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RESEARCH ARTICLE

Effects of postnatal exposure to phthalate, bisphenol a, triclosan, parabens, and per- and poly-fluoroalkyl substances on maternal postpartum depression and infant neurodevelopment: a korean mother-infant pair cohort study

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Abstract

Exposure to endocrine-disrupting chemicals (EDCs) can promote infant neurodevelopmental impairment and maternal postpartum depression (PPD). However, the associations between lactation exposure to EDCs, maternal PPD, and infant neurodevelopment are unclear. Hence, we investigated these relationships in infants aged 36–42 months. We recruited 221 Korean mothers and analyzed 29 EDCs. The Edinburgh Postnatal Depression Scale (EPDS) was used to assess maternal PPD. Bayley scales of infant development; the Swanson, Nolan, and Pelham rating scale (SNAP); and the Child Behavior Checklist (CBCL) were used to assess neurodevelopment in infants exposed to the top 30% of EDC over three years. Multiple regression analyses were adjusted for maternal age, pre-pregnancy body mass index, education, income, employment, residence, and infant age and sex. The rates of infants with clinically abnormal diagnoses on neurologic developmental tests (Balyey, SNAP, and CBCL scales) ranged from 7.7 to 38.5% in this study, with the motor and hyperactivity/impulsivity areas scoring the highest among 65 boys and girls. Mono-2-ethylhexyl phthalate (MEHP) and mono-isononyl phthalate (MiNP) levels in breast milk significantly correlated with infant inattention and hyperactivity. Perfluorononanoic acid (PFNA) and perfluorooctyl sulfonate (PFOS) levels correlated significantly with motor development of BSID-III and total CBCL score which mean infant might have lower developmental status. EDC concentrations in breast milk were not associated with maternal PPD. Overall, lactational exposure to EDCs during the postpartum period can exert a negative effect on maternal PPD and infant neurodevelopment.

Keywords Cohort study · Endocrine-disrupting chemical · Lactational exposure · Neurodevelopment · Perfluoroalkyl and polyfluoroalkyl substances · Postpartum depression

Introduction

In addition to nutrients, minerals, and vitamins, breast milk contains immune substances and microbiota that protect infants from infection and inflammation (Australian Breastfeeding Association). Breastfeeding also benefits mothers because it initiates oxytocin production, which promotes the recovery of pre-pregnancy uterus size and prevents postpartum bleeding (Uvnäs Moberg et al. 2020). Owing to these benefits, the World Health Organization recommends breastfeeding exclusively for newborns during the first 6 months of life (WHO). However, recent birth cohort studies in several countries have reported the presence of endocrine-disrupting chemicals (EDCs), such as phthalates, bisphenol A (BPA), parabens, triclosan (TCS), and per- and poly-fluoroalkyl

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substances (PFASs), in breast milk (Arbuckle et al. 2016; Bever et al. 2018; Fromme et al. 2011; Kim et al. 2018; Kim et al. 2020a, b), suggesting that breastfed infants are at risk of exposure to EDCs (Kim et al. 2018; Latini et al. 2009).

PPD is a major depressive episode that occurs during or after pregnancy with an incidence rate of 7–20% among all pregnancies worldwide (Kim et al. 2021a, b; Schiller et al. 2015; Lubotzky-Gete et al. 2021). The occurrence of PPD is affected by various factors, such as reproductive hormones (estrogen and progesterone), lifestyle (smoking and alcohol), and history of depression. Recently, epidemiological studies have reported that EDC or PFAS exposure may increase the risk of PPD (Kim et al. 2021a, b; Jacobson et al. 2021, 2022; Vuong et al. 2020). Because infants develop interpersonal skills via face-to-face interactions with their mothers, maternal depression can have a major impact on early and late childhood development (Murray and Cooper 1997). PPD has also been associated with adverse effects on early cognitive, emotional, and social development (Murray and Cooper 1997). Despite these risks, few studies have focused on the relationship between postnatal exposure to EDCs and PPD.

Earlier epidemiological and laboratory animal studies have reported that exposure to EDCs was associated with hyperactivity and reduced mental and psychomotor development (Braun et al. 2011; Casas et al. 2015; Evans et al. 2014; Chen et al. 2014; Choi et al. 2013; Li et al. 2017; Johansson et al. 2008; Polanska et al. 2014; Lien et al. 2015; Neugebauer et al. 2015; Goudarzi et al. 2016). Several meta-analysis studies have suggested that exposure to BPAs and phthalates affects neurodevelopment and is associated with hyperactivity (Ejaredar et al. 2015; Lee et al. 2018a, b; Rochester et al. 2018; Minatoya and Kishi 2021). Because PFAS do not degrade under normal environmental conditions and accumulate in human and animal tissues, they may affect neuropsychological development and promote the development of attention-deficit/hyperactivity disorder (ADHD) (Forns et al. 2020; Tran and Miyake 2017; Skogheim et al. 2021; Spratlen et al. 2020; Carrizosa et al. 2021; Tsai et al. 2017; Strøm et al. 2014). Although the mechanism by which PFAS may contribute to ADHD is unclear, possible causes include oxidative stress; epigenetics; and brain, thyroid, or endocrine disruption (Minatoya and Kishi 2021; Darras 2008; Matthews et al. 2014).

Many studies have reported an association between EDC exposure (measured in urine or blood) and altered neurological development, but only a few studies showing contradictory results have assessed the effects of exposure through lactation in infant neurodevelopment. For example, lactation exposure to some phthalates has been associated with a developmental delay in 9-month-old infants and delayed mental and psychomotor development in 1–2-year-old infants (Kim et al. 2018; Dong et al. 2019). In contrast, perinatal exposure to perfluorooctyl sulfonate (PFOS) and perfluorooctanoic acid (PFOA) did not affect infant neuropsychological development (Forns et al. 2020).

Recent research indicates that multiple exposures to EDCs, including PFAS and phthalates, can have a synergic effect on maternal health and fetal growth and neurodevelopment (Hamid et al. 2021). Therefore, the current study aimed to describe the effects of simultaneous multiple lactation exposures to EDCs and PPD on the neurodevelopment of 36–42-month-old infants in Korean mother-infant pairs. We analyzed the contents of 29 types of commonly encountered persistent and non-persistent EDCs, including phthalates, BPA, parabens, TCS, and PFAS, in breast milk; only primiparous women's breast milk was used to avoid the effect of fertility. We encouraged the participation of qualified medical staff, such as nurses, doctors, clinical psychologists, and expert analysts, to increase the reliability and validity of the data collection and analysis.

Materials and methods

Study design and population

The Korean Mother–Infant Pair cohort study (2018–2022) is a prospective cohort study evaluating exposure to EDCs in Korean mothers and infants. From 2018–2019, we reported that the occurrence of 31 EDCs in the breast milk and urine of mother-infant pairs was associated with lifestyle changes (Kim et al. 2020a, b, 2021a; Kim et al. 2023). In 2020, we formulated an intervention program to reduce EDC exposure (Kim et al. 2021a, b). From 2021–2022, we conducted neurodevelopmental assessments on infants. We evaluated the concentrations of 29 of the 31 EDCs (10 phthalate metabolites; three types of parabens, BPA, and TCS; and 14 types of PFAS) in breast milk, PPD data collected in the first year of recruitment (2018), and infant neurodevelopment data after 3 years of exposure (2021).

The study population consisted of mothers receiving breastfeeding coaching at breastfeeding clinics located across South Korea. We divided Korea into four regions (Seoul Metropolitan area, Chugcheong, Honam, and Yeongnam) to obtain a stratified sample from each region based on the average fertility rate (2015–2017). To avoid the potential effects of fertility on EDC concentrations in breast milk, we only recruited healthy primiparous women within 4 weeks after parturition. Mothers with inflammation, such as mastitis, or a history of depressive disease were excluded. Finally, 221 postpartum women were recruited in the study. We followed the infants over 36 months for neurodevelopmental assessments. Only infants whose mothers had breast milk EDC concentrations in the top 30% for each substance were selected. A total of 70 mother and infant pairs consented participating in a neuro-developmental assessment. However,

five of the mother-infant pairs could not participate owing to immigration or loss of contact; thus, 65 mother-infant pairs were included in the neuro-developmental assessment.

Data collection

From October 2021 to January 2022, infant neurodevelopment evaluations were performed at clinical facilities in seven Korean cities (Seoul, Seongnam, Suwon, Cheonan, Busan, Daegu, and Gwangju). A qualified nurse explained the purpose and procedures of the study to each mother, who provided written consent as the infant's guardian. The nurse recorded the mother and infant's sociodemographic characteristics (e.g., age, sex, and residential area) and measured the infant's height and weight.

Neurodevelopment was evaluated using the Bayley scales for infant and toddler development third edition (BSID-III) (Lee et al. 2014), Achenbach's Child Behavior Checklist (CBCL) (Oh et al. 1997; Oh and Kim 2009), and the Swanson, Nolan, and Pelham (SNAP) rating scale (Swanson et al. 2001). The BSID-III evaluation was performed by pediatric psychologists or qualified experts with at least three years of clinical experience and a first-class clinical psychology license. The mothers responded to the CBCL and SNAP-IV tests in the form of a self-reported questionnaire. These three tools evaluate neurodevelopmental status and behavior problems in infants independently; BSID-III evaluates cognitive, language, motor, social-emotional, and adaptive behavior, SNAP-IV assesses inattention and hyperactivity, and CBCL-1.5–5 examines internal and external development.

Postpartum depression and neurodevelopmental assessments

To assess and quantify maternal PPD, we used the Edinburgh postnatal depression scale (EPDS) (Cox et al. 1987)—a widely used self-reported 10-item scale. Participants selected one of four responses corresponding most to the emotion experienced within the last 7 days; scores ranged from 0 to 30. Consultation with a clinical expert was recommended for patients with EPDS scores > 9.

The BSID is a validated and widely used neurodevelopmental tool to measure cognitive and psychomotor development in 1–42-month-old infants and toddlers. We used the Korean BSID-III (K-BSID-III) in this study (Lee et al. 2014). The K-BSID-III measures adaptive behavior and cognitive, language, motor, and socio-emotional development. A developmental index of 90 or higher indicates normal development; 70–89 indicates delayed or below-average development; and 69 or lower indicates significantly delayed development. The K-BSID-III was used for scoring according to the official guidelines. Developmental delays were categorized as mild, moderate, or severe.

SNAP-IV is a revision of the 1983 SNAP questionnaire (Swanson et al. 2001) based on the diagnostic criteria of the DSM-IV. It measures attention deficit and hyperactivity/impulsivity and comprises 18 items divided evenly into two sections, with each item measured on a 4-point scale. The score is presented as the average rating per item (ARI); the cutoff score varies according to each section and the sex of the child. Children scoring in the top 5% are considered to have ADHD. The cutoff point for inattention was 1.38 for boys and 1.02 for girls. The cutoff point for hyperactivity and impulsivity was 0.98 for boys and 0.62 for girls.

The CBCL is an extensively validated survey that uses the reports of parents to identify behavioral problems in their children. We used the Korean-CBCL version 1.5–5 (K-CBCL 1.5–5) for infants and children aged 18 months to 5 years, which was translated and standardized by Oh et al. (Oh et al. 1997; Oh and Kim 2009). The K-CBCL 1.5–5 includes 99 items and is evaluated on a 3-point scale from 0 (not true) to 2 (very or often true). The evaluation includes seven subscales, including emotionally reactive, anxious/depressed, somatic complaints, withdrawal, sleep problems, attention problems, and aggressive behavior. It also contains 10 syndrome scales that include internalizing problems (emotionally reactive, anxious/depressed, somatic complaints, and withdrawal), externalizing problems (attention problems and aggressive behavior), and total problems. The results of this assessment are presented as raw T scores normalized according to sex and age, which fell into the normal range (T score < 60) or clinical range (T score ≥ 60). A higher T score indicates that parents reported more behavioral problems.

Analysis of EDCs and PFAS

We analyzed five environmental phenols and 10 phthalate metabolites. The five environmental phenols included BPA, methylparaben (MP), ethyl-paraben (EP), propylparaben (PP), and TCS. The 10 phthalate metabolites included mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP), mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP), mono-n-butyl phthalate (MnBP), mono-benzyl phthalate (MBzP), mono-(carboxyoctyl) phthalate (MCOP), mono-isobutyl phthalate (MiBP), mono-isononyl phthalate (MiNP), mono-2-ethylhexyl phthalate (MEHP), and monoethyl phthalate (MEP). A total of 15 target analytes and mass-labeled internal standards were purchased from Cambridge Isotope Laboratories ($^{13}C_{12}$-BPA, $^{13}C_{12}$-triclosan, $^{13}C_4$-MEHHP, $^{13}C_4$-MEOHP, $^{13}C_4$-MECPP, $^{13}C_4$eMnBP, $^{13}C_4$-MBzP, $^{13}C_4$-MCOP, $^{13}C_2$-MiBP, $^{13}C_2$-MiNP, $^{13}C_2$-MEHP, and $^{13}C_2$-MEP; Andover, MA, USA) and Toronto Research Chemicals (D_4-methylparaben, D_4-ethylparaben, and D_4-propylparaben; North York, ON, Canada). The reagents for the chemical

analysis of the phthalate metabolites were acetonitrile, water, n-hexane, acetic acid, phosphoric acid (HPLC grade ≥ 98.0%), β-glucuronidase/sulfatase from *Helix pomatia* (Sigma-Aldrich, St. Louis, MO, USA) for BPA, TCS, parabens, and β-glucuronidase from *E. coli* K_{12} (Hoffmann-La Roche, Basel, Switzerland). Native and mass-labeled standards were used as internal standards for the measurement of environmental phenols and phthalate metabolites as previously described (Kim et al. 2020a, b; Calafat et al. 2004; Ye et al. 2008). Specifically, 2.0 mL of each sample was placed in a test tube and maintained at − 20 °C until use. Next, 100 µL (200 µL for the phthalate metabolites) of 1 M phosphoric acid buffer solution was added to the sample, which was thawed at room temperature and shaken. We added 2.0 mL of internal standard and enzyme buffer solutions and incubated the sample at 37 °C for 90 min. Next, 10 mL of acetonitrile was added, the sample was shaken for 10 min, and 3.0 g (1.0 g for the phthalate metabolites) of magnesium sulfate, 1.0 g of sodium citrate tribasic dehydrate, and 1.0 g (0.5 g for the phthalate metabolites) of sodium citrate dibasic sesquihydrate were added, after which the sample was shaken for 10 min and centrifuged at 2800 rpm for 20 min. We added 4.0 mL of n-hexane (C18 powder for phthalate metabolites) to the separated 4 mL of upper solution and then stirred and centrifuged the sample for 10 min. Then, 5.0 mL of the separated upper layer solution was concentrated by drying under nitrogen, and 1.0 mL of the water/acetonitrile (50/50, v/v) solution was used to reconstitute the samples (water:acetonitrile = 1:1 v/v). The resulting solution was filtered with a 0.2-µm membrane filter (polytetrafluoroethylene) for use in the analysis. The standard solution was added to the blanks at the same concentration and prepared under the same conditions as the samples.

Liquid chromatography (LC; Agilent 1290 Infinity system; Agilent Technologies, Santa Clara, CA, USA) and tandem mass spectrometry (MS/MS; Agilent 6490 Triple Quadrupole; Agilent Technologies) were performed simultaneously rather than gas chromatography, which requires a larger sample volume (Ye et al. 2008). We used an ACE 5 C18 (2.1 mm × 150 mm, 5.0 µm) HPLC-column (Advanced Chromatography Technologies, Aberdeen, Scotland). Solvent A was water, and solvent B was acetonitrile for the mobile phases. The LC conditions were as follows: flow rate, 0.2 mL/min; column temperature, 30 °C; and injection volume, 5 µL. We applied electrospray ionization and the multiple reaction monitoring mode for MS/MS.

EDC analysis in breast milk samples, including quality control (QC) and quality assurance, was performed as previously described by measuring the blank samples and internal quality controls (Kim et al. 2020a, b). The QC comprised the linearity test, accuracy test, precision test, and estimation of the limit of detection (LOD). Briefly, the calibration curve consisted of five points across the concentration range of pooled breast milk, with $R^2 > 0.99$ for the linearity tests. The accuracy test was performed to evaluate the recovery rate at each of the three concentrations (low, medium, and high) by spiking the pooled breast milk sample with the reference materials. For all analytes, the recovery percentages ranged from 93 to 115%. The precision test included a comparison of the inter- and intra-day samples. The maximum value of the relative standard deviation (RSD) was ≤ 10.0% for both the intra- and inter-day tests of phenols and phthalate metabolites. The LODs for each analyte were as follows: 0.139 mg/L for MEHP, 0.131 mg/L for MEP, 0.188 mg/L for MiBP, 0.043 mg/L for MiNP, 0.282 mg/L for MnBP, 0.082 mg/L for MBz, 0.139 mg/L for MEHHP, 0.154 mg/L for MEOHP, 0.113 mg/L for MECPP, 0.040 mg/L for MCOP, 0.076 mg/L for BPA, 0.035 mg/L for TCS, 0.035 mg/L for EP, 0.101 mg/L for MP, and 0.134 mg/L for PP. A total of 30 samples were analyzed using the same protocol across laboratories to ensure external QC.

Four perfluoroalkyl sulfonates (PFSAs), 10 perfluoroalkyl carboxylic acids (PFCAs), and mass-labeled PFAS standards were purchased from Wellington Laboratories (Guelph, ON, Canada). Ammonium acetate, a solution of 25% ammonium hydroxide, tetrabutylammonium hydrogen sulfate (TBA), and sodium carbonate were purchased from Sigma-Aldrich. The PFAS analysis was performed as previously described by ion-pairing and solid-phase extraction (Kim et al. 2023; Lee et al. 2018a, b) using acetonitrile, water, n-hexane, acetic acid, phosphoric acid, and beta-glucuronidase/sulfatase as reagents. After spiking with internal standards (5 ng), an ion-pairing buffer, including 0.25 M sodium carbonate and 0.5 M TBA solutions, was added to the breast milk samples (~ 3 mL). The samples were extracted with methyl tertiary butyl ether by a mechanical shaker for 30 min, the organic phase was separated from the samples by centrifugation, and the process was repeated twice more. A total of 15 mL of extract was evaporated using a nitrogen evaporator; the dried samples were re-dissolved in 5 mL of methanol and diluted with 45 mL of Milli-Q water. An Oasis WAX 6 cc cartridge 150 mg, 30 µm (cartridge No. 186002493, Waters Corporation, Milford, MA, USA) was used for cleaning with 0.1% ammonium hydroxide in methanol, methanol, and Milli-Q water. Fourteen PFASs were analyzed using a Vanquish UPLC system coupled to a TSQ Quantis mass spectrometer with a Thermo Scientific Accucore RP-MS column (Thermo Fisher Scientific). Blank samples were used to check for background contamination during all experimental procedures, and the trace levels of PFAS detected in the blank samples were subtracted from the measured concentrations in the test samples. One of the calibration curve standards was repeatedly analyzed to verify instrumental stability. The RSD of the concentration standard was within a threshold range of 30%. Native standards were spiked into 10 selected samples to verify the efficiency of the analysis. Except for

perfluoropentanoic acid (PFPeA) (21 ± 8%), perfluorotridecanoic acid (PFTrDA) (54 ± 6%), and perfluorotetradecanoic acid (PFTeDA) (26 ± 5%), the recoveries of the spiked native standard concentrations ranged from 70–130%. The recoveries of the spiked mass-labeled PFASs were 84–118%, except for 13C2-PFHxA (57 ± 14%). The levels of quantitation (LOQs) calculated for PFASs were as follows: 0.017 ng/mL for perfluorobutane sulfonate (PFBS), 0.017 ng/mL for perfluorohexane sulfonate (PFHxS), 0.017 ng/mL for PFOS, 0.033 ng/mL for perfluorodecane sulfonate (PFDS), 0.017 ng/mL for PFPeA, 0.017 ng/mL for perfluorohexanoic acid (PFHxA), 0.017 ng/mL for perfluoroheptanoic acid (PFHpA), 0.007 ng/mL for PFOA, 0.003 ng/mL for perfluorononanoic acid (PFNA), 0.003 ng/mL for perfluorodecanoic acid (PFDA), 0.007 ng/mL for perfluoroundecanoic acid (PFUnDA), 0.007 ng/mL for perfluorododecanoic acid (PFDoDA), 0.007 ng/mL for PFTrDA, and 0.007 ng/mL for PFTeDA.

Statistical analysis

For chemicals that were detected in ≥ 70% of the population, values lower than the LOD were substituted for the LOD/square root 2 (Hornung and Reed 1990). For chemicals found in < 70% of the population, only the detected values were used for statistical analysis to minimize the influence of non-detects (Kim et al. 2018). We performed a log transformation of the chemical concentrations due to a skewed distribution in the breast milk data. The characteristics of the participants are presented as descriptive statistics, including the frequency, percentage, mean, and standard deviation (SD). Concentrations of the target analytes are expressed as a geometric mean (SD) and median (min–max). Spearman's correlation test was used to identify relationships between the chemical concentrations in breast milk and infant neurodevelopment. EPDS scores were used to divide the participants into a PPD and non-PPD group based on a cutoff score of 9; the difference between the two groups was verified using a *t*-test and Mann–Whitney U test. We performed logistic regressions to confirm the associations between EDC concentrations and maternal PPD. Logistic regression yielded chemicals that were detected in > 70% of the participants (MnBP, MEHP, MiNP, and EP) and PFAS (PFHxS, PFOS, PFHxA, PFOA, PFNA, and PFDA). Multiple regression analyses were used to assess the influence of the EDCs in breast milk on infant neurodevelopment (based on K-BSID-III, K-CBCL 1.5–5, and SNAP-IV). MEHP, MiNP, PFNA, and PFOS, which had significant correlations with neurodevelopmental assessment scores, were included in the regression model (Table 1). The following covariates were adjusted based on previous studies (Kim et al. 2018; Kim et al. 2020a, b): maternal age (years), pre-pregnancy BMI (kg/m^2), education (< college/ ≥ college), household income (≤ $5,000/month; > $5,000/month), employment status (no/yes), residence (metropolitan/non-metropolitan), infant age (months), and infant sex (male/female). SPSS version 24.0 (IBM SPSS, Armonk, NY, USA) and R software (The R Foundation, Vienna, Austria) were used for all statistical analyses and graphics.

Results

Characteristics of the study population

Table 1 presents the general characteristics of the study population. The average age of the mothers was 31.3 years (SD = 3, range: 19–42 years). The mean maternal pre-pregnancy BMI (kg/m^2) was 21.31 (SD = 3.1, range: 16.0–33.4). The mean delivery period was at 39.2 weeks, which differed according to the child's sex ($p = 0.048$). A total of 197 mothers (89.1%) graduated college, and 124 mothers (56.6%) had a monthly household income under $5,000. Maternal employment status varied significantly according to the child's sex, with employment reaching 82.2% for mothers of boys and 69.3% for mothers of girls ($p = 0.035$). Moreover, 141 mothers (63.8%) lived in a non-metropolitan area. The mean PPD score of 221 mothers was 9.1 (SD = 4.3). There were 126 patients (57%) in the non-PPD group and 95 (43%) in the PPD group. The average age of infants was 40.5 months (SD = 1.5), with an average height of 98.7 cm (SD = 4.3) and an average weight of 15.6 kg (SD = 2.1).

Concentrations of EDCs in breast milk

Table 2 presents the chemical profiles of 21 EDCs (6 phthalate metabolites, 3 parabens, BPA, TCS, and 10 PFAS). MCOP, MECP, MEOHP, MEHHP, PFBS, PFDS, PFDoDA, and PFTeDA were excluded because they were detected in less than 1% of the specimens. EP was the most frequently detected chemical (88.7%), followed by MEHP (83.3%), MnBP (72.9%), MiNP (71.9%), and MiBP (69.2%); the median concentration of each chemical was 0.62, 1.72, 0.89, 0.08, and 0.49 μg/L, respectively. PFOS, PFOA, and PFDA were detected in 100% of the specimens, followed by PFHxS (87.4%), PFNA (87.0%), and PFHxA (72.9%); the median concentration of each chemical was 0.05, 0.1, 0.007, 0.031, 0.007, and 0.033 ng/mL, respectively.

Assessment of infant neurodevelopment and maternal PPD

Table 3 presents the results of the neurodevelopmental assessments of the infants. The motor and hyperactivity/impulsivity areas were the most prominent in 23 and 25 infants. In the motor area, the scores of the boys were

Table 1 Characteristics of the study population

Variables	Categories	Total ($N=221$)		Boys ($n=107$)		Girls ($n=114$)		x^2 / t (p value)
		N (%)/Mean (SD)	Median (Min–Max)	*N* (%)/Mean (SD)	Median (Min–Max)	*N* (%)/Mean (SD)	Median (Min–Max)	
Maternal characteristics ($N=221$)								
Age (years)		31.3 (3.8)	31 (19–42)	31.0 (14.3)	31.0 (23–42)	31.5 (3.9)	31.0 (19–42)	-0.93 (.352)
Pre-pregnancy BMI (kg/m^2)		21.31 (3.1)	20.6 (16.0–33.4)	21.2 (3.2)	20.7 (16.6–16.4)	21.4 (3.0)	20.6 (17.4–16.0)	-0.29 (.775)
Gestational weight gain (kg)		5.7 (5.4)	5.0 (-10.0–28.0)	5.5 (4.9)	5.0 (-5–23)	6.0 (5.8)	5.8 (-10.0–28.0)	-0.69 (.490)
Postpartum depression (PPD)		9.1 (4.3)						
Delivery weeks		39.2 (1.3)	39.4 (34.0–41.6)	39.0 (1.4)	39.4 (34.0–41.4)	39.4 (1.2)	39.4 (35.6–41.6)	-1.99 (.048)
Delivery method	NSVD	105 (47.5)		46 (43.0)		59 (51.8)		1.70 (.192)
	C/S	116 (52.5)		61 (57.0)		55 (48.2)		
Education	< college	24 (10.9)		9 (8.4)		15 (13.2)		1.29 (.257)
	≥ college	197 (89.1)		98 (91.6)		99 (86.8)		
Household income ($/month)	≤ 5,000	124 (56.6)		59 (54.2)		67 (57.9)		0.31 (.858)
	> 5,000	95 (43.4)		48 (44.8)		47 (41.2)		
Employment status	No	53 (24.1)		19 (16.8)		35 (30.7)		6.72 (.035)
	Yes	167 (75.9)		88 (82.2)		79 (69.3)		
Residence area	Metropolitan	80 (36.2)		35 (32.7)		45 (39.5)		1.09 (.296)
	Non-metropolitan	141 (63.8)		72 (67.3)		69 (60.5)		
Infant characteristics (N = 221)								
Age (months)		40.5 (1.5)	41.0 (38–43)	40.3 (1.2)	40.0 (38.0–43.0)	40.6 (1.6)	41.0 (38.0–43.0)	-0.73 (.470)
Birth weight (kg)		3.2 (0.4)	3.2 (2.2–4.3)	3.3 (0.4)	3.3 (2.2–4.1)	3.2 (0.4)	3.2 (2.2–4.3)	1.20 (.230)
Birth height (cm)		50.4 (2.3)	50.0 (40.0–57.0)	50.6 (2.2)	51.0 (44.0–56.0)	50.2 (2.3)	50.0 (17.0–40.0)	1.33 (.187)
Height (cm)		98.7 (4.3)	98.6 (90.3–110.7)	99.1 (3.8)	99.1 (92.4–107.0)	98.3 (4.7)	97.8 (90.3–110.7)	0.77 (.446)
Weight (kg)		15.6 (2.1)	15.0 (12.0–22.0)	15.8 (1.9)	15.5 (13.1–20.5)	15.5 (2.3)	15.0 (12.0–22.0)	0.67 (.503)

NSVD, normal spontaneous vaginal delivery; C/S, cesarean section; SD, standard deviation

significantly higher than those of the girls ($t=-2.13$, $p=0.037$). The mean PPD score of 221 mothers was 9.1; the score of the non-PPD group (4.0) was significantly lower than that of the PPD group (12.8; $t=-20.94$, $p<0.001$).

Association between EDC concentrations in breast milk and maternal PPD

Table 4 lists the associations between the EDC concentrations in breast milk and maternal PPD. The multiple logistic regression results showed that the EDC concentrations were not associated with maternal PPD ($p=0.053$–0.977). However, comparing the groups with EPDS scores less than and greater than 9 at a significance level of 0.1 showed that increasing MEHP (odds ratio [OR] = 1.13, $p=0.053$) and EP concentrations (OR = 1.17, $p=0.091$) were associated with PPD (Table 5).

Effect of lactation exposure to EDCs on infant neurodevelopment

Table 5 shows coefficients of correlation between chemicals and neuro-developmental assessment. Table 6 presents the associations between the EDC concentrations found in breast milk and infant neurodevelopment. MEHP exposure was positively associated with inattention which means poor attention ability of infant, as assessed by SNAP-IV ($\beta=0.317$, $p=0.008$). MiNP exposure was positively associated with infant hyperactivity and impulsivity ($\beta=0.327$, $p=0.004$) which means infant has lower developmental status of hyperactivity and impulsivity. PFNA exposure was positively associated which means better motor development, as assessed by the BSID-III ($\beta=0.311$, $p=0.012$). PFOS exposure was negatively associated with the total T score determined by the CBCL 1.5–5 ($\beta=-0.283$, $p=0.022$) which means infant has lower developmental score.

Table 2 Concentrations of chemicals in breast milk

Analyte (ng/mL)	DF (% > LOD)	LOD /LOQ	GM	SD	Percentile				
					5	25	50	75	95
EDCs (ng/mL) ($N=221$)									
MEP	102 (46.2)	0.13	0.17	2.37	< LOD	< LOD	< LOD	0.27	1.96
MnBP	161 (72.9)	0.28	0.83	3.16	< LOD	< LOD	0.89	1.86	8.46
MiBP	153 (69.2)	0.19	0.47	3.19	< LOD	< LOD	0.49	0.93	7.44
MBzP	12 (5.4)	0.08	0.06	1.37	< LOD	< LOD	< LOD	< LOD	0.10
MEHP	184 (83.3)	0.14	1.44	6.00	< LOD	0.35	1.72	4.88	24.38
MiNP	158 (71.9)	0.04	0.10	2.84	< LOD	< LOD	0.08	0.22	0.61
BPA	107 (48.4)	0.08	0.12	2.91	< LOD	< LOD	< LOD	0.23	0.88
TCS	57 (25.8)	0.04	0.04	2.62	< LOD	< LOD	< LOD	0.04	0.29
MP	130 (58.8)	0.10	0.33	5.61	< LOD	< LOD	0.18	1.12	10.34
EP	196(88.7)	0.04	0.46	5.23	< LOD	0.14	0.62	1.62	4.60
PP	93(42.1)	0.13	0.21	3.30	< LOD	< LOD	< LOD	0.39	2.17
PFAS (ng/mL) ($N=207$)									
PFHxS	181 (87.4)	0.017	0.055	0.089	0.012	0.023	0.031	0.052	0.159
PFOS	207 (100)	0.017	0.058	0.039	0.026	0.039	0.050	0.069	0.108
PFPeA	8 (3.9)	0.017	0.013	0.005	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ
PFHxA	151 (72.9)	0.017	0.048	0.046	0.012	0.012	0.033	0.064	0.145
PFHpA	15 (7.25)	0.017	0.012	0.002	< LOQ	< LOQ	< LOQ	< LOQ	0.018
PFOA	207 (100)	0.007	0.114	0.102	0.047	0.070	0.100	0.136	0.217
PFNA	180 (87.0)	0.003	0.009	0.013	0.002	0.005	0.007	0.011	0.020
PFDA	207 (100.0)	0.003	0.007	0.006	0.004	0.005	0.007	0.009	0.011
PFUnDA	89 (43.0)	0.007	0.008	0.008	< LOQ	< LOQ	< LOQ	0.009	0.017
PFTrDA	68 (32.9)	0.007	0.007	0.004	< LOQ	< LOQ	< LOQ	0.007	0.013

LOD, level of detection; LOQ, Level of quantitation; GM, geometric mean; SD, Standard deviation. MEP, mono ethyl phthalate; MnBP, mono-N-butyl phthalate; MiBP, mono-isobutyl phthalate; MBzP, monobenzyl phthalate; MiNP, mono-isononyl phthalate; MEHP, mono (2-ethylhexyl) phthalate; BPA, bisphenol A; TCS, triclosan; MP, methyl paraben; EP, ethyl paraben; PP, propyl paraben; PFBS. perfluorobutane sulfonate; PFHxS, perfluorohexane sulfonate; PFOS, perfluorooctane sulfonic acid; PFDS, perfluorodecane sulfonate; PFPeA, perfluoropentanoic acid; PFHxA, perfluorohexanoic acid; PFHpA, perfluoroheptanoic acid; PFOA, perfluorooctanoic acid; PFNA, perfluorononanoic acid; PFDA, perfluorodecanoic acid; PFUnDA, perfluoroundecanoic acid; PFDoDA, perfluorododecanoic acid; PFTrDA, perfluorotridecanoic acid; PFTeDA, perfluorotetradecanoic acid

Maternal PPD and infant neurodevelopment

The PPD scores showed a significant negative association with socio-emotional and adaptive behavior, as assessed by the BSID-III, and a positive association with inattention, hyperactivity, and impulsivity, as assessed by SNAP-IV and an external T score determined using the CBCL 1.5–5 ($\beta = -0.272$ to 0.396, $p = 0.001$–0.039).

Discussion

This epidemiological cohort study confirmed an association between the EDC levels in breast milk and maternal PPD and revealed the effects of postpartum lactation exposure to EDCs on infant neurodevelopment.

We reported a similar level of contamination in breast milk to that in previous studies (Kim et al. 2020a, b; Kim et al. 2023). Briefly, the detection rates and concentrations of phthalate metabolites, BPA, parabens, and TCS in the breast milk of South Korean mothers were lower than those in previous reports (Kim et al. 2020a, b). In contrast, the concentrations of PFAS were higher than those found in other countries, and the concentration of PFOA in the breast milk increased by approximately three-fold (278%) from before 2007 to 2018 (Lee et al. 2018a, b; Kim et al. 2023, 2011; Kang et al. 2016). The reason for this variation in EDC concentrations may be related to the strict South Korean regulations on phthalate, BPA, TCS, and some parabens, while a relaxed policy is applied for persistent organic pollutants, such as PFAS (Kim et al. 2023; Korea 2015). In this study, the clinically abnormal rate in

Table 3 Infant neurodevelopment and postpartum depression assessments

Variables		Total ($N=65$)		Number of clinical range (%)	Boys ($N=27$)		Number of clinical range (%)	Girls ($N=38$)		Number of clinical range (%)	t (p value)
		N (%)/Mean (SD)	Median (Min–Max)		N (%)/Mean (SD)	Median (Min–Max)		N (%)/Mean (SD)	Median (Min–Max)		
BSID-III	Cognitive	99.5 (12.0)	100.0 (70.0–125.0)	9 (13.8)	97.6 (10.3)	100.0 (70.0–120.0)	4 (14.8)	100.9 (13.0)	100.0 (70.0–125.0)	5 (13.2)	-1.10 (.274)
	Language	100.8 (11.9)	103.0 (61.0–121.0)	6 (9.2)	100.3 (10.3)	100.0 (61.0–115.0)	1 (3.7)	101.1 (13.0)	103.0 (64.0–121.0)	5 (13.2)	-0.27 (.792)
	Motor	95.8 (15.1)	94.0 (46.0–129.0)	23 (35.4)	91.2 (14.8)	91.0 (46.0–124.0)	12 (44.4)	99.1 (14.6)	97.0 (67.0–129.0)	11 (28.9)	-2.13 (.037)
	Social-emotional	114.7 (18.8)	115.0 (75.0–145.0)	6 (9.2)	112.6 (19.5)	110.0 (80.0–145.0)	2 (7.4)	116.2 (18.5)	115.0 (75.0–145.0)	4 (10.5)	-0.76 (.453)
	Adaptive behavior	98.7 (9.2)	98.0 (65.0–121.0)	5 (77)	99.5 (9.8)	101.0 (73.0–121.0)	3 (11.1)	98.0 (8.8)	98.0 (65.0–120.0)	2 (5.4)	0.64 (.526)
SNAP- IV	Inattention	0.69 (0.43)	0.67 (0.0–1.89)	10 (15.4)	0.63 (0.43)	0.67 (0.0–1.89)	1 (3.7)	0.72 (0.43)	0.67 (0.0–1.67)	9 (23.7)	0.82 (.417)
	Hyperactivity/ Impulsivity	0.64 (0.46)	0.56 (0.0–1.78)	25 (38.5)	0.71 (0.49)	0.56 (0.0–1.78)	7 (25.9)	0.59 (0.44)	0.56 (0.0–1.67)	18 (47.4)	-1.02 (.310)
CBCL 1.5–5	Internal	50.1 (7.8)	50.0 (31.0–69.0)	8 (12.3)	50.4 (7.4)	50.0 (36.0–69.0)	3 (11.5)	50.0 (8.2)	51.0 (31.0–63.0)	5 (13.2)	0.20 (.843)
	External	50.8 (8.2)	51.0 (31.0–73.0)	8 (12.3)	50.3 (10.2)	49.5 (31.0–73.0)	4 (15.4)	51.1 (6.50)	51.0 (31.0–63.0)	4 (10.5)	-0.37 (0.714)
	Total	51.1 (9.6)	53.0 (7.0–75.0)	7 (10.8)	49.5 (12.7)	52.5 (7.0–75.0)	2 (7.7)	52.3 (6.5)	53.5 (38.0–62.0)	5 (13.2)	-1.16 (.252)
Variables		Total (N = 221)			Non-PPD Group (N = 126)			PPD Group (N = 95)			t (p value)
		Mean (SD)			Mean (SD)			Mean (SD)			
EPDS		9.1 (4.3)			4.0 (2.7)			12.8 (3.4)			-20.94 (< 0.001)

Clinical range = Number of children with abnormal clinical range of neurodevelopment

Bayley Scales of Infant Development, BSID; Swanson, Nolan and Pelham, SNAP; Child Behavior Checklist, CBCL

Table 4 Association between chemicals and maternal postpartum depression

	Crude OR	95% CI	*p*	Adjusted OR	95% CI	*p*
MnBP	0.95	0.61–1.37	0.541	0.94	0.64–1.38	0.745
MEHP	1.12	1.04–1.14	0.050	1.13	1.03–1.12	0.053*
MiNP	0.22	0.44–1.38	0.330	0.23	0.04–1.35	0.394
EP	1.18	0.99–1.40	0.089	1.17	0.99–1.32	0.091*
PFHxS	0.97	0.44–2.34	0.986	0.98	0.43- 2.40	0.992
PFOS	3.39	0.07– 6.19	0.407	3.40	0.06- 6.16	0.404
PFHxA	0.72	0.02– 5.73	0.915	0.79	0.01- 5.99	0.977
PFOA	1.85	0.12- 2.83	0.367	1.84	0.12- 2.82	0.368
PFNA	0.38	0.01- 6.17	0.115	0.39	0.01- 6.67	0.114
PFDA	0.19	0.10- 7.98	0.561	0.18	0.11- 8.01	0.560

Crude OR means an OR of unadjusted model. Logistic regression models are adjusted for age, pre-pregnancy body mass index, education, income, employment, residence, and infant age and gender

Reference values: EPDS cutoff score < 9. OR, odds ratio; CI, confidence interval

MnBP, mono-N-butyl phthalate; MEHP, mono (2-ethylhexyl) phthalate; MiNP, mono-isononyl phthalate; EP, ethyl paraben; PFHxS, perfluorohexane sulfonate;PFOS, perfluorooctane sulfonic acid; PFHxA, perfluorohexanoic acid; PFOA, perfluorooctanoic acid; PFNA, perfluorononanoic acid; PFDA, perfluorodecanoic acid

*$p < 0.1$

the neurodevelopmental assessment was 7.7–38.5%, with the motor and hyperactivity/impulsivity areas showing the highest rates of abnormality. This is a slightly higher rate than previously reported (6–10%) (Kim et al. 2018; Dong et al. 2019; Bornehag et al. 2018), which may be explained by differences in the biological sample type (matrix), chemical type, exposure period, neurodevelopmental assessment tools, and child age. Because the infants participating in the neurodevelopmental assessment were exposed to the top 30% of EDCs and PFASs in breast milk, this can explain the higher rate of clinically abnormal neurodevelopment when compared to those found in previous studies.

In this study, high levels of MEHP and MiNP in breast milk were associated with an increase in infant inattention and hyperactivity, which is consistent with the findings of previous prenatal and postpartum studies (Kim et al. 2018; Polanska et al. 2014; Dong et al. 2019; Braun et al. 2017; Jankowska et al. 2019; Miodovnik et al. 2014). A Chinese epidemiological study reported that lactation exposure to DEHP metabolites was associated with delayed gross motor development in girls aged 1–9 months (Dong et al. 2019); the presence of low-molecular-weight phthalates (LMWPs), including MMP, MEP, MiBP, and MnBP, was associated with delays in infant development. A previous Korean study reported that high MEHP levels in breast milk were associated with a decreased mental development index (Kim et al. 2018). This trend is more evident in analyses of urine. A study conducted in Poland, using the BSID-III assessment, found a negative association between the presence of high-molecular-weight phthalates, including MEHP and MiNP, and child motor development (Polanska et al. 2014). A German study reported that the metabolites of DnBP and DMP can cause a decrease in IQ, particularly in mathematical skills, in early-school-aged children (Jankowska et al. 2019). However, other studies have reported no association between phthalate exposure and neurodevelopment (Gascon et al. 2015). This variation in study findings may be explained by differences in the age of infants exposed to phthalates, the type of assessment tool, and the characteristics of the participants.

Several hypotheses exist regarding the possible mechanisms by which phthalates adversely affect neurodevelopment in infants and young children. First, exposure to some phthalates can alter thyroid function, reducing the levels of circulating thyroid hormones and adversely impacting the child's brain development (Miodovnik et al. 2014). Second, exposure to DEHP can alter lipid metabolism and profiles in fetal brains, leading to impaired neurodevelopment (Xu et al. 2007). Third, exposure to phthalates can affect the structural and functional plasticity of the hippocampus (Holahan and Smith 2015), with widespread hippocampal disruption potentially leading to impaired development. Finally, long-term exposure to phthalates can decrease neuron and synapse numbers in the medial prefrontal cortex (Kougias et al. 2018). Some previous studies reported sex-specific differences in neurodevelopmental impairment due to prenatal and postpartum exposure to phthalates, but this could not be tested in the current study due to the small sample size. Two studies from the USA reported that, unlike its effect in boys, DEHP metabolite exposure was negatively associated with mental development in girls (Téllez-Rojo et al. 2013; Doherty et al. 2017). Boys exposed to LMWPs also showed an increased psychomotor developmental index,

Table 5 Correlation between chemicals and both postpartum depression and neurodevelopment

		BSID-III					SNAP-IV		CBCL 1.5–5			
		Cognitive	Language	Motor	Social- emotional	Adaptive behavior	Inattention	Hyperactivity	Total	Internal	External	
phthalates	MEHP	–0.073	0.185	0.104	0.153	0.098	0.280*	0.286*	0.126	0.200	0.118	0.4–0.6
	MiBP	0.185	0.021	0.127	0.099	–0.080	0.139	0.095	0.001	0.042	0.005	0.2–0.4
	MiNP	0.019	0.029	0.098	0.259*	0.294*	0.275*	0.451**	0.137	0.234	0.125	0–0.2
	MnBP	0.223	0.113	0.186	0.078	0.040	0.098	0.125	–0.080	0.019	–0.051	0
parabens	EP	–0.138	–0.133	0.027	0.012	0.267*	0.080	0.124	–0.042	–0.063	–0.013	-0.2–0
PFAS	PFHxS	–0.086	–0.064	0.093	–0.031	0.092	–0.236	–0.238	–0.138	–0.020	–0.210	-0.2–0.4
	PFOS	0.024	0.046	0.279*	–0.160	–0.198	–0.148	–0.342**	–0.274*	–0.209	–0.257*	-0.4–0.6
	PFHxA	–0.135	0.167	0.018	–0.036	0.059	0.225	0.196	0.282*	0.148	0.249	
	PFOA	0.040	0.041	0.329**	–0.174	–0.135	–0.001	–0.066	–0.104	–0.164	–0.005	
	PFNA	0.078	0.062	0.314*	–0.207	–0.124	–0.027	–0.131	–0.052	–0.141	0.033	
	PFDA	0.113	0.221	0.342**	–0.155	–0.152	0.183	–0.101	–0.088	–0.053	0.004	
PPD		0.148	0.132	0.143	0.304*	0.328**	0.287*	0.457**	0.245	0.248*	0.246	

Please note that the values corresponding to the different colors are provided in a key to the right of table

* $p < 0.05$, ** $p < 0.01$

MEP, mono ethyl phthalate; MnBP, mono-N-butyl phthalate; MiBP, mono-isobutyl phthalate; MBzP, monobenzyl phthalate; MiNP, mono-isononyl phthalate; MEHP, mono (2-ethylhexyl) phthalate; BPA, bisphenol A; TCS, triclosan; MP, methyl paraben; EP, ethyl paraben; PP, propyl paraben; PFBS. perfluorobutane sulfonate; PFHxS, perfluorohexane sulfonate; PFOS, perfluorooctane sulfonic acid; PFDS, perfluorodecane sulfonate; PFPeA, perfluoropentanoic acid; PFHxA, perfluorohexanoic acid; PFHpA, perfluoroheptanoic acid; PFOA, perfluorooctanoic acid; PFNA, perfluorononanoic acid; PFDA, perfluorodecanoic acid; PFUnDA, perfluoroundecanoic acid; PFDoDA, perfluorododecanoic acid; PFTrDA, perfluorotridecanoic acid; PFTeDA, perfluorotetradecanoic acid., PPD, postpartum depression

Table 6 Association between chemicals and neurodevelopment

	BSID-III						SNAP-IV			CBCL 1.5–5				
	Motor		Social-emotional		Adaptive		Inattention		Hyperactivity		Total		External	
	β (95%CI)	*p*	β (95%CI)	*p*	β (95%CI)	*p*	β (95%CI)	*p*	β (95%CI)	*p*	β (95%CI)	*p*	β (95%CI)	*p*
MEHP	0.105 (-1.798, 4.431)	0.401	-0.101 (-5.251, 2.089)	0.392	-0.056 (-2.271, 1.426)	0.649	0.317 (0.031, 0.195)	0.008 ***	-0.253 (-0.181, -0.011)	0.027 **	-0.056 (-2.451, 1.576)	0.665	-0.088 (-25.85, 1.103)	0.488
MiNP	0.048 (-18.43, 26.942)	0.709	-0.169 (-45.158, 7.462)	0.157	-0.233 (-25.2, -0.002)	0.050	-0.130 (-0.972, 0.311)	0.307	0.327 (0.284, 1.429)	0.004 ***	-0.207 (-16.201, 13.165)	0.837	-0.046 (-14.594, 10.159)	0.721
PFNA	0.311 (4.208, 33.246)	0.012 **	0.192 (-4.446, 33.672)	0.130	0.205 (-2.019, 17.161)	0.119	-0.018 (-0.497, 0.438)	0.899	0.206 (-0.077, 0.835)	0.101	0.120 (-6.233, 15.582)	0.394	-0.011 (-9.577, 8.824)	0.935
PFOS	0.253 (-0.190, 23.277)	0.054	0.078 (-9.935, 18.911)	0.535	0.176 (-2.214, 11.974)	0.173	0.054 (-0.279, 0.416)	0.695	0.254 (0.020, 0.688)	0.038 **	-0.283 (-15.457, -1.261)	0.022**	0.180 (-2.187,11.244)	0.182

Regression models are adjusted for age, pre-pregnancy body mass index, education, income, employment, residence infant age and gender

MiNP, mono-isononyl phthalate; MEHP, mono (2-ethylhexyl) phthalate; PFOS, perfluorooctane sulfonic acid; PFNA, perfluorononanoic acid; PPD, postpartum depression; Bayley Scales of Infants Development, BSID; Swanson, Nolan and Pelham, SNAP; Child Behavior Checklist, CBCL

* $p < 0.1$, ** $p < 0.05$, *** $p < 0.01$

as assessed by the BSID-II test, while girls presented the opposite trend (Qian et al. 2019). Therefore, exposure to phthalates during periods of vulnerability, such as pregnancy or early childhood, will likely affect the neurological development of infants and young children.

Our results showed that PFOS exposure had significant association with the total T score, as determined by the CBCL 1.5–5; PFNA exposure was significantly associated with motor development, as assessed by the BSID-III, suggesting that PFOS and PFNA may improve neurological development, though the potential mechanism is unclear. This unexpected result contrasts with that of most previous studies showing that PFAS had a negative effect on the neurological development of infants and children (Vuong et al. 2020; Spratlen et al. 2020; Carrizosa et al. 2021; Harris et al. 2018). A cohort study analyzing perfluorinated compounds in the cord blood of 302 participants reported that PFNA had a negative effect on psychomotor development and verbal IQ (Spratlen et al. 2020). A longitudinal cohort study in Spain reported a marginally positive association between PFOS and PFNA exposure and cognitive development in children aged 4–5 years (Carrizosa et al. 2021). Additionally, several studies have reported no association between PFAS exposure and neurodevelopment (Forns et al. 2020, 2015; Strøm et al. 2014; Oulhote et al. 2016). A Norwegian cohort study of 843 infants aged 6 to 24 months also reported that lactation exposure to PFOS and PFOA did not increase the risk of impaired neurological development (Forns et al. 2015). This could be because PFAS may activate the human peroxisome proliferator-activated receptor gamma, thus producing a neuroprotective and anti-inflammatory effect on the central nervous system, especially in those with unmedicated diabetes (Power et al. 2013; Stein et al. 2013; Vanden Heuvel et al. 2006; Kapadia et al. 2008). To definitively elucidate the role of PFAS exposure through breast milk on neurodevelopment, future studies should evaluate larger infant cohorts exposed to various levels of PFAS. Another possible explanation is that a non-linear dose–response can occur at low doses. According to this concept, substances that are toxic at high doses can sometimes be beneficial at low doses (Calabrese and Mattson 2017). Recently, some studies have reported nonlinear dose responses between lead and IQ, between PM2.5 and mortality, and between benzene and leukemia (Lanpher 2017; Lee 2018).

In this study, BPA, TCS, MP, and PP were not included in the final regression model because their detection rates in breast milk were less than 70%. Previous studies reported that prenatal or postpartum exposure to BPAs was associated with problems with adaptive behavior, ADHD-related symptoms, and impairments to social, language, and psychomotor development (Casas et al. 2015; Pan et al. 2019; Lim et al. 2017). However, studies of the association between TCS concentrations and child neurodevelopment also showed

inconsistent results (Guo et al. 2020; Etzel et al. 2018; Jiang et al. 2019) (see also 80). Few studies have been conducted on the relationship between paraben exposure and human neurodevelopment. One epidemiological study reported that prenatal exposure to parabens was associated with cognitive impairment in 2-year-old infants (Jiang et al. 2019). In an animal model, butylparaben exposure promoted anxiety-like behavior and learning impairment, which may be related to the dysregulation of the cytokine network—an essential immune network for normal neurodevelopment and encephalopathy (Yesumanipreethi et al. 2021).

Finally, we did not find an association between the EDC concentrations in breast milk and the occurrence of maternal PPD. However, at a significance level of 0.1, exposures to MEHP and EP were associated with PPD, suggesting that high-dose EDC exposure may promote PPD. An American study reported a significant association between phthalate exposure and PPD, especially for DnOPs and DiNPs, which was associated with a reduction in progesterone levels during pregnancy; the urinary DnOP concentration was 1.48-fold higher in patients of the PPD group than that in patients of the non-PPD group (Jacobson et al. 2022). Vuong et al. (Vuong et al. 2020) also reported an association between exposure to polybrominated diphenyl ethers and depression in pregnant women. Although the mechanism by which EDCs cause PPD is unclear, previous studies have reported estrogenic effects on the hypothalamus and amygdala, changes in neurotransmitter-regulating brain organs, and DNA and ultraviolet B-induced damage (Yesumanipreethi et al. 2021; Darbre and Harvey 2008; Walf and Frye 2006; Xu et al. 2012, 2015). And, we previously reported the main sources of phthalate exposure in Korean mothers. Frequent consumption of fish, cup noodles, plastic-disposable food containers, air fresheners, make-up products, and new furniture were significant predictors of higher phthalate concentrations (Kim et al. 2020a, b). In this study, we found that maternal PPD negatively affected the socio-emotional, adaptive, inattention, hyperactivity, and external behavior of infants, which is consistent with the findings of most previous studies (Lubotzky-Gete et al. 2021; Caparros-Gonzalez et al. 2017; Duan et al. 2019). A recent study also showed that PPD had a strong association with delayed language, social, interpersonal, fine motor, and adaptive skill development (Lubotzky-Gete et al. 2021). A recent review of the relationship between perinatal depression and infant neurodevelopment reported structural changes in the amygdala and prefrontal cortex, decreased hippocampal growth, and decreased cortical thickness in infants and toddlers of mothers with PPD (Duan et al. 2019). Consistent with these results, EDC exposure is associated with maternal PPD. Nevertheless, we observed a strong association between maternal PPD and the neurodevelopment of infants, including cognitive function and social behavior. However, further research is needed to elucidate the separate, interactive, additive, and antagonistic roles of the various extrinsic and intrinsic factors affecting infant neurodevelopment. Future studies of maternal PPD should consider the simultaneous analysis of samples from different sources to elucidate the discrepancy in EDC concentrations between sources and identify EDCs that are most likely to be transferred to infants.

This study had some limitations. First, although the total number of participants was 221, only 65 infants underwent neurodevelopmental assessment. Therefore, caution should be taken in the generalization of our results. Second, emotional variables, such as family and parenting style, have an important influence on the occurrence of PPD (Murray and Cooper 1997); however, we only considered the influence of demographic variables. Third, only one breast milk sample was obtained within 4 weeks of childbirth, which would not be representative of extended lactation exposure. Nevertheless, this is the first study to confirm the adverse effect of PFAS, phthalate, and paraben in breast milk on maternal PPD and infant neurodevelopment. We measured EDC concentrations in the breast milk of 221 primiparous mothers while controlling for confounding factors (race, parity, and direct breast milk extraction). Neurodevelopmental assessments included the expert-conducted Bayley test and self-reported questionnaire completed by mothers observing their children. Although the absolute sample size was small, our study provides meaningful scientific evidence emphasizing the importance of managing public exposure to EDCs. Several recent epidemiological studies have also reported associations between simultaneous exposure to multiple EDCs in breast milk and fetal neurodevelopment with small sample sizes. PFAS concentrations were investigated in a USA study of breast milk in 50 mothers (Zheng et al. 2021), a South African study of neonatal development in 50 mothers (Macheka et al. 2022), and an Irish study of neonatal health effects in 16 mothers (Abdallah et al. 2020).

Conclusions

This study is the first to confirm the effects of PFAS, phthalate, and paraben in maternal breast milk on PPD and infant neurodevelopment. The neurodevelopmental assessment showed a clinically abnormal rate of 7.7–38.5%, in which the motor and hyperactivity/impulsivity area T scores were the highest. The concentration of some phthalates (MEHP and MiNP), PFAS (PFOA and PFNA), and maternal PPD were significantly associated with the neurodevelopment of 3–4-year-old infants in South Korea.

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Data availability None.

Declarations

Institutional review board statement This study was approved by the Institutional Review Board of Kyung Hee University, South Korea (approval number KHSIRB-18–029).

Informed consent statement Informed consent was obtained from all subjects involved in the study.

Conflicts of interest The authors declare no conflict of interest.

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