03	−0.04	−0.02	−0.01	−0.10 *	−0.01	−0.02	−0.09	−0.02	0.00	0.00
MEP	beta	0.03	−0.07	0.04	−0.07	−0.11	−0.19	0.06	0.01	0.09	0.00	−0.01	−0.04	−0.02	−0.02	−0.10	0.00	−0.17	0.05
MCPP	beta	0.02	0.00	0.01	−0.01	0.00	−0.01	0.00	−0.01	0.00	0.00	−0.01	−0.02	−0.01	0.00	−0.03	0.00	−0.01	0.00
MBzP	beta	0.02	0.02	0.01	−0.01	−0.01	−0.03	0.01	0.00	−0.01	0.01	0.01	0.00	0.00	0.01	0.01	0.00	0.06	0.02
MMP	beta	0.00	0.00	**0.03** *	−0.01	−0.01	0.00	0.01	−0.01	0.00	0.00	0.00	0.00	**0.02** *	0.01	−0.01	0.01	0.02	0.00
MEOHP	beta	0.05	0.03	0.01	0.02	−0.01	−0.02	0.01	−0.01	−0.04	0.01	−0.01	−0.01	0.00	0.02	0.00	−0.02	0.14	−0.01
MEHHP	beta	0.05	0.04	0.00	0.02	−0.01	0.01	0.01	−0.01	−0.04	0.01	−0.02	−0.01	0.00	0.01	0.04	−0.03	**0.23** *	0.01
MECPP	beta	0.05	0.05	0.00	0.02	−0.01	0.00	0.03	−0.01	−0.05	0.01	−0.02	−0.04	0.00	0.02	−0.01	−0.03	0.18	0.01
MiBP	beta	**0.15** *	0.02	−0.05	0.02	0.06	0.06	−0.01	−0.01	−0.07	0.00	0.02	−0.08	−0.01	−0.04	−0.12	−0.05	−0.09	0.02
BPA	beta	0.03	0.01	0.03	0.01	−0.01	0.04	0.02	0.00	0.01	0.00	0.02	0.00	0.01	0.00	0.04	0.00	**0.12** *	0.00
BPF	beta	**0.07** *	0.04	−0.02	0.00	−0.01	0.05	0.02	−0.02	−0.01	−0.01	−0.02	−0.04	−0.03	−0.01	0.06	−0.02	**0.18** *	0.01
BPS	beta	0.00	0.01	−0.02	0.03	−0.04	0.03	0.00	−0.01	0.01	0.01	−0.01	**0.05** *	0.01	0.01	0.00	0.00	0.10	−0.01
TCS	beta	−0.01	0.00	0.00	**0.03** *	0.02	−0.02	0.00	0.01	0.01	0.00	0.00	**0.02** *	0.02	0.00	−0.02	0.00	0.04	0.01
BP-3	beta	0.03	−0.04	0.02	0.00	−0.04	−0.03	0.01	−0.02	0.06	0.00	0.02	0.03	0.02	−0.01	0.05	0.00	0.20	0.07
MP	beta	0.05	0.03	0.00	0.08	−0.17 *	0.10	0.06	0.02	0.00	−0.02	0.00	0.05	0.02	−0.01	−0.01	0.01	−0.13	**0.21** *
EP	beta	0.08	0.03	0.04	0.02	−0.07	−0.01	**0.14** *	**0.10** *	0.08	0.03	**0.09** *	0.04	−0.04	0.04	−0.11	0.00	−0.46	0.04
PP	beta	−0.02	0.06	−0.01	0.01	−0.10 *	−0.03	0.04	0.00	0.00	0.00	−0.01	0.04	0.01	0.03	−0.12	0.01	−0.05	0.10
BP	beta	−0.01	0.00	**0.04** *	0.00	0.00	0.03	−0.01	0.00	0.00	0.01	0.01	**0.03** *	0.01	0.01	0.04	0.01	−0.06	0.01
1-OHP	beta	0.01	0.00	**0.02** *	0.01	0.00	0.00	**0.02** *	0.00	**0.02** *	**0.01** *	**0.01** *	0.00	0.00	0.01	**0.04** *	**0.01** *	**0.10** *	−0.01
2-NAP	beta	0.00	−0.01	0.04	**0.07** *	0.00	0.07	0.02	0.00	0.02	0.02	0.03	−0.01	−0.01	**0.06** *	−0.04	**0.05** *	0.01	−0.02
1-PHE	beta	0.03	−0.01	0.02	−0.01	0.00	−0.03	0.00	−0.01	−0.01	−0.01	0.00	−0.01	0.01	0.00	−0.02	−0.01	−0.01	0.00
2-FLU	beta	0.00	0.00	**0.02** *	0.01	−0.01	0.01	0.00	0.01	0.00	0.00	0.00	0.00	0.00	0.00	−0.01	0.01	0.00	0.00
t,tMA	beta	0.01	0.00	0.05	0.04	0.05	0.09	**0.07** *	0.03	0.05	0.04	0.01	0.01	0.00	−0.03	−0.05	0.00	0.20	−0.02
BMA	beta	−0.03	−0.04	0.05	−0.02	0.04	0.08	−0.04	0.00	0.02	−0.02m	0.00	−0.05	−0.03	−0.02	−0.02	0.02	0.02	0.05

Multiple linear regression results adjusted for maternal age, early-pregnancy body mass index, education, income, parity, gestational age, and maternal urine cotinine level after natural log transformation for chemical concentrations; *p*, *p*-value; bold and asterisk (*) characters indicate a statistically significant positive association ($p < 0.05$). MnBP, mono-N-butyl phthalate; MEP, mono ethyl phthalate; MCPP, mono(3-carboxypropyl) phthalate; MBzP, monobenzyl phthalate; MMP, mono(2-methylpropyl) phthalate; MEOHP, mono(2-ethyl-5-oxohexyl) phthalate; MEHHP, mono(2-ethyl-5-hydroxyhexyl) phthalate; MECPP, Mono(2-ethyl-5-carboxypentyl) phthalate; MiBP, mono-isobutyl phthalate; BPA, Bisphenol A; BPF, Bisphenol F; BPS, Bisphenol S; MP, Methylparaben; EP, Ethylparaben; BP, Butylparaben; PP, Propylparaben; TCS, Triclosan; BP-3, Benzophenon-3; 1-OHP, 1-hydroxypyrene; 2-NAP, 2-hydroxynaphthalene; 1-PHE, 1-hydroxyphenanthrene; 2-FLU, 2-hydroxyfluorene; t,t-MA, trans, trans-muconic acid; BMA, benzylmercapturic acid.

Table 5. Associations between chemicals in maternal urine and dietary factors and consumer products in the postpartum period (n = 119).

Chemical		Dietary Factors									Consumer Products							
		Fish	Dairy Products	Fermented Foods	Frozen Foods	Cup Noodle	Popcorn	Skincare Products	Makeup Products	Manicure	Perfume	Antimicrobial Products	Sunscreen	New Furniture	Plastic Bowl	Detergent	Polish	Air Freshener	Pesticide
		B											B						
MnBP	beta	0.020	−0.009	0.023	−0.023	−0.016	0.097	−0.056	−0.007	−0.204	0.114	0.004	−0.043	−0.008	−0.033	−0.037	0.031	−0.027	0.058
MEP	beta	0.067	−0.003	−0.011	0.027	0.063	**0.258** *	0.051	0.150	0.780	0.016	0.024	0.087	0.138	−0.037	0.009	−0.048	0.000	0.212
MCPP	beta	−0.001	0.016	0.002	−0.004	−0.005	0.011	−0.004	0.007	0.051	0.024	−0.006	−0.011	−0.022	0.003	0.003	−0.034	−0.009	**0.068** *
MBzP	beta	−0.011	0.016	0.011	−0.004	**0.053** *	0.053	0.018	0.030	**0.227** *	−0.003	0.004	0.006	−0.022	−0.004	0.012	−0.040	0.007	−0.016
MMP	beta	0.014	−0.021	0.021	−0.012	−0.051	0.038	−0.020	−0.023	−0.164	0.045	−0.003	−0.032	0.024	0.012	−0.014	−0.075	−0.044	0.004
MEOHP	beta	0.01	−0.01	0.01	−0.01	0.02	−0.04	−0.01	0.04	−0.40	0.25	0.03	−0.04	−0.08	0.00	−0.01	−0.20	0.00	0.02
MEHHP	beta	0.02	−0.01	0.01	0.00	0.05	−0.04	−0.01	0.03	−0.38	0.21	0.03	−0.05	−0.08	0.01	0.00	−0.27 *	−0.01	0.01
MECPP	beta	0.02	0.02	0.04	0.02	0.06	0.04	−0.02	0.05	−0.11	0.23	0.05	−0.06	−0.10	0.01	−0.02	−0.23 *	0.00	0.04
MiBP	beta	0.03	−0.02	0.06	0.07	0.03	0.19	0.00	0.03	−0.68	**0.47** *	−0.01	0.00	−0.03	0.05	0.00	−0.16	−0.07	0.12
BPA	beta	−0.04	0.02	−0.02	−0.05	−0.06	0.07	0.02	−0.01	−0.02	0.07	−0.02	−0.01	−0.02	0.00	0.02	0.04	−0.03	−0.05
BPF	beta	−0.01	0.00	−0.01	−0.01	−0.01	**0.09** *	−0.01	−0.02	−0.04	−0.01	0.00	0.00	0.01	−0.01	−0.01	−0.03	0.00	−0.02
BPS	beta	0.01	−0.07	−0.03	−0.01	0.05	−0.02	−0.01	0.06	0.05	0.07	0.02	0.03	−0.02	−0.01	−0.02	−0.03	0.00	−0.03
TCS	beta	−0.08 *	−0.03	−0.08 *	−0.06	−0.11 *	−0.04	0.03	0.02	−0.18	0.15	0.02	−0.01	−0.01	−0.02	0.02	0.02	−0.04	−0.07
BP-3	beta	−0.08 *	−0.03	−0.08 *	−0.06	−0.11 *	−0.04	0.03	0.02	−0.18	0.15	0.02	−0.01	−0.01	−0.02	0.02	0.02	−0.04	−0.07
MP	beta	−0.13	0.00	−0.06	−0.04	−0.07	0.11	0.13	0.08	−0.21	0.57	0.04	0.05	0.06	−0.10	−0.03	−0.05	−0.01	0.18
EP	beta	0.01	0.03	−0.24 *	−0.27 *	−0.26	−0.34	0.06	−0.09	0.06	0.20	−0.08	0.00	−0.01	−0.11	−0.05	0.18	0.03	−0.01
PP	beta	−0.07	0.01	−0.02	−0.01	−0.09	0.00	0.07	0.14	0.00	**0.37** *	0.02	0.06	0.01	−0.07	−0.04	−0.02	−0.06	0.10
BP	beta	0.00	0.01	0.01	−0.01	0.01	0.05	0.01	0.01	0.16	−0.01	0.01	0.00	0.01	0.00	0.00	**0.14** *	0.01	0.00
1-OHP	beta	0.00	0.01	0.01	−0.01	0.01	0.05	0.01	0.01	0.16	−0.01	0.01	0.00	0.01	0.00	0.00	**0.14** *	0.01	0.00
2-NAP	beta	0.00	0.01	0.01	−0.01	0.01	0.05	0.01	0.01	0.16	−0.01	0.01	0.00	0.01	0.00	0.00	**0.14** *	0.01	0.00
1-PHE	beta	0.00	0.01	0.01	−0.01	0.01	0.05	0.01	0.01	0.16	−0.01	0.01	0.00	0.01	0.00	0.00	**0.14** *	0.01	0.00
2-FLU	beta	0.00	0.01	0.01	−0.01	0.01	0.05	0.01	0.01	0.16	−0.01	0.01	0.00	0.01	0.00	0.00	**0.14** *	0.01	0.00
t,tMA	beta	0.00	0.01	0.01	−0.01	0.01	0.05	0.01	0.01	0.16	−0.01	0.01	0.00	0.01	0.00	0.00	**0.14** *	0.01	0.00
BMA	beta	0.05	0.02	0.04	−0.06	−0.06	0.07	−0.01	−0.08	0.04	0.15	−0.02	−0.07	−0.02	−0.02	−0.05	0.00	−0.05	0.18

Multiple linear regression results adjusted for maternal age, early-pregnancy body mass index, education, income, parity, maternal urine cotinine level, and neonatal sex after natural log transformation for chemical concentrations; *p*, *p*-value; bold and asterisk (*) characters indicate statistically significant positive association ($p < 0.05$). MnBP, mono-N-butyl phthalate; MEP, mono ethyl phthalate; MCPP, mono(3-carboxypropyl) phthalate; MBzP, monobenzyl phthalate; MMP, mono(2-methylpropyl) phthalate; MEOHP, mono(2-ethyl-5-oxohexyl) phthalate; MEHHP, mono(2-ethyl-5-hydroxyhexyl) phthalate; MECPP, mono(2-ethyl-5-carboxypentyl) phthalate; MiBP, mono-isobutyl phthalate; BPA, Bisphenol A; BPF, Bisphenol F; BPS, Bisphenol S; MP, Methylparaben; EP, Ethylparaben; BP, Butylparaben; PP, Propylparaben; TCS, Triclosan; BP-3, Benzophenon-3; 1-OHP, 1-hydroxypyrene; 2-NAP, 2-hydroxynaphthalene; 1-PHE, 1-hydroxyphenanthrene; 2-FLU, 2-hydroxyfluorene; t,t-MA, trans, trans-muconic acid; BMA, benzylmercapturic acid.

4. Discussion

We found that some phthalates and PAHs in maternal urine were significantly associated with ante- and postpartum depression and confirmed the relationship between dietary and lifestyle factors and depression. However, it is difficult to discuss the relationship between EDC exposure and perinatal depression, because few studies have compared them. Therefore, we compared our results with those of previous studies in other population groups, such as children, adults in general, and the elderly.

In the present study, we found that the secondary metabolites of MEHP (MECPP, MEOHP, and MEHHP) in the maternal urine were significantly associated with ante- and postpartum depression, which is supported by several previous studies [9,11,21,24,25]. A Chinese epidemiological study involving 278 pregnant women reported that exposure to a mixture of phthalates, bisphenols, and parabens resulted in a 1.03-fold increase in postpartum depression [11]. Another Chinese study demonstrated an association (OR = 1.490, 95% CI = 1.051–2.112) and a mediating effect (β = 0.1027, 95% CI = 0.0288–0.1971) between MEHP levels in urine samples from the general elderly population and depressive symptoms [21]. Another study found that MECPP was significantly related to depressive symptoms in American adults [24], and concentrations of DEHP metabolites, including MEOHP, MEHHP, and MECPP, were positively associated with an increased risk of depressive symptoms in a Korean elderly population (OR = 1.92, 95% CI = 1.17–3.13) [25]. In toxicological animal studies, female rats exposed to multiple EDCs showed a multigenerational reduction in maternal behaviors such as nursing, grooming, and licking their babies, which is similar to human postpartum depression symptoms [37]. In another animal study, mice exposed to dibutyl phthalate in the peri-gestational period showed impaired maternal behavior, regarded as typical symptoms in maternal postpartum depression [38].

With respect to the link between PAHs and depression, we found that some PAHs (1-OHP, 2-NAP, and 2-FLU) were significantly associated with ante- and postpartum depression, similar to the results of previous studies [23,27,28]. A recent meta-analysis concluded that prenatal exposure to PAHs can be associated with an increased risk of social behavior (OR = 1.60), attention deficits (OR = 2.99), motor skill deficits (OR = 1.91), and other neurodevelopmental problems (OR = 2.10) in children [27]. In addition, exposure to 2-hydroxyfluorene in the general adult population could increase the risk of depression (OR = 1.43). A study in the US that assessed the association between PAH metabolites and the risk of depression using the National Health and Nutrition Examination Survey (NHANES) [23] revealed positive associations between the urinary 1-NAP (OR = 2.78) and 2-NAP level (OR = 3.17) and depressive symptoms in women within the highest quantile of exposure [28].

However, in our study, there was no significant relationship with perinatal depression for bisphenols, parabens, phenols, and VOCs, with the exception of some phthalates and PAHs. A Chinese birth cohort study found that maternal exposure to BPA and BPF during pregnancy was associated with higher postpartum depression scores, suggesting that pregnancy constituted an important window of vulnerability [11]. Another longitudinal study determined the association between exposure to total volatile organic compounds (TVOCs) by air freshener use and maternal postpartum depression symptoms at 6–8 months after delivery (OR = 1.19) [22]. Environmental tobacco smoke, a complex mixture of nicotine, tar, carbon monoxide, carbon dioxide, and PAHs, represents one of the main pollutants influencing maternal depression [4]. A recent meta-analysis found that perinatal exposure to secondhand smoke in non-smoking women significantly increased the risk of maternal depression symptoms at any time during pregnancy or the postpartum period (OR = 1.77) and increased antenatal suicidal ideation (OR = 1.75) [26]. The range of outcomes in these studies can be understood as differences in populations, sample sizes,

mixture effects, time when depression was measured, and research design. While our study measured depression in the first trimester of pregnancy (before the 14 week), a previous study measured depression in the second trimester (14–28 weeks) and focused on twin pregnancies [11]. Differences in the composition of reproductive hormones between these trimesters [2] may also feature here.

To the best of our knowledge, limited studies have reported mixture effects of non-persistent EDC exposure on perinatal depression to date [11]. This implies that the present univariate models may underestimate or overestimate the health effects compared to the more advanced mixture model approach like BKMR. In this study, we evaluated the mixture effect of 24 non-persistent EDCs on antepartum and postpartum depression scores after adjusting covariates. Although no chemicals showed a statistically significant association with the depression score at the significance level of $p < 0.05$ in both periods, a distinct trend difference between two periods was observed. Our result aligns with those of a previous study, which reported weak mixture effects of non-persistent EDCs on anxiety and depression during pregnancy and the postpartum period using BKMR and quantile-based g-computation methodologies [11].

In the present study, the consumption of fish, fermented foods, cup noodles, and popcorn and use of nail polish and perfume, plastic tableware, paint, and pesticides were significantly associated with an increased phthalate urinary concentration in pregnant women. This was consistent with the results of previous studies [12,39–46]. Phthalates are classified into low-molecular-weight types (dimethyl, diethyl, dibutyl, and diisobutyl phthalate) and high-molecular-weight types (di(2-ethylhexyl), diisononyl, and diphenyl phthalate). The former are used as solvents in personal hygiene products, cosmetics, and pharmaceuticals, while the latter are used as plasticizers in PVC products, including medical devices and children's toys [47]. Most environmental phenols are also significantly associated with the consumption of fermented foods; frozen foods; cup noodles; and the use of skin care products, makeup products, sunscreen products, perfumes, and pesticides, as reported in previous studies [12,13,48–52]. Increased PAH levels in urine are significantly associated with the use of detergents, polishes, air fresheners, and paints, as well as the use of personal hygiene products such as skin care, perfume, hand wash, and sunscreen products [53–55]. These are compounds of interest in human biomonitoring because of their potential to bioaccumulate and exert carcinogenic, mutagenic, and teratogenic effects [53]. The most common sources of exposure to PAHs are factory and traffic exhaust derived from gasoline and diesel fuels, residential fossil fuel heating, wood-burning ovens and fireplaces, cigarette smoke, fires, and charcoal-based food smoke [55,56]. The present study confirmed that most exposure to EDCs occurs in everyday life, such as from food commonly consumed by pregnant women, personal hygiene, household products, and automobile exhaust. Therefore, pregnant women who are environmentally vulnerable and sensitive should avoid these products and exposures as much as possible.

This study was subject to some limitations. First, we measured depression levels during the first trimester of pregnancy. However, as pregnancy is a time when reproductive hormones change dramatically depending on the trimester, depression scores from that trimester are not representative for the entire pregnancy period. Secondly, the successful follow-up rate of pregnant women was low at approximately 50%. Third, discrepancies in time point between urine sample collection and food and lifestyle factors were observed. Thirdly, we did not have information on family interactions or social support, such as intimacy with the husband, receiving aid from the mother's family, and relationships with friends, which are known to influence perinatal depression. Fourth, compared to other countries, South Korea exhibits greater homogeneity in factors such as ethnicity, marital status, cohabitation with a spouse, and insurance coverage. This introduces limitations

in generalizing or extrapolating the findings from the cohort of pregnant women in this study to populations of pregnant women in other countries or regions. Additionally, it should be noted that many participants in this study were residents of metropolitan areas with relatively higher levels of education and income, which should be considered when interpreting and comparing the results. Despite these limitations, our study targeted hard-to-reach pregnant women and was able to obtain information on EDC exposure and depressive symptoms from the same study participants, both during pregnancy and postpartum. Additionally, we attempted to measure the effects of a mixture of 24 EDCs that can be obtained in everyday life.

5. Conclusions

We observed an association between exposure to non-persistent chemicals and an increased risk of ante- or postpartum depression and its association with dietary and lifestyle factors. Our findings provide meaningful information about the identification of toxic chemicals potentially linked to perinatal depression. It is imperative that clinical obstetricians, psychologists, public health organizations, and harmful chemical regulatory governance provide practical guidelines and counseling to mitigate exposure to toxic chemicals. Pregnant women and their families should also pay attention to reducing their exposure to multiple EDCs that are commonly absorbed through various pathways to help prevent antenatal and postnatal depression.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/environments12010015/s1, Figure S1: Distribution of antepartum and postpartum depression score.

Author Contributions: Conceptualization, J.H.K.; methodology, J.H.K.; software, N.M.; validation, N.M.; formal analysis, N.M., S.J.H. and J.H.K.; investigation, N.M., S.J.H. and J.H.K.; resources, N.M. and J.H.K.; data curation, N.M., S.J.H. and J.H.K.; writing—original draft preparation, N.M., S.J.H. and J.H.K.; writing—review and editing, N.M., S.J.H. and J.H.K.; visualization, N.M.; supervision, J.H.K.; project administration, J.H.K.; funding acquisition, J.H.K. All authors have read and agreed to the published version of the manuscript.

Funding: This study was supported by the National Research Foundation of Korea (NRF) and funded by the Korean Government (Ministry of Science, ICT) [grant number NRF-2021R1A2C4001788].

Data Availability Statement: Data is available on request due to privacy restrictions. The data used in this study contains sensitive pregnancy-related information about the participants and can only be made available upon reasonable request to the corresponding author.

Conflicts of Interest: The authors declare no conflicts of interest.

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